Irreversible Electroporation for Locally Advanced Pancreatic Cancer

Florentine E.F. Timmer, MSc1 Bart Geboers, MD1 Alette H. Ruurds, MD, Evelien A.C. Schouten, MSc, Sanne Nieuwenhuizen, MD, Robbert S. Puijk, MD, Jan J.J. de Vries, MD, Martijn R. Meijerink, MD, PhD, and Hester J. Scheffer, MD, PhD

Several minimally invasive image guided tumor ablation techniques have been added to the treatment spectrum for locally advanced pancreatic cancer (LAPC). Irreversible electroporation (IRE) might have a significant additive value in the management of this difficult-to-treat disease. As opposed to thermal ablative techniques, IRE induces cell death by the delivery of high-voltage electrical pulses. The electrical energy disrupts the cellular membrane integrity, causes loss of cellular homeostasis and ultimately results in cell death. The extracellular matrix of connective tissue in surrounding delicate structures such as bile ducts, bowel wall, and larger blood vessels is spared. The preservation of these structures makes IRE attractive for the treatment of pancreatic cancers that are unresectable due to their anatomical location (ie, LAPC and local recurrence after surgical resection). In addition to its cytoreductive abilities, evidence is emerging on IRE’s capability to induce systemic immunomodulation through active in vivo vaccination against pancreatic cancer cells. These effects in combination with immunotherapy may offer a new treatment paradigm for tumors with low immunogenic potential like pancreatic ductal adenocarcinoma (PDAC).

This review discusses several practical and technical issues of IRE for LAPC: clinical evaluation, indications, patient preparations, procedural steps, imaging characteristics, clinical results, and “tricks of the trade” used to improve the safety and efficacy of the treatment. Future directions such as the combination of IRE with immunotherapy will be shortly addressed.

Tech Vasc Interventional Rad 23:100675 © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license. (http://creativecommons.org/licenses/by/4.0/)

KEYWORDS irreversible electroporation, image-guided, ablation, locally advanced pancreatic cancer, immunomodulation, immunotherapy, abscopal effect

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive tumor types, with an overall 5-year survival of less than 10%.1 Of the patients with PDAC, about one third encompasses non-metastatic locally advanced pancreatic cancer (LAPC). LAPC is broadly defined by its encasement of the superior mesenteric artery or celiac axis, or encasement of mesenteric-portal axis without possibility of reconstruction after resection. LAPC is considered unresectable due to the vascular encasement. Moreover, the adjacent vulnerable and inlaying structures surrounding the pancreatic tumor make resection and reconstruction challenging, consequently making an R0 resection difficult in most cases. For this group of patients, the current standard of care

Department of Radiology and Nuclear Medicine at the Amsterdam University Medical Center, Vrije Universiteit-Cancer Center Amsterdam in Amsterdam, The Netherlands.
Address reprint requests to B. Geboers, MD, Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location VUmc, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
E-mail: b.geboers@amsterdamumc.nl
1Share first authorship.
includes chemotherapy with or without radiation therapy.\textsuperscript{2,3} Despite the introduction of new and stronger chemotherapeutic regimens, the response still remains only temporary. Therefore, different approaches to treat LAPC are required. Minimally invasive ablation techniques present a promising method for the focal destruction of LAPC.\textsuperscript{4-8} It comprises both thermal methods, including radiofrequency ablation, microwave ablation and cryo-ablation, and a primarily non-thermal method, known as irreversible electroporation (IRE). The latter technique, in contrast to thermal ablation methods, employs electrical energy in the form of high-voltage electrical pulses that alter the existing cellular transmembrane potential. The pulsed electrical fields provoke either immediate and irreversible breakdown of the membrane, or secondary membrane disruption due to abundant transmembrane transfer of intracellular electrolytes and adenosine triphosphate (ATP). Both lead to loss of cellular homeostasis which in turn results in cell death through both apoptosis and necrosis.\textsuperscript{9} The high-voltage electrical pulses are administered through 2 or more needle electrodes, forming electrical fields between each electrode pair. The needles are precisely placed in and around the tumor including a tumor-free margin and aiming for complete tumor destruction.

IRE has distinct advantages over the use of thermal ablation methods that render it particularly attractive to treat LAPC. First, the use of mainly non-thermal electrical energy preserves the delicate surrounding tissue structures, including the walls of large vessels, bile ducts, and the intestines.\textsuperscript{10,11} Second, the efficacy of thermal ablation methods is impeded by the “heat-sink effect”, resulting in potentially incomplete ablation. IRE obviates this “heat-sink effect” due to the mainly non-thermal use of energy. Finally, a field of study related to the treatment of PDAC more recently touched upon is the combinatory approach of ablation with immunotherapy.\textsuperscript{12} Compared to thermal ablation methods, IRE leads to pronounced antigen release and T cell activation consistent with the establishment of a systemic immune response.\textsuperscript{13-15} This observation can be utilized in future treatment protocols combining IRE with immunotherapy, paving the way for the patients’ own immune system to destroy the malignant tumor remnants from the inside out.

This review discusses the practical and technical issues of IRE for LAPC, as well as some “tricks of the trade.” Future, more experimental directions such as the combination of IRE with immunotherapy are shortly addressed.

**Clinical Evaluation and (Contra-)Indications**

IRE for pancreatic cancer is currently used as cytoreductive modality for patients with an unresectable tumor that lacks signs of distant disease (ie, LAPC). Due to the inherent nature of LAPC surrounded by vulnerable structures, procedures are considered high risk.\textsuperscript{5} Hence, patients must be carefully assessed prior to treatment. Assessment should include overall patient performance, comorbidities and both a full anaesthetic and cardiac review. For IRE, patients must be able to undergo general anaesthesia. Each patient should be discussed in a multidisciplinary team comprising at least a radiologist, interventional radiologist, surgical oncologist, medical oncologist, hepatogastroenterologist, and radiation therapist.

**Work-up**

Histological proof of pancreatic cancer is required. Neo-adjuvant chemotherapy is generally favored, to identify patients with an aggressive tumor biology who will presumably not benefit from ablative treatment.\textsuperscript{16} In addition, potential down-sizing to resectability should be envisioned, in some cases allowing an R0 resection.\textsuperscript{17} Furthermore, a decrease in tumor volume yields a more efficacious and safer IRE procedure. In our experience, an upper limit of 5 cm in tumor diameter is highly recommended when utilizing IRE for LAPC. Pervasive involvement of the duodenum is considered an absolute contra-indication. If the patient suffers from biliary obstruction, adequate biliary drainage must be guaranteed prior to treatment. This can be achieved either through placement of a biliary endoprosthesis (Fig. 2) or by constructing a surgical biliodigestive anastomosis, for percutaneous or open IRE, respectively. For tumors in close vicinity to the common bile duct it is highly recommended to ensure biliary protection prior to treatment, as post-IRE swelling can impede passage through the central bile ducts. Furthermore, if a patient presents with a partially occluded portal vein prior to IRE, portal vein stenting (Fig. 1) should be performed to prevent acute complete occlusion due to postprocedural swelling.

**In- and Exclusion Criteria**

Given the high-risk profile of pancreatic IRE procedures, it is important to consider absolute and relative contra-indications (Table 1). Due to the procedure’s substantial strain on the heart, several cardiac-related illnesses are indicated as absolute or relative contra-indications. Consultation with a cardiologist is particularly recommended in these instances. Metal stents within the ablation zone have been a topic of discussion regarding safety and efficacy.\textsuperscript{18-20} This led to efforts of Scheffer et al. to explore the effects of IRE on metallic stent temperatures and ablation zones in a gel and animal model.\textsuperscript{4} No significant heating of the stent was found compared to surrounding tissue. They concluded that patients with metal stents should not be automatically withheld from IRE treatment but should be discussed individually and thoroughly.

**Preprocedural Imaging**

A comprehensive review of cross-sectional imaging is critical to assess the exact measurements of the lesion and its vicinity to other structures such as large blood vessels, bile ducts, and the intestines. A contrast-enhanced computed tomography (ceCT) is employed to image the upper abdominal area according to a 3-mm-slice-multiphase-pancreatic tumor protocol. The ceCT provides valuable information about tumor
size, precise location, and geometrical features, which are essential for treatment planning. In addition to ceCT, endoscopic ultrasound (EUS) can be used to assess tumor volume and ingrowth in the duodenum or stomach. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)-CT is another imaging modality used as a diagnostic imaging tool for pancreatic tumors. A recent meta-analysis reports its diagnostic value in identifying primary pancreatic cancer, with a sensitivity of 91% and a specificity of 81%. In comparison, the same meta-analysis reports the diagnostic value of ceCT and MRI, both with a sensitivity of 89% and specificity of 90% vs 89%, respectively. In our institution, 18F-FDG-PET-CT is currently not standardized as imaging modality for pancreatic cancer at any of the clinical imaging stages (ie, diagnosis, intra-procedural, or follow-up). 18F-FDG-PET-CT scans before and after pancreatic IRE treatment have been used for research purposes (Fig. 3). The 18F-FDG tracer remains a non-specific tissue binder highly dependent on glucose metabolism. Distinguishing between benign and malignant pancreatic illnesses can therefore be a complicated process. Moreover, not all pancreatic carcinomas are 18F-FDG avid, especially making smaller tumors difficult to observe. Novel and more specific tracers are needed that target specific molecules on pancreatic cancer cells, which would allow for better and earlier detection. One such molecular target is integrin αvβ6. This cell surface receptor is elevated in 80%-100% of patients with PDAC and with significantly higher expression than in normal or inflamed pancreatic tissue. Radioactive tracers are being developed to target this protein. The PANSAN study aims to clinically translate the integrin αvβ6-targeted PET-CT tracer for early detection of pancreatic cancer.

**Table 1 Contra-indications irreversible electroporation (IRE).** Overview of absolute and relative contra-indications for the treatment of locally advanced pancreatic cancer (LAPC) with IRE.

| Absolute Contra-Indications | Relative Contra-Indications |
|----------------------------|----------------------------|
| History of (ventricular) arrhythmias | Atrial fibrillation |
| Implanted cardiac stimulation devices | Coronary artery disease |
| Uncontrollable hypertension | Combined severe stenosis of the common hepatic artery and main portal vein branch |
| History of epilepsy | Metallic foreign object in the ablation zone |
| Congestive heart failure (NYHA class 2) | Impeded liver function |
| | Irreversible bleeding disorders |
| | Uncontrolled infections |
| | Patients that have received chemotherapy or immunotherapy in the 4 weeks prior to treatment |

**Equipment Needed**

The NanoKnife (AngioDynamics, Queensbury, NY), a low-energy direct-current electroporation device, is currently the only commercially available IRE system. This system includes 19-gauge unipolar needle electrodes with an adjustable active tip length (5 - 40 mm), a generator, and a footswitch. An Accusync electrocardiogram (ECG)-device (model 72; Milford, CT) is utilized to prevent pulse-induced arrhythmias. This device is connected to a 5-lead ECG, which synchronizes pulse delivery within the refractory period of the heart (the R-wave on the ECG). Complete muscle relaxation must be established before the start of pulse delivery to prevent generalized muscle contractions. IRE can be conducted in a surgical (open and laparoscopic) or percutaneous setting with US or CT fluoroscopy needle guidance. However, preference is given to CT fluoroscopy over US due to its multiplanar reconstruction ability.
Procedural Steps

Protocol

All procedures are performed under general endotracheal anaesthesia and in supine position. On exception a dorsal approach can be used in which the patient lays in prone position, eg, due to extensive ventral portosystemic collaterals. For optimal CT image quality during percutaneous procedures, arms should be placed behind the patient’s head. The tumor size, location, and geometrical features are assessed using ceCT during preprocedural planning and determine the number and configuration of the needle electrodes. In our institution the CT arteriography technique is used, in which a catheter is placed with its tip cranial from the celiac artery, allowing for optimal intraprocedural imaging (see tricks of the trade section for details). Following the catheter placement and preprocedural imaging, needle electrodes will be advanced in and around the tumor using CT fluoroscopy guidance and small doses of intra-arterial contrast. The interventional radiologist should aim for an interelectrode distance of 20 mm (15-24 mm) and a tumor-free margin of at least 5 mm. Due to the high conductivity of pancreatic cancer tissue as opposed to liver, the active tip length of the needles is routinely set to 15 mm. Needles should be placed in parallel (maximum angulation 10°) to ensure uniform energy delivery, resulting in the intended geometry and a homogenous ablation zone. Following needle placement, correct interelectrode distances are validated with CT in perpendicular plane using multiplanar reformating. Next, 10 test-pulses of 1500 V/cm and 90 μs are delivered between the selected electrode pairs. The NanoKnife apparatus returns information on the delivered current of the test-pulses, with a target current between 20 and 40 A. Voltage settings are manually adjusted in case of pending under- (<20 A) or overcurrent (>40 A). Next, the remaining 90 pulses are administered between all electrode pairs, totaling 100 pulses per vector pair as per our institution’s protocol. For larger tumors that require >6 needles, electrodes are repositioned to perform overlapping ablations. Likewise, for tumors with a depth of >15 mm, the deepest tumor part is treated first, followed by a pullback of the electrodes to ablate the superficial part.

Ablation Monitoring

Upon completion of the procedure, monitoring to attain details on the ablation zone is established using ceCT. In our institution, a postprocedural portal venous phase CT is obtained to verify sufficient tumor coverage and to check for early complications. The observed intraläsional gas pockets (Fig. 2E) may be the result of water electrolysis or

Figure 2 Irreversible electroporation (IRE) for locally advanced pancreatic cancer (LAPC) treatment timeline. 56-year-old female patient with LAPC on the basis of encasement of the first bifurcation of the superior mesenteric vein (180°) and involvement of the superior mesenteric artery (90°-180°). A biliary stent (black arrows in A, B, C, E, F) was placed using endoscopic retrograde cholangiopancreatography (ERCP), encompassing the bile ducts from the major duodenal papilla to the proximal common bile ducts. (A) ceCT of the LAPC in the head of the pancreas (white arrows) and biliary stent (black arrow) prior to IRE treatment. (B) Axial view of 3 of the 7 needle electrodes in situ. (C) Coronal view of all 7 needle electrodes in situ. The needles were successfully placed, bypassing all major blood vessels. (D) Sagittal view of 3 of the 7 needle electrodes in situ. (E) ceCT directly post IRE treatment. The white arrows depict the outline of the ablated lesion, in which intra-lesional gas pockets are visible (just to the left of the asterisk). (F) ceCT 24 hours post IRE treatment. The ablated region with hyperattenuating peripheral rim is outlined by the white arrows. A large amount of ascites was observed (black asterisk), likely due to stenosis of the portal vein/splenic vein bifurcation, possibly in combination with the intra-procedural need for transgastric placement of multiple needle electrodes. A 3-month scan was not yet available for this patient.
vaporization, or a combination of both. The area appears hypodense, usually presenting with a hyperattenuating peripheral rim due to reactive hyperaemia after 24 hours (Fig. 2F). Several studies have demonstrated that the apparent ablation zone on CT grossly corresponds to the pathological zone of cell death.33,34

Postablative Treatment
A median hospital stay of up to 3-4 days, including day of treatment, can be expected. Pain is reported as moderate 1 day post treatment5 and can be controlled using acetaminophen combined with an anti-inflammatory drug and, if needed, an opioid. Furthermore, due to the inevitable ablation of healthy pancreatic tissue to obtain a sufficient margin, de novo or worsened exocrine pancreatic insufficiency can occur. For this, pancreatic enzyme replacement therapy, specifically pancrelipase delayed-release capsules, has proven valuable.35-37

Clinical Follow-up
In the weeks following IRE, ceCT is used to identify complications and to discriminate between normal and abnormal postablative changes. In contrast to imaging of liver ablation, where a well-demarcated ablation zone is often visible, imaging of the pancreas presents a more challenging task.38 This is in large part due to little surrounding healthy pancreatic tissue and the presence of reactive edema post-IRE, hampering the exact delineation of the ablation zone and complicating differentiation between potential residual disease. 39

Initially, an increase in volume can be seen within the first 6 weeks due to reactive edema, with a subsequent decrease thereafter.30 In our institution, clinical follow-up by ceCT is performed after 6 weeks and then every 3 months to evaluate the ablation zone for local disease progression, defined as a focal or diffuse growing mass within 1 cm of the ablated region compared to the new baseline scan at 6 weeks post-IRE. Potential small local recurrent disease may be treated again, provided that no metastases are identified.

Response Evaluation Criteria
Tumor response remains a difficult-to-measure endpoint in IRE for LAPC. Criteria such as the Response Evaluation Criteria In Solid Tumors and those proposed by the World Health Organization exclusively depend on tumor size reduction.40,41 However, tumor size alone does not fully encompass tumor response and may thus lead to inaccurate conclusions. For this reason, a preferable method of evaluation is the combination of response in tumor and ablation size together with functional information such as alterations in enhancement, development of vascular or biliary stenoses or occlusions and tumor marker CA 19-9 levels.

Tricks of the Trade
Precise electrode placement is the cornerstone of a successful ablation. This accounts specifically for pancreatic IRE due to the retroperitoneal and difficult-to-reach nature of this organ. To avoid transgressing vital intervening structures such as the stomach or bowel, it is recommended to either use gantry tilt or virtual gantry tilt. Moreover, a freely available web-based tool (Visiﬁeld: https://www.visifield.com) has been developed as a proof of concept to facilitate in the treatment planning process of IRE procedures. Medical images are uploaded by the clinician and parameters can be adjusted to visualize the ablation zone outcome.42 Misplacement of needles by a small margin of millimetres can result in residual tumor or complications. Hence, careful treatment planning and reliable intraprocedural visualization are crucial for a successful pancreatic IRE procedure.

Optimizing Target Visibility
Determining the demarcation of tumor tissue, vascular structures, and ablation zone on an unenhanced CT in patients with LAPC is a difﬁcult task, especially when they have been pretreated with chemo- or radiotherapy. For this reason, ceCT is employed. However, there is a limitation of contrast agent dose to be used per procedure. This consequently
means that upon reaching this dose, further intraoperative imaging is restricted. This issue can be dealt with in 2 ways. The first is bolus chasing, in which the contrast dosage is lowered, allowing for pre- and postablation contrast imaging. Second, in our institution we use the CT arteriography technique, in which an intra-aortal catheter is placed transfemorally, with its tip cranial from the celiac artery. This allows for the repeated delivery of small doses of intra-arterial contrast and provides valuable real-time information on inlaying vascular structures, allowing for refinement of precise probe placement and increased procedural safety.5

**Electrode Steering**

Needle placement is a challenging feat and thus requires knowledge regarding protective measures and the correct needle steering technique. From a ventral perspective, the pancreas lies behind several major structures including the stomach and intestines. In order to safely pilot the needle electrodes towards the pancreas, a “lever”-technique can be employed. This technique requires placement of a different, blunt needle which is percutaneously inserted to push vital structures aside, paving the way for the sharp needle electrodes to be securely placed in the pancreatic tumor. Furthermore, other protective techniques including pneumo- and hydrodissections can be employed for adjacent structures that require protection. Precise electrode placement is further impeded by the floppy nature of the electrodes. Approaching the tumor in a straight line is usually not a problem, but when a deviating approach is required, simply correcting the angle will cause the probe to bow, resulting in a deviation even further away from the target. Instead, the probe should be angled in the opposite direction so that upon advancing, the electrode will follow a curved path towards the tumor (Fig. 4).

**Complications**

A recent systematic review by Ruarus et al. provides an overview of the morbidity and mortality rates for pancreatic IRE.43 Several studies examining safety and efficacy of surgical and percutaneous IRE have been conducted over the years. The average cumulative morbidity for surgical and percutaneous IRE was 36% vs 24%, with an average peri-procedural mortality rate of 2% vs 0%, respectively.44 Most frequently encountered adverse events comprise GI-related complaints including pain, diarrhoea, nausea, vomiting, loss of appetite and delayed gastric emptying. The most severe complications include vessel occlusion, bleeding, severe pancreatitis, and death. Despite the predominantly non-thermal effect of this technique, some element of heat production near the electrodes remains inevitable, also known as secondary Joule heating.45,46 Employing stronger protocols that use aggressive energy regimens have a substantial effect on the extent and volume of thermal distribution. Moreover, even though the work presented by Scheffer et al. demonstrated no heating of the metallic stent, they did show higher temperatures near the electrodes. This is important when considering electrode placement near vital surrounding structures. Provided that the underlying rationale and clinical application paradigms of IRE are largely based on its non-thermal nature, specific emphasis must be laid on the development and utilization of protocols to reduce potential detrimental thermal effects. In this regard active cooling electrodes were evaluated in porcine livers and are able to reduce tissue temperatures and electric current while maintaining similar lesion sizes.47 Further characterization of thermal effects and related complications are paramount to ensure safe clinical application and effective treatment planning.

**Clinical Results**

IRE for pancreatic tumors is currently used for patients with histologically proven unresectable LAPC. To date, increasing evidence from the literature suggests that IRE in combination with neo-adjuvant chemotherapy and/or radiotherapy elicits a survival benefit for this set of patients, confirming safety and efficacy of the procedure.5,7,16,48-50 Moreover, IRE treatment has been found to not adversely affect quality of life in the short term.51 A recent systematic review by Moris et al. provides an elaborate overview of all studies that have utilized IRE for LAPC, with a median overall survival (OS)
following IRE between 7 and 27 months (Table 2). This variance may pertain to selection bias, the utilized IRE approach, the diverse LAPC tumor biology (passive vs aggressive), personalized (neo-) adjuvant chemotherapeutic treatment can be used as an effective way to select patients who are likely to benefit from ablation. A coinciding prognostic factor after IRE was reported by Scheffer et al. and Narayanan et al. They both reported tumor size to correlate with OS, specifically describing tumors larger than 3 cm to predict worse survival outcomes. More recently, these findings were confirmed by Ruarus et al. in their PAN-FIRE-II trial. Furthermore, they found pre-IRE CA 19-9 levels of more than 2000 U/ml or a decrease in CA 19-9 levels of 50% or less 3 months post-IRE to correlate with poor survival.

**Future Perspectives**

To guarantee long-term success of IRE as an established tool for the treatment of LAPC, we must strive for continuous improvement of the technique, aiming for minimal complications and maximal attainable results. Important physical factors influencing these outcome values include the adjustable parameter settings of the IRE apparatus. These individually adjustable parameters include number, length and duration of the electrical pulses, interval between the pulses, pulse delivery protocol, interelectrode distance, voltage, number of needle electrodes, and their geometry. Hence, for optimization of IRE procedures it is essential to elucidate the exact effect of each parameter on the ablation zone in terms of geometry and homogeneity.

One such advancement in treatment protocol was reported by Appelbaum et al., stating that application of a cyclical pulse protocol (10-30-30-30) in lieu of a continuous pulse protocol (10-90) resulted in a larger ablation zone and higher tissue conductivity in in vivo porcine livers. This may consequently lead to lower treatment temperatures. Similarly, a novel IRE variant named high frequency IRE (H-FIRE) has been introduced, in which monopolar 90 μs pulses are substituted with a burst of shorter bipolar pulses between 0.25 and 5 μs. The shorter pulse length should, theoretically, be better at penetrating heterogenous tissue and produce more predictable ablations as well as eliminate the need for intraoperative paralytics and cardiac synchronization. However, current knowledge regarding various physical parameter settings and local tissue properties and their exact influence on ablation zone geometry is still limited, requiring further research and refinement of protocols, and tools such as the Visifield 3D imaging software.

Clinically, IRE could thrive in a setting where it is complemented by other treatment modalities. IRE is currently often combined with chemotherapy. Although improvements in chemotherapy regimens, such as FOLFIRINOX, in terms of patient OS have been established over the last years, there has not yet been a major leap in improvement for the treatment of LAPC and prognosis remains dismal.

One potential advancement in combination therapy integrates immunotherapy with IRE (and chemotherapy), referred to as “electroimmunotherapy”. This is based on the latest findings that IRE induces a systemic immune response following apoptosis and necrosis of tumor cells, resulting in the release of antigens and damage-associated molecular pattern molecules (DAMPs). These DAMPs induce maturation of dendritic cells (DCs) and other antigen presenting cells (APCs) that can subsequently take up the released antigen epitopes, thereby causing systemic activation of the immune system. The activation of lymph nodal T-cells by these APCs could potentially induce a durable antitumor T-cell response, in essence providing active in vivo antitumor vaccination. When robust enough, this systemic T-cell response could then lead to regression in distant metastases, a process known as the "abscopal effect". However, pancreatic cancers are known for their severely immunosuppressive micro-environment, making it difficult for the activated proinflammatory T-cells to participate in tumor destruction. In order to leverage the patients' own activated immune system through the IRE procedure, a combination with immunotherapy in the form of checkpoint inhibitors or other active immune enhancing drugs may be able to create a synergistic effect. A recent preclinical study involving immunocompetent mice with PDAC that received combined treatment with IRE and an anti-PD1 checkpoint inhibitor, demonstrated significant survival benefit. Furthermore, in a clinical study for unresectable LAPC, a combination of IRE and allogeneic natural killer cells achieved significant improvement in OS over IRE alone. Although these are optimistic results, more research is imperative to determine
clinical safety and efficacy of such combinatory treatments. For this reason, our research group is currently preparing the PANFIRE-III study, a prospective trial in which electroimmunotherapy will be achieved through pancreatic IRE in combination with a Toll-like receptor ligand and anti-PD1 checkpoint inhibition.

Conclusion
IRE offers LAPC patients an efficacious treatment option when combined with chemotherapy. Several studies have confirmed overall survival benefit compared to current standard-of-care treatment with chemotherapy alone. Nevertheless, due to the possibility of major complications and even death, the procedure should be considered high-risk. In depth knowledge on how to practically perform smart and skilful techniques regarding IRE for LAPC will accomplish safer and more efficacious use of this technique. Furthermore, electroimmunotherapy based on the synergy between immunotherapy and IRE represents a new treatment paradigm for interventional radiologists and immuno-oncologists. When smart and strong collaborations are formed, these treatments may have the potential to create a breakthrough in cancer research.

References
1. Netherlands Comprehensive Cancer Organisation (IKNL). 2019. Available online: http://www.iknl.nl/netherlands-cancer-registry.
2. Niederhuber JE, Brennan MF, Menck HR. The National Cancer Data Base report on pancreatic cancer. Cancer 76:1671-1677, 1995
3. Loehrer PJ Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: An Eastern Cooperative Oncology Group trial. J Clin Oncol 29:4105-4112, 2011
4. Schefler HJ, Stam AGM, Geboers B, et al. Irreversible electroporation of locally advanced pancreatic cancer transiently alleviates immune suppression and creates a window for antitumor T cell activation. Oncology 8:1652532, 2019
5. Schefler HJ, Vroomen LG, de Jong MC, et al. Ablation of locally advanced pancreatic cancer with percutaneous irreversible electroporation: Results of the phase II/I PANFIRE study. Radiology 282:585-597, 2017
6. Niessen C, Beyer LP, Pregler B, et al. Percutaneous ablation of hepatic tumors using irreversible electroporation: A prospective safety and mid-term efficacy study in 34 patients. J Vasc Interv Radiol 27:480-486, 2016
7. Martin RC, 2nd Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: Safety and efficacy. Ann Surg 262:486-494, 2015
8. Mansson C, Bergenfeldt M, Brahmstaedt R, et al. Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Anticancer Res 34:289-293, 2014
9. Geboers B, Schefler HJ, Grayhill PM, et al. High-voltage electrical pulses in oncology: Irreversible electroporation, electrochemotherapy, gene electrotransfer, electrofusion, and electroimmunotherapy. Radiology 295:254-272, 2020
10. Vroomen LGPH, Petre EN, Cornelis FH, et al. Irreversible electroporation and thermal ablation of tumors in the liver, lung, kidney and bone: What are the differences? Diagnost Intervent Imaging 98:609-617, 2017
11. Vogel JA, van Veldhuisen E, Agnass P, et al. Time-dependent impact of irreversible electroporation on pancreas, liver, blood vessels and nerves: A systematic review of experimental studies. PloS One 11, 2016: e0166987-e
12. Chu KF, Dupuy DE. Thermal ablation of tumours: Biological mechanisms and advances in therapy. Nat Rev Cancer 14:199, 2014
13. White SB, Zhang Z, Chen J, et al. Early immunologic response of irreversible electroporation versus cryoaablitation in a rodent model of pancreatic cancer. J Vasc Intervent Radiol 29:1764-1769, 2018
14. Shao Q, O’Flanagan S, Lam T, et al. Engineering T cell response to cancer antigens by choice of focal therapeutic conditions. Int J Hyperthermia 36:130-138, 2019
15. Bulvik BE, Rozenblum N, Gourewich S, et al. Irreversible electroporation versus radiofrequency ablation: A comparison of local and systemic effects in a small-animal model. Radiology 280:413-424, 2016
16. Ruarus AH, Vroomen L, Geboers B, et al. Percutaneous irreversible electroporation in locally advanced and recurrent pancreatic cancer (PANFIRE-2): A multicenter, prospective, single-arm, phase II study. Radiology 2019:191109
17. Vogel JA, Rombout S, de Rooij T, et al. Induction chemotherapy followed by resection or irreversible electroporation in locally advanced pancreatic cancer (IMPALA): A prospective cohort study. Ann Surg Oncol 24:2734-2743, 2017
18. Dunkl-Jacobs EM, Philips P, Martin RC. 2nd Evaluation of thermal injury to liver, pancreas and kidney during irreversible electroporation in an in vivo experimental model. BJA Surg 101:1113-1121, 2014
19. Mansson C, Nilsson A, Karlson BM. Severe complications with irreversible electroporation of the pancreas in the presence of a metallic stent: A warning of a procedure that never should be performed. Acta Radiol 295:254-272, 2020
20. Neal RE, 2nd Smith RL, Kavnoudias H, et al. The effects of metallic implants on electroporation therapies: Feasibility of irreversible electroporation for brachytherapy salvage. Cardiovasc Intervent Radiol 36:1638-1645, 2013
21. Schefler HJ, Vogel JA, van den Bos W, et al. The influence of a metal stent on the distribution of thermal energy during irreversible electroporation. PLoS One 11:e0148457, 2016
22. Chung I, Sanagappalli S, Stota A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol 24:2047-2060, 2018
23. Nguyen VX, Nguyen CC, Nguyen BD: (18)F-FDG PET/CT imaging of the pancreas: Spectrum of diseases. Jop 12:557-566, 2011
24. Best LM, Rawji V, Pereira SP, et al. Imaging modalities for characterising focal pancreatic lesions. Cochrane Database Syst Rev 4:CD01213, 2017
25. Sipos B, Hahn D, Carceller A, et al. Immunohistochemical screening for beta(6)-integrin subunit expression in adenocarcinomas using a novel monoclonal antibody reveals strong up-regulation in pancreatic ductal adenocarcinomas in vivo and in vitro. Histopathology 45:226-236, 2004
26. de Geus SW, Booher RS, Swijnenburg RJ, et al. Selecting tumor-specific molecular targets in pancreatic adenocarcinoma: Paving the way for image-guided pancreatic surgery. Mol Imaging Biol 18:807-819, 2016
27. Hackel BJ, Kimura RH, Miao Z, et al. 18F-fluorobenzoate-labeled cystine knot peptides for PET imaging of integrin alphabetah. J Nucl Med 54:1101-1105, 2013
28. Steiger K, Schlienger A-M, Weichert W, et al. Perspective of angiopep-2 imaging for clinical management of pancreatic carcinoma and its precursor lesions. Mol Imaging 16:1356012117709384, 2017
29. Thomson KR, Cheung W, Ellis SJ, et al. Investigation of the safety of irreversible electroporation in humans. J Vasc Intervent Radiol 22:611-621, 2011
30. Schefler HJ, Melenhorst MC, Vogel JA, et al. Percutaneous irreversible electroporation of locally advanced pancreatic carcinoma using the dorsal approach: A case report. Cardiovasc Intervent Radiol 38:760-765, 2015
31. Meijerink M, Schefler H, Narayanan G. Irreversible electroporation in clinical practice. 2018
32. Knavel EM, Brace CL: Tumor ablation: common modalities and general practices. Tech Vasc Intervent Radiol 16:192-200, 2013
33. Appelbaum L, Ben-David E, Farooq M, et al. Irreversible electroporation ablation: Creation of large-volume ablation zones in vivo porcine liver with four-electrode arrays. Radiology 270:416-424, 2014
Irreversible Electroporation for Locally Advanced Pancreatic Cancer

34. Scheffer HJ, Melenhorst MC, Echenique AM, et al: Irreversible electroporation for colorectal liver metastases. Tech Vasc Interv Radiol 18:159-169, 2015
35. Tseng DSJ, Molenaar IQ, Besselaar MG, et al: Pancreatic exocrine insufficiency in patients with pancreatic or peripancreatic cancer: A systematic review. Pancreas 45:325-330, 2016
36. Saito T, Hirano K, Isayama H, et al: The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer: A prospective cohort study. Pancreas 46:341-346, 2017
37. Kuhn RJ, Gelrud A, Munck A, et al: CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. Adv Ther 27:895-916, 2010
38. Dollinger M, Jung EM, Beyer L, et al: Irreversible electroporation ablation of malignant hepatic tumors: Subcutane and follow-up CT appearance of ablation zones. J Vasc Interv Radiol 25:1599-1604, 2014
39. Vroomen L, Scheffer HJ, Melenhorst M, et al: MR and imaging characteristics and ablation zone volumetry of locally advanced pancreatic cancer treated with irreversible electroporation. Eur Radiol 27:2521-2531, 2017
40. Nagtegaal ID, Odze RD, Khmastra D, et al: The 2019 WHO classification of tumours of the digestive system. Histopathology 76(2):182-188, 2020
41. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:288-249, 2009
42. Mansson C, Brahmstaedt R, Nygren P, et al: Percutaneous irreversible electroporation for the treatment of unresectable, locally advanced pancreatic cancer: Initial clinical experience. Pancreas 46:341-346, 2017
43. Miklovic T, Latouche EL, DeWitt MR, et al: A comprehensive characterization of parameters affecting high-frequency irreversible electroporation lesions. Ann Biomed Eng 45:2324-2334, 2017
44. Arena CB, Sano MB, Rylander MN, et al: Theoretical considerations of tissue electroporation with high-frequency bipolar pulses. IEEE Trans Bio-med Eng 58:1474-1482, 2011
45. Siddiqui IA, Latouche EL, DeWitt MR, et al: Induction of rapid, reproducible hepatic ablations using next-generation, high frequency irreversible electroporation (H-FIRE) in vivo. HPB (Oxford) 18:726-734, 2016
46. Rombouts SJ, Walma MS, Vogel JA, et al: Systematic review of resection rates and clinical outcomes after FOLIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 23:4352-4360, 2016
47. Vincent A, Herman J, Schulick R, et al: Pancreatic cancer. Lancet 378:607-620, 2011
48. He C, Wang J, Sun S, et al: Immunomodulatory effect after irreversible electroporation in patients with locally advanced pancreatic cancer. J Oncol 2019:9346017, 2019
49. Pandit H, Hong YK, Li Y, et al: Evaluating the regulatory immunomodulation effect of irreversible electroporation (IRE) in pancreatic adenocarcinoma. Ann Surg Oncol 26:800-806, 2019
50. Mole RH: Whole body irradiation, radiobiology or medicine? Br J Radiol 26:234-241, 1953
51. Zhao J, Wen X, Tian L, et al: Irreversible electroporation reverses resistance to immune checkpoint blockade in pancreatic cancer. Nat Commun 10:899, 2019
52. Lin M, Alnaggar M, Liang S, et al: An important discovery on combination of irreversible electroporation and allogeneic natural killer cell immunotherapy for unresectable pancreatic cancer. Oncotarget 8:101795-101807, 2017
53. Lin M, Liang S, Wang X, et al: Percutaneous irreversible electroporation combined with allogeneic natural killer cell immunotherapy for patients with unresectable (stage III/IV) pancreatic cancer: A promising treatment. J Cancer Res Clin Oncol 143:2607-2618, 2017
54. Mannion C, Brahmstaedt R, Nilsson A, et al: Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. Eur J Surg Oncol 42:1401-1406, 2016
55. Paella S, Butturrini G, Frigerio I, et al: Safety and feasibility of irreversible electroporation (IRE) in patients with locally advanced pancreatic cancer: Results of a prospective study. Digest Surg 32:90-97, 2015
56. Kluger MD, Eppelboym I, Schroe BA, et al: Single-institution experience with irreversible electroporation for T4 pancreatic cancer: First 50 patients. Ann Surg Oncol 23:1736-1743, 2016
57. Lambert L, Horejs J, Kriska Z, et al: Treatment of locally advanced pancreatic cancer by percutaneous and intraoperative irreversible electroporation: General hospital cancer center experience. Neoplasma 63:269-273, 2016
58. Belfiore MP, Ronza FM, Romano F, et al: Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: Our preliminary experience. Int J Surg 21(Suppl 1):S34-S39, 2015
59. Stillström D, Nilsson H, Jesse M, et al: A new technique for minimally invasive irreversible electroporation of tumors in the head and body of the pancreas. Surg Endosc 31:1982-1985, 2017
60. Spliotis J, Kopanakis N, Terras A, et al: Irreversible electroporation for Stage III locally advanced pancreatic cancer: Single-center experience. J BUON 23:1203-1204, 2018
61. Sugimoto K, Moriyasu F, Tsuchiya T, et al: Irreversible electroporation for nonthermal tumor ablation in patients with locally advanced pancreatic cancer: Initial clinical experience in Japan. Int Med (Tokyo, Japan) 57:3225-3231, 2018