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Percutaneous irreversible Electroporation in Locally Advanced Pancreatic Cancer: A Review of Current Literature

Serena Carriero[1], Carolina Lanza[1], Giuseppe Pellegrino[1*], Caterina Sattin[1], Mariachiara Basile[1], Maria Teresa Contaldo[1], Pierpaolo Biondetti[2], Salvatore Alessio Angileri[3], Filippo Piacentino[4], Massimo Venturini[4], Giuseppe Guzzardi[5], Anna Maria Ierardi[3], Gianpaolo Carrafiello[6]

Abstract

Pancreatic cancer (PC) is a highly lethal disease with a 5-year survival rate of 5-6%. To date, the only potentially curative option for PC remains surgical resection with microscopically negative margins. Given the poor survival rate of locally advanced PC (LAPC) patients, several studies explored the combination of conventional therapies with ablation therapies, showing promising results. Several studies showed that thermal ablation in PC, due to its anatomical localization, can induce heat-related damage to bile ducts, adjacent vessels, and gastrointestinal structures. Irreversible Electroporation (IRE) is a locoregional nonthermal ablative technique that induces cellular death by creating nanopores avoiding the aforementioned complications. Our review aims to provide an overview of the technique and highlight its current standpoint in the treatment of LAPC.

Keywords: Irreversible Electroporation; Electroporation; IRE; local Ablation; Thermal Ablation; Ablation; Pancreatic Cancer; Locally Advanced Pancreatic Cancer; Immunotherapy

Introduction

Pancreatic cancer (PC) is a highly lethal disease with a 5-year survival rate of 5-6%, being the third leading cause of death from cancer in both males and females in the USA [1]. To date, the only potentially curative option for PC remains surgical resection with microscopically negative margins, but due to a diagnostic delay attributable to a typical onset of the symptoms in later stages of the disease, only 15% of patients present with resectable disease [2, 3]. For this reason, the majority of patients present with unresectable disease: locally advanced PC (LAPC) in 30% of cases and metastatic PC (MPC) in 50% of cases [4]. According to the American Joint Committee on Cancer (AJCC) guidelines, a locally advanced tumor cannot be completely resected because of the invasion of nearby structures and/ or present with distant metastases [5]. MD Anderson Cancer Centre gives more precise indications about the resectability of pancreatic tumors: a locally advanced, hence unresectable, PC is defined by encasement of superior mesenteric artery greater than 180°, encasement and no technical reconstructive options of celiac axis or hepatic artery, and occlusion and no technical reconstructive options of superior mesenteric vein or portal vein, with no signs of distant metastases [6, 7]. Previously, chemotherapy with gemcitabine with or without radiation therapy has been the standard of care for LAPC with overall survival (OS) of 9-11 months [8]. More recently, due to the implementation of treatments including the association of nab-paclitaxel or FOLFIRINOX (5-fluorouracil, leucovorin,

Affiliation:

[1]Postgraduate School of Radiodiagnostics, University of Milan, Milan, Italy

[2]Università Degli Studi di Milano, Via Festa del Perdono 7 – 20122, Milan, Italy

[3]Department of Diagnostic and Interventional Radiology, Foundation IRCCS Cà Granda – Ospedale Maggiore Policlinico, Via Francesco Sforza 35 – 20122, Milan, Italy

[4]Diagnostic and Interventional Radiology Department, Circolo Hospital, ASST-Sette Laghi, 21100 Varese, Italy

[5]Department of Radiology, Unit of Interventional Radiology, Ospedale Maggiore della Carità, Corso Giuseppe Mazzini 18 – 28100, Novara, Italy

[6]Università Degli Studi di Milano, Via Festa del Perdono 7 – 20122, Milan, Italy

***Corresponding author:**
Giuseppe Pellegrino, Postgraduate School of Radiodiagnostics, University of Milan, Milan, Italy

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irinotecan, and oxaliplatin) with gemcitabine as neoadjuvant setting, the OS increased to 6-13 month [9]. The goal of these therapies is to obtain the surgical eligibility of patients, even though only a small minority of patients fall within the limits of PC resectability criteria after the aforementioned therapies. Given the poor survival rate of LAPC patients, several studies explored the combination of conventional therapies with ablation therapies, showing promising results [7, 10]. The most commonly employed Thermal Ablation (TA) techniques are radiofrequency ablation (RFA) and microwave ablation (MWA) [11-14]. Nevertheless, despite their reported efficacy, several researches showed that TA can induce heat-related damage to bile ducts, adjacent vessels, and gastrointestinal structures. Irreversible Electroporation (IRE) is locoregional nonthermal ablative technique that induces cellular death by creating nanopores [15]. The very first report of its deployment dates 2009, in a study theorizing the possibility of developing an IRE system that could be both safe and effective in the treatment of human pancreatic malignancies [16], successively tested on a swine model with a good safety profile [17].

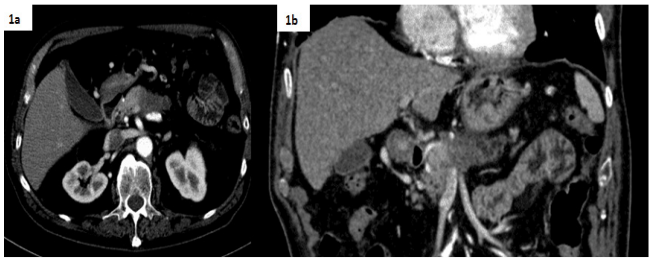
In consideration of the potential opportunities given by this technique, IRE has then been widely tested on human PC, mainly in the context of LAPC treatment, with the objective to achieve a greater overall survival (OS) and progression-free survival (PFS) compared to the conventional treatments, to improve quality of life (QoL), and relieve symptoms related to the advanced stage of the disease [10, 18, 19].

Our review aims to provide an overview of percutaneous IRE technique and highlight its current standpoint in the treatment of LAPC.

Percutaneous Irreversible Electroporation Technique and Procedure

Irreversible Electroporation is a non-thermal ablative technique based on high-voltage electrical pulses (HEVPs) of up to 3000 V delivered in 70-80 microseconds and applied between needle electrodes inserted within the tumor.

This ablative technique creates multiple microscopic holes in cellular membranes inducing the irreversible permeabilization that leads to programmed cell death [20]. IRE-induced cellular apoptosis of pancreatic pathologic tissue takes place at temperatures inferior to 50 C°: this allows the preservation of the underlying matrix, vessels, and biliary ducts included in the ablation area, avoiding the typical heat-sink effect and without causing coagulation necrosis [13]. To perform an IRE procedure, general anesthesia with a complete neuromuscular block, to reduce contractions of muscles induced by HEVPs, is required. During the procedure, the operator inserts two to six needles (depending on the size and shape of the tumor) within the target lesion. To assure maximum efficacy, it is important to insert each needle parallel to the others with a distance of no less than 1 cm and not more than 2.5 cm. Most recent studies treated tumors whose diameter was up to 6.5 cm [21], but according to several research, the ideal interval, both in terms of prolonged OS and safety, for an IRE procedure ranges between 3-4cm. In fact, Fang et al. reported a survival advantage in patients undergoing IRE with a median OS of 16.2 and 9.9 months for tumors that are ≤ 3 mm and > 3 cm, respectively [22]. Narayanan et al. [23] demonstrated that among different variables, such as age, CA 19-9 values or number of lines of chemotherapy, a tumor size ≤ 3 cm was the only factor significantly associated with better overall survival. In percutaneoud approach, needle insertion can be either under ultrasound (US) or computed tomography (CT) guidance; given the thinness of the needles (22G), in experienced hands trans hepatic or trans gastric approaches are also possible [24]. A case of LAPC treated with IRE using a percutaneous trans-gastric approach is shown in Figures 1, 2, and 3. Specific parameters, such as tumor size, location, and body structure, as well as operators' expertise, are factors to be considered to choose the best approach. The advantages of a percutaneous approach include shorter procedure time and lower invasivity, hence reducing complication rates and procedural costs. Percutaneous IRE is an "off-label" procedure for stage III PC. The inclusion criteria are different from center to center, and mainly comprise a confirmed diagnosis of a LAPC with a maximum diameter of 4 cm, adequate performance status (mainly evaluated with ECOG), and liver, renal, blood functionalities and with an anesthesiologist's consult to assess the safety of general anesthesia [25]. Contraindications to the procedure can be tumor-related (metastatic disease, diameter > 5 cm) or patient-related (cardiac diseases, poor liver or renal function, low-performance status). Epilepsy, atrial fibrillation, or other forms of cardiac conditions also represent contraindications to the procedure, because pulses emitted during the procedure could result in de-synchronizations of either brain or cardiac electric waves [26].



Abbreviations –CT: computed tomography.

Figure 1: Pre-procedural contrast-enhanced CT (arterial phase) in axial (1a) and coronal planes (1b) shows a lesion in the pancreatic body measuring 31x26mm.

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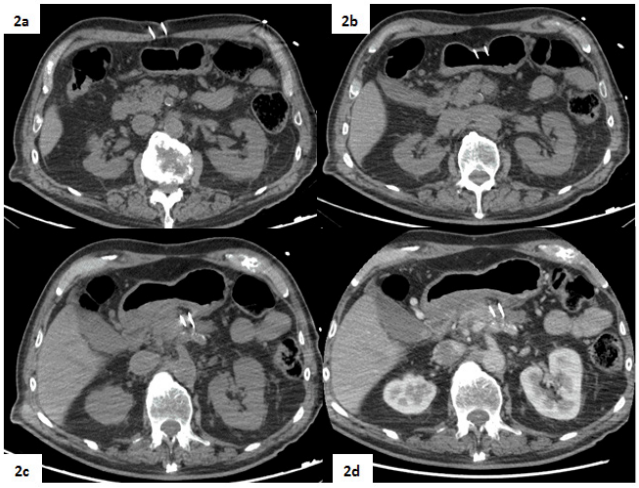
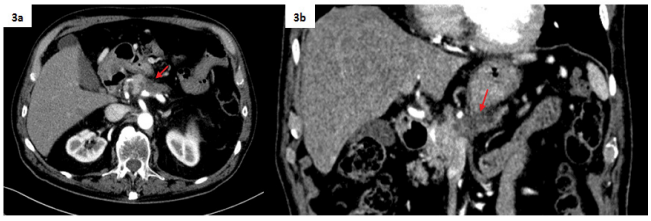


Abbreviations –CT: computed tomography.

Figure 2: Peri-procedural non-enhanced (2a, 2b, 2c) and contrast-enhanced arterial phase CT scans (2d) acquired during the procedure show the correct positioning of the two needles in the surroundings of the target lesion via trans-gastric approach.



Abbreviations – CECT: contrast-enhanced computed tomography.

Figure 3: CE-CT (arterial phase) acquired 1 month after the procedure in axial (3a) and coronal planes (3b). The final result is a dimensional reduction of the treated pancreatic lesion (22x19 mm vs 31x26 mm).

IRE Treatment for LAPC

Multiple studies have been conducted on the efficacy of local treatments such as IRE, which can be used in combination with induction therapy to obtain down staging and surgical eligibility of LAPC. According to current literature, the clinical outcomes of IRE treatments strongly depend on the timing of the procedure. Studies reported that upfront IRE therapies (performed before chemotherapy cycles) yielded modest increases in median OS, whereas when executed after a systemic treatment granted better results both in terms of clinical efficacy and safety [27, 28]. These results may suggest that modifications to the tumoral microenvironment operated by chemotherapy could catalyze the efficacy of locoregional treatments. Tumor biology and performance status are important factors for the selection of patients who would benefit from neoadjuvant therapy and this synergistic effect. The LAP-PIE feasibility trial is the first UK-based randomized controlled trial of pancreas IRE in patients with LAPC, enrolling 50 patients in whom LAPC remained localized and unresectable after FOLFIRINOX (3-6 cycles). Eligible patients with LAPC who have undergone first-line 5-FluoroUracil, Leucovorin, Irinotecan, and Oxaliplatin chemotherapy were randomized to receive either a single session of IRE followed by (if indicated) further chemotherapy or chemotherapy alone (standard of care). The study will investigate whether IRE improves survival, and health-related QoL [29]. However, the potential increased survival reported in this trial should be carefully evaluated since it may be due to patient selection for IRE rather than the effect of IRE (selection bias). Even in surgery, Oba et al with the SLING trial demonstrated that administration of NAT (neoadjuvant treatment) and CA 19-9 levels are two of the eight prognostic factors of overall survival (OS) in the preoperative setting. Concerning timing, the highest OS rates were observed with IRE after induction chemotherapy, up to 27 months, using FOLFIRINOX in 1st-line treatment, and gemcitabine as a 2nd-line treatment. Some have indicated that ≥8 months of NAT is associated with better prognosis and resectability. Efficacy increases with six or more cycles, but further studies are needed to identify the most appropriate number of cycles of therapy [30].

The phase II PANFIRE study that aimed to compare the efficacy of combining NAT with IRE vs NAT with conversional surgery. The study retrospectively enrolled a total of 140 patients with either LAPC or local recurrence of a previously treated PC, who underwent CT from August 2015 to March 2020. 31 patients underwent chemotherapy, 4 chemotherapy + resection, 64 chemotherapy + IRE, 44 of which then underwent NAT. The median survival was 16.9 months. In the chemotherapy-only group, the mean survival was 8.9 months, lower than in the groups in which chemotherapy was combined with IRE (24 months) or resection (25.3 months), with values even closer with the addition of NAT after IRE. Obviously, characteristics such as tumor size (better outcomes when <4cm) and blood values of CA19.9 were relevant factors to the primary outcome of the trial which was the achievement of a target median OS, exceeded in both patients with locally advanced pancreatic cancer and with local recurrence (respectively 17 and 16 months of OS) [31]. Contrasting results were instead obtained from the IMPALA study, a prospectic cohort study which compared surgery with IRE enrolling 132 patients with LAPC from Semptember 2013 to March 2015, who received 3 months of CT (FOLFIRONOX or gemcitabine) followed by surgery or IRE if non-progressive, IRE-elegible tumors based on RECIST 1.1 criteria. The results showed promising survival rates after resection but no apparent benefit of IRE, despite considerable morbidity [32].

Concluding, preliminary studies emphasize the role of IRE in increasing OS in the treatment of LAPC. However, the survival gains can be confounded by the results of improved systemic therapies and by selection bias, hence further RCTs

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are needed. IRE can be considered an alternative to surgical resection in LAPC that remains unresectable after induction therapy (75%), often due to persistent local invasion [33].

Clinical Outcomes of IRE in the Treatment of LAPC

Woeste et al. reported the outcomes of 187 patients treated with an open IRE approach, showing an OS of 30.7 months and a PFS of 22.4 with a complication rate of 16%. This study reports the results of IRE treatments in LAPC and shows that an accurate patient selection can result in survival times of over 2 years [34]. Veldhuisen et al. and Ruarus et al. report only considered a CT-guided percutaneous approach with an OS respectively of 17.2 months and 17 months [8, 35, 36]. Numerous independent predictive factors were found to influence patients' survival: according to Woeste et al., abnormal CA19-9 values before IRE, and chemotherapy duration ≤ 5 months were predictors of a worse survival rate; on the other hand, age ≤ 61 years and no prior radiotherapy predicted an improvement of OS [34]. Among the most representative included studies (Table 1) the median overall survival (OS) of all patients was 22.7 months (range: 13 –31 months), and the median progression-free survival (PFS) was 11.2 months (range: 7 – 23 months) and the median recurrence-free survival (RFS) was 8 months range. 2.7-12.4).

Two studies reported prognostic factors associated with OS among patients undergoing IRE. Narayanan et al. reported that tumor size was the only factor associated with OS; patients with tumors ≤ 3 cm had a survival advantage [37]. Scheffer et al. reported that early local progression following IRE was the only predictor of worse OS [38]. The most relevant and achievable goal in the management of LAPC appears to be good palliation of symptoms [39]. Results of Phase I/II PANFIRE study [40] showed that, up to 6 months after IRE treatment, overall pain perception and QoL were not affected. After 6 months, several items worsened but they reported that this might reflect disease progression rather than the effect of IRE, also adding that IRE may be a useful adjuvant to slow disease progression and to pre-preserve QoL. M. Lin et al. [41] studied QoL after IRE treatment and NK cell immunotherapy, using the KPS as an index for QoL posttreatment. Results analysis showed QoL markedly improved.

Safety and Complications of IRE in the Treatment of LAPC

Safety was assessed based on the onset of complications, graded according to the Clavien-Dindo Classification of Surgical Complications (0-IV), in which severe complications are graded as III/IV [42]. The most frequent complications of IRE in the treatment of LAPC are acute pancreatitis, portal or mesenteric thrombosis, pancreatic fistula, perforations of the gastro-enteric tracts (duodenal or transverse colon), hemorrhages (superior mesenteric artery), vascular lesions (aneurysm and pseudoaneurysm), ascites, lymphatic fistula, delayed gastric emptying/bowel passage, biliary complications, pancreatic leak, chyle leak [43]. These are believed to be directly IRE-related because they are uncommon events in agreement to the literature [43]. Among patients undergoing percutaneous IRE, morbidity was 24.3% and no periprocedural mortality was reported among patients undergoing percutaneous IRE [44]. The percutaneous approach is minimally invasive and has lower complication rates. Patients with stable LAPC and poor performance status should likely be considered for this approach [45]. The largest study of percutaneous IRE, by Leen et al., includes 75 patients, only six (8%) experienced severe toxicities, and no patients died during the first three months.

The rates of IRE's complications detected in different studies (Table 2) go from 8% to 100% [46, 47], while the percentage of severe complications [48] goes from 0% to 45% [38, 46, 49-55]. The variability in the reported complication rates across studies may be due to the heterogeneity in tumor size, in median of 2.8-4.5 cm, location and treatment protocols [56]. Further studies about its potentialities may increase general awareness about this technique, inducing more interventional radiologists to learn and start practicing this procedure more and more.

Radiological response to IRE

Imaging evaluation in tumor response after ablation has an essential role to define the treatment success, the assessment of procedure-related complications, and for the evaluation of the remaining vital tumor. Radiological findings are associated to the type of treatment, the time of response assessment and to the type of imaging technique [69]. Histological findings after IRE demonstrated a necrotic treated area encapsulated in fibrous tissue, with signs of apoptosis and reduced vital signs [69]. Nowadays MRI and CT are the most used diagnostic tools to assess response to IRE [70]. CT is the standard imaging modality in the follow-up for PC and has an accuracy of 93.5 % for the detection of local recurrence [71, 72]. Several studies evaluated the feasibility of contrast-enhanced MRI (CEMRI) for the characterization of solid pancreatic diseases [73] and the assessment of quantitative parameters associated with tumor perfusion, vessel permeability, and extravascular space composition [73, 74]. CE-MRI with T1-weighted GE is particularly effective in discerning treated from untreated areas after ablation treatment, showing hyperintense enhanced areas versus hypointense unenhanced areas [74, 75]. Vroomen et al. [72] aimed to assess specific imaging characteristics after IRE treatment for LAPC and to quantify tumor and ablation-zone volumes with CECT and CEMRI. They reported that ablation zone volume increased on both modalities in the first 6 weeks, followed

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Table 1: Clinical studies reporting results of IRE in treatment of LAPC.

Authors	Date	LAPC n.	OS (months)	pfs/RFS (months)
Woeste [57]	2022	187	22.4	16.1
Rudno-Rudzin´Ska [58]	2021	9	45	-
Heger [59]	2021	14	28	7
He [60]	2021	64	26	12
Kwon [47[	2021	12	13.5	8.6
Ruarus [61]	2020	50	17	10
Veldhuisen [49]	2020	52	17.2	9.9
Hep [49]	2020	32	24	7.1
Holland [62]	2019	152	30.7	22.8
Flak [63]	2019	33	18	-
Mansson [64]	2019	24	13	-
Leen [65]	2018	75	27	15
Huang [66]	2018	70	22	15.4
Sugimoto [55]	2018	8	24	-
Scheffer [38]	2017	15	16	12
Vogel [52]	2017	25	17	-
Narayanan [37]	2016	50	27	-
Mansson [67]	2016	24	17.9	2.7
Lambert [53]	2016	21	10	-

Abbreviations –LAPC= Local Advanced Carcinoma Pancreas; R= recurrence; OS overall survival; PFS= progression-free survival; CT= chemotherapy; RT= radiotherapy; N: number of patients.

Table 2: Incidence and severity of complications reported in clinical studies of IRE treatment of LAPC.

Authors	**Date**	**Method of Delivery**	**All Complications (%)**	**Severe Complications (Clavien-Dindo ≥ III) (%)**	**Mortality (%)**
Heger [59]	2021	Percutaneous	71.4	14	0
Kwon [47]	2021	Percutaneous	100	25	8
Ruarus [61]	2020	Percutaneous	58	42	4
Veldhuisen [49]	2020	Percutaneous	37	0	0
He [46]	2020	Percutaneous	8	0	0
Holland [62]	2019	Percutaneous	18	13	2
Flak [63]	2019	Percutaneous	33	21	5
Mansson [64]	2019	Percutaneous	46	13	4
Leen [65]	2018	Percutaneous	25	8	0
Sugimoto [55]	2018	Percutaneous	75	45	0
Ierardi [50]	2018	Percutaneous	20	0	0
Zhang [68]	2017	Percutaneous	19	0	0
Scheffer [38]	2017	Percutaneous	48	-	0
Vogel [52]	2017	Percutaneous	53	-	0
Narayanan [37]	2016	Percutaneous	62	20	0
Mansson [67]	2016	Percutaneous	46	13	0
Lambert [53]	2016	Percutaneous	24	-	0
Belfiore [54]	2015	Percutaneous	10	0	0

Abbreviations –LAPC= Local Advanced Carcinoma Pancreas

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by a decrease in volume. Both CEMRI and CECT revealed absent or decreased contrast enhancement and a hyperintense rim surrounding the IRE ablation zone was found in 71% of the patients. Moreover, they found a DWI-b800 hyperintense spot at 6 weeks follow-up that predated recurrence on CT. However, when the treatment zone is small, susceptibility effects may obscure small areas of recurrence or create false positives, hence reducing the potential capability of DWI-b800 to interpret the ablated area. The most used criteria to assess a radiological response to treatments are response evaluation criteria in solid tumors (RECIST) and also the "CHOI criteria", both related to the change in tumor size and in tumor attenuation [71, 72, 74, 76]. In the evaluation of an IRE treatment, the ablation zone size, both in CECT and in CEMRI, is not a reliable indicator of the true extent of the treated area, despite having a good correlation with the histological ablation zone [77, 78]. The evidence of a reduction in viable cells may not always reflect a change in tumor size [72, 77]. Akinwande et al. performed a prospective review soft tissue ablation registry on patients who underwent IRE for LAPC. They concluded that the ablation zone appeared larger than the original target, without clearly demarcated margins, and the nearby vascular structures were narrowed. This aspect is related to the inclusion of the reactive post-procedural area, characterized by edema and hyperemia in the ablation zone [21, 79].

Edema, hyperemia, and granulation tissue decreased over time and facilitated the visualization of the true ablation zone. When the inflammatory process is resolved, postprocedural CT imaging reveals the true ablation zone size, reporting: smaller "true" ablation zone, compared to the treated area, an increased enhancement of the ablation zone (likely linked to the formation of granulation tissue and fibrosis) and that blood vessel caliber came back to normal or remained stable.

Currently, there is no consensus on the ideal post-treatment interval to measure the ablation zone. Histological studies showed that after IRE treatments, the target area becomes necrotic and encapsulated in fibrous tissue [69]. For this reason, is fundamental the use of imaging criteria, which take into account the viability and not only the size of the lesion to assess tumoral response attempting differentiation of fibrosis from residual tumor [69]. Moreover, a positive response in LAPC after IRE should be associated with a decreased metabolism, without a significant reduction in tumor size [74].

The evaluation of any reduction in metabolic activity is more predictive of tumor response than morphological criteria alone. PET criteria in solid tumors (PERCIST) evaluate both the morphological criteria and the fluorodeoxyglucose uptake reduction [80]. FDG PET can differentiate post-therapy changes from recurrence in PC, it is complementary to morphological imaging with CT; therefore, integrated PET/CT imaging provides optimal images for interpretation [81]. In patients that underwent prior or post- IRE radiation therapy, persistent isolated vessel narrowing must be followed with serial imaging, clinical evaluation, CA19-9 serum tumor markers, and, as above, for equivocal cases, PET/CT may play a role in differentiating postablative changes from recurrence [81, 82]. Actually, in addition to the radiological response, Vroomen et al [72] reported in their follow-up study analysis that local recurrence detected at CECT was accompanied by a significant increase in CA 19.9. It would be useful to correlate dimensional and metabolic changes of target lesions to biochemical data, such as tumoral markers, in order to properly assess the effective response to IRE treatment [77]. Response to IRE treatment is a multifactorial results of the anatomical localization of the mass, mechanism of action of given therapeutic strategy, morphological and functional criteria used for each imaging modality [83].

Immunotherapy and IRE

Pancreatic carcinoma tumoral microenvironment (TME) has a desmoplastic stroma with a crucial role in the foundation of a highly immunodepressant setting that potentially makes immunotherapeutic treatments less effective [84]. PC has a "cold" immune status, and its TME has a dense extracellular matrix that acts as a physical, rigid barrier resulting in elevated tumor pressure, with reduced vascularization and impaired diffusion of immunotherapeutic agents. Additionally, "cold" immune status is due to downregulation by tumor cells of antigen-presenting pathways as MHC-I, the upregulation of suppressive regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), and the restriction of dendritic cell (DC) maturation. All these factors increase apoptotic resistance of tumor cells. Moreover, Tregs of TME limit antitumor-T cells' effectiveness by over-expressing inhibitory receptors (e.g., CTLA-4) and expressing great quantities of PD-L1 and PD-L2, ligands to the inhibitory receptor PD-1 [85]. On the other hand, IRE's action triggers immune responses, with a direct effect on both innate and adaptive immunity. IRE-induced apoptosis is associated with a release of antigens that result in the secretion of potent proinflammatory cytokines, hence activating the immune system against tumor cells. IRE has a pivotal role because can switch the prior PC "cold" immune status to "hot", favoring a pro-inflammatory and antitumorigenic microenvironment [86]. Several different immunotherapeutic strategies have been tried along with IRE to enhance the activity of the immune system against PC.

He et al evaluated 85 patients divided into IRE group (70) and IRE + Toripalimab group (15). The IRE plus Toripalimab group showed longer OS (44.33 months versus 23.37 months) and PFS (27.5 months versus 10.6 months) compared with IRE group. Authors concluded that the combined therapy might improve the OS of patients with LAPC (Table 1) [87]. Lin et al. investigated the safety and clinical efficacy in III/IV

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PC treated with IRE and allogeneic natural killer (NK) cell immunotherapy, evaluating PFS and OS, authors concluded that combination therapy increased median PFS and median OS in stage III PC and extended the median OS of stage IV PC [88]. IRE was also evaluated in combination with DC transfer (DC vaccine) [89]. Promising results have been observed, with only common side effects like fatigue and/or flu-like symptoms, and the median OS was 7.7 months (Table 1) [90]. The combination of IRE + DC vaccine may cause immunogenic cell death and relieve of immunosuppressive components in PC microenvironment: this combination therapy exerted a synergistic effect, enhancing the activity of the immune system.

Another relevant pathway in PC is TGF-β, which has a contrasting role as both tumor suppressor and promoter [91]. Expression of TGF-β type II receptor correlates with reduced survival in patients with PC. Using glutathione-responsive degradable mesoporous silica nanoparticles loaded with SB525334, an inhibitor of TGF-β receptor, Peng et al. demonstrated that local inhibition of TGF-β within the tumor microenvironment promotes neutrophil addressing to an antitumor phenotype, enhances PC response to combined IRE and PD1 therapy, and induces long-term antitumor memory [91]. Nowadays the study of tumor immunophenotype has an important role and may offer opportunities to prolong the immune response following IRE [92]. O'Neill et al using mass cytometry studied the differences in lymphocyte populations in patients who underwent IRE and in patients who did not. They showed that patients without evidence of recurrence had a robust early immune response to IRE with the establishment of significantly higher levels of CD4 and CD8 central memory populations as well as enhanced early NK response [92].

A 2020 clinical trial investigated the antitumor efficacy of IRE plus allogeneic γδ T cells enrolling 62 LAPC patients, the OS in patients with combination therapy was higher than in the other group (Table 3) [93]. These trials with encouraging results are related to a small minority of patients with selected biomarkers, but the majority of trials with promising preclinical data have failed. Immunotherapy and targeted therapy did not yield practice-changing results in PC, probably because pancreatic ductal adenocarcinoma (PDAC) TME and pancreatic carcinoma tumor immune microenvironment are peculiar compared to most tumors, as is the genomic landscape that accompanies this disease. More research efforts are crucial to better select patients that could benefit from immunotherapy and to develop efficient TME modification mechanisms that could make the tumor more immunosensitive [94].

A 2022 review by Ullman et al. [95], summarizes the mechanisms of immunosuppression within the PDAC tumor microenvironment and provides an up-to-date review of completed and ongoing clinical trials using various immunotherapy strategies. While the COMBAT trial offered promising results [96], other studies evaluating CXCR4 inhibition have resulted in poorer treatment responses. [97]. Despite the conduction of several interesting preclinical studies, the translation into clinical practice has proved to be challenging, due to the existence of a complex TME that protects the tumor against a cytotoxic immune response. The intricate pathways of immune evasion will likely require a combination approach to improve efficacy. In conclusion, the alterations of the tumor environment from IRE offer plenty of hope for IRE + immunotherapy, but most studies have not demonstrated a convincing response yet. There is no definite treatment pathway to date the treatment superior to the others, but the combination of IRE with anti-PD-L1 is more studied and employed than the other regimens, albeit in need of further studies. Fortunately, many ongoing clinical trials are evaluating combination immunotherapies, which at the minimum, will be able to shed light on mechanisms of immune evasion to educate future trials [95].

Table 3: Clinical studies comparing OS, PFS, or QoL after IRE combined with different immunotherapic strategies in LAPC.

Authors	Ref.	Date	n.	Diagnosis	Treatment	OS (month)	PFS(month)
He	[57]	2021	85	LAPC	70 IRE	33.37	10.6
					15 IRE + TOR	44.33	27.5
Lin	[70]	2020	62	LAPC	32 IRE	11	
					30 IRE + γδT	14.5	
Lin	[58]	2017	67	35 STAGE III	16 IRE	12.2	7.9
					19 IRE + NK	13.6	9.1
				32 STAGE IV	14 IRE	9.1	
					18 IRE + NK	10.2	
Mehrota	[59]	2017	12	LAPC	DCs	7.7	

Abbreviations – OS: overall survival; PFS: progression free survival; QoL: Quality of Life; IRE: Irreversible electroporation; LAPC: locally advanced pancreatic cancer patients.

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Conclusion

The encouraging results reported by these studies suggest that IRE, especially when used in combination with pre-operative chemotherapy, could increase OS and PFS values in a LAPC setting.

Moreover, its potential use in combination with chemotherapy and immunotherapy is a field of great interest, but despite its potential promise, much about IRE remains unknown, and more prospective randomized controlled trials are necessary.

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All authors declare that they have no conflict of interest and that they have nothing to disclose.

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