International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
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ARTICLE TITLE	EFFECTS OF IRREVERSIBLE ELECTROPORATION ON THE TUMOR MICROENVIRONMENT IN PANCREATIC DUCTAL ADENOCARCINOMA: A NARRATIVE REVIEW
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5783
RECEIVED	19 February 2026
ACCEPTED	21 May 2026
PUBLISHED	25 May 2026
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EFFECTS OF IRREVERSIBLE ELECTROPORATION ON THE TUMOR MICROENVIRONMENT IN PANCREATIC DUCTAL ADENOCARCINOMA: A NARRATIVE REVIEW

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, largely due to late diagnosis, aggressive tumor biology, and marked resistance to conventional treatment and immunotherapy. A major contributor to therapeutic failure is the highly immunosuppressive and desmoplastic tumor microenvironment (TME), which limits drug delivery, restricts cytotoxic immune-cell infiltration, and promotes immune evasion.

This narrative literature review evaluates the effects of irreversible electroporation (IRE) on the PDAC microenvironment and assesses its potential role as an immune-sensitizing strategy capable of enhancing antitumor immunity and improving responsiveness to immunotherapy.

English-language review articles, preclinical and clinical studies published between 2011 and 2025, were investigated, with a particular focus on evidence from 2020 to 2025. The reviewed literature suggests that IRE can induce immunogenic cell death by releasing danger-associated molecular patterns, enhance antigen presentation, remodel the fibrotic stroma, reduce hypoxia, and promote infiltration of cytotoxic T lymphocytes. Several studies also report reductions in immunosuppressive cell populations and improved responses to immune checkpoint blockade following IRE.

Overall, IRE appears to be a promising local treatment modality with systemic immunomodulatory potential in PDAC. However, most evidence remains preclinical, and further prospective clinical studies are required to define its long-term efficacy, safety profile, optimal technical parameters, and best integration with systemic immunotherapy.

KEYWORDS

Irreversible Electroporation, Pancreatic Ductal Adenocarcinoma, Tumor Microenvironement

CITATION

Anna Skrzypek, Hanna Maruchniak, Wiktoria Marzec, Paulina Biedroń, Maciej Hutkowski, Mikołaj Zbrożek, Zuzanna Chwostek, Bartłomiej Kosiarski, Patrycja Markowicz, Krzysztof Biłyk. (2026) Effects of Irreversible Electroporation on the Tumor Microenvironment in Pancreatic Ductal Adenocarcinoma: A Narrative Review. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5783

Introduction

Pancreatic cancer remains one of the deadliest malignancies in oncology and is responsible for almost 5% of cancer-related deaths worldwide [1]. Despite recent therapeutic advances, the 5-year survival rate remains low, at approximately 13% [2]. Incidence rates continue to rise and are expected to increase further over the coming decades [3]. This trend may partly reflect the growing prevalence of established risk factors, including smoking, obesity, and diabetes, particularly in high-income countries. At the same time, the persistently high mortality associated with pancreatic cancer is largely attributable to its oligosymptomatic early stage, lack of sufficiently sensitive and specific biomarkers, aggressive tumor biology, and resistance to conventional therapies at the time of late-stage diagnosis [4].

Complete surgical resection remains the only potentially curative treatment; however, it is available to only 10–15% of patients whose tumors are localized at diagnosis [5]. Most patients, therefore, require systemic therapy, either in combination with surgery or as palliative treatment for unresectable or metastatic disease [4]. Current systemic approaches include adjuvant and neoadjuvant chemotherapy, with FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) remaining one of the principal frontline regimens [6]. However, despite the success of similar multimodal strategies in other malignancies, the prognosis of pancreatic ductal adenocarcinoma remains poor, emphasizing the urgent need for novel therapeutic approaches.

Although immunotherapy has transformed the treatment landscape of several cancers, its effects in PDAC remain unsatisfactory. This limited efficacy is largely attributed to the highly desmoplastic and immunosuppressive tumor microenvironment, which restricts immune-cell infiltration, impairs antigen presentation, and promotes immune evasion [7,8]. Irreversible electroporation (IRE), a non-thermal ablative technology, has gained attention not only as a local treatment option for anatomically complex pancreatic tumors, but also as a potential modulator of the tumor microenvironment. This review, therefore, aims to explore the immunomodulatory effects of IRE on the PDAC microenvironment, with particular focus on immunogenic cell death, stromal remodeling, macrophage polarization, antigen presentation, cytotoxic T-cell infiltration, and immune checkpoint regulation. It also evaluates the translational rationale for combining IRE with immunotherapy.

Methodology

A literature review was conducted using the PubMed and Google Scholar databases. The search focused on English-language articles published between 2011 and 2025, with particular emphasis on studies from 2020 to 2025 investigating the effects of IRE on the microenvironment of pancreatic ductal adenocarcinoma.

The search terms included: "PDAC", "pancreatic ductal adenocarcinoma", "pancreatic cancer", "irreversible electroporation", "IRE", "immunogenic cell death", "danger-associated molecular patterns", "DAMPs", "tumor microenvironment", "immunotherapy", "immune checkpoint blockade", "macrophage polarization", and "desmoplasia". Preclinical and clinical studies were considered eligible when they addressed the biological, stromal, vascular, or immunological consequences of IRE in PDAC.

Studies without available full text, articles not published in English, and studies with limited relevance to the immunological or stromal effects of IRE were excluded. Because this was a narrative rather than a systematic review, the aim was not to provide a quantitative synthesis but to integrate mechanistic and translational evidence on the potential role of IRE as an immune-sensitizing intervention in PDAC.

Tumor Microenvironment and Immunotherapy Resistance in PDAC

The resistance of PDAC to immunotherapeutic strategies is largely attributed to its highly desmoplastic and immunosuppressive tumor microenvironment (TME). This fibrotic stromal network is characterized by a heterogeneous cellular infiltrate composed predominantly of cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), immune cells, and extracellular matrix (ECM) components [9–12]. Activated CAFs and PSCs synthesize large quantities of ECM proteins, including collagen, fibronectin, laminin, and hyaluronic acid, forming a dense mechanical barrier around malignant cells [9,10]. Progressive ECM deposition and collagen cross-linking increase interstitial pressure and compress intra-tumoral vasculature, leading to hypoperfusion, impaired drug delivery, and reduced infiltration of cytotoxic immune cells [9–11].

Beyond their structural role, CAFs and PSCs actively promote immune suppression by secreting cytokines, chemokines, and growth factors, including transforming growth factor-β (TGF-β), interleukin-6 (IL-6), CXCL12, colony-stimulating factor 1 (CSF-1), and vascular endothelial growth factor (VEGF) [10–12]. These mediators promote extracellular matrix remodeling, angiogenesis, and recruitment of immunosuppressive immune populations. Concurrently, the resulting tumor vasculature remains structurally abnormal and functionally inefficient, further exacerbating intra-tumoral hypoxia [10].

Hypoxia is increasingly recognized as a central driver of immune resistance in PDAC. Reduced oxygen diffusion stabilizes hypoxia-inducible transcription factors (HIFs), which promote tumor proliferation, metabolic adaptation, epithelial-mesenchymal transition, and angiogenic signaling [10,11]. In parallel, hypoxic conditions favor the accumulation of immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarized tumor-associated macrophages (TAMs) [10–12]. Among these, M2 TAMs play a particularly important role in sustaining tumor progression by secreting IL-10 and TGF-β, promoting fibrosis, and suppressing cytotoxic CD8+ T-cell activity [10,12].

Immune evasion in PDAC is further reinforced through immune checkpoint signaling within the TME. Both TAMs and tumor cells express programmed death-ligand 1 (PD-L1) and other checkpoint-associated ligands that contribute to functional exhaustion of CD8+ cytotoxic T lymphocytes [10,12]. Moreover, cytokine-driven polarization of CD4+ T cells toward Th2, Th17, and regulatory phenotypes further perpetuates the immunosuppressive milieu [10].

Given the profound stromal and immunological barriers characteristic of PDAC, increasing attention has been directed toward therapeutic strategies that modulate the tumor microenvironment and enhance anti-tumor immune responses. One emerging approach involves combining systemic treatment with irreversible electroporation (IRE), a non-thermal ablative modality increasingly recognized for its potential immunomodulatory effects [11–14].

Biomechanisms of Irreversible Electroporation

Irreversible electroporation (IRE) is a non-thermal ablative technique that induces tumor-cell death by applying high-voltage electrical pulses without extreme temperatures [13,14]. During the procedure, electrodes positioned within or around the tumor generate short electrical pulses of sufficient amplitude and duration to disrupt cellular membrane integrity. Exposure to an electric field can raise the transmembrane potential above its critical threshold, leading to a permanent rearrangement of the phospholipid bilayer and the formation of nanoscale membrane pores [13]. Loss of membrane homeostasis subsequently permits uncontrolled ionic flux, osmotic dysregulation, and ultimately irreversible cellular injury leading to apoptosis and secondary necrosis.

A major advantage of IRE is its relative preservation of surrounding connective tissue structures, including blood vessels, bile ducts, and nerves [11,13]. Because cell death is primarily induced by membrane permeabilization rather than thermal coagulation, extracellular collagen architecture and vascular integrity remain comparatively preserved. This characteristic makes IRE particularly suitable for tumors located adjacent to major vascular or biliary structures, where conventional thermal ablation techniques may carry substantial procedural risk.

In contrast, conventional thermal ablation modalities such as radiofrequency ablation (RFA) and microwave ablation (MWA) induce tumor destruction through tissue heating and coagulative necrosis [15,16]. Exposure of tissues to cytotoxic temperatures exceeding approximately 50 °C results in protein denaturation, microvascular thrombosis, membrane disruption, and irreversible cellular injury [15]. However, thermal diffusion into surrounding tissues may additionally produce collateral damage to adjacent anatomical structures, thereby limiting the safety and efficacy of these techniques in anatomically complex regions.

Another important limitation of thermal ablation is the heat-sink effect [15–18]. This phenomenon refers to the dissipation of thermal energy by blood flow within adjacent vessels, particularly those greater than 3 mm in diameter. Continuous blood flow acts as a thermal reservoir, reducing local tissue temperatures near vascular structures and preventing uniform heat distribution within the target lesion [16–18]. Consequently, incomplete ablation may occur in perivascular tumor regions, increasing the risk of residual disease and local recurrence [15,17].

Because IRE relies on electrical rather than thermal energy, its efficacy is not significantly limited by vascular heat dissipation [11,13]. More homogeneous ablation may therefore be achieved even in lesions located adjacent to major blood vessels. In addition to its procedural advantages, increasing evidence suggests that IRE may exert broader biological effects on the tumor microenvironment, including modulation of stromal architecture, enhancement of antigen presentation, and activation of antitumor immune responses [11,14].

Immunomodulatory Effects of IRE

DAMP-Mediated Immunogenic Cell Death

One of the principal mechanisms underlying the immunomodulatory effects of irreversible electroporation (IRE) is the induction of immunogenic cell death (ICD). Following electroporation-induced cellular injury, intracellular molecules that are normally concealed from the immune system are released into the tumor microenvironment and function as danger-associated molecular patterns (DAMPs) [15–17]. Several studies have demonstrated increased extracellular release of high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), calreticulin (CRT), and heat-shock proteins following IRE treatment [15–17]. Together, these mediators activate innate immune signaling pathways and promote initiation of adaptive antitumor immune responses [15,16].

Among these DAMPs, HMGB1 appears to play a central role in post-IRE inflammatory signaling. Following release from damaged tumor cells, HMGB1 interacts with pattern-recognition receptors, including the receptor for advanced glycation end-products (RAGE) and Toll-like receptors (TLR2 and TLR4), thereby activating downstream MAPK and NF-κB signaling cascades [15,18]. He et al. demonstrated that this post-IRE activation of the HMGB1-RAGE-p38 MAPK axis promoted macrophage polarization toward the pro-inflammatory M1 phenotype. This shift is associated with increased production of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12), as well as enhanced antigen presentation and cytotoxic immune activation [18].

Extracellular ATP released after electroporation-induced membrane disruption also exerts important immunological effects. ATP functions as a potent “find me” signal released during tissue injury. It recruits dendritic cells and other antigen-presenting cells by activating purinergic receptors, particularly P2X7 receptors. Subsequent activation of the NLRP3 inflammasome promotes the secretion of interleukin-1β (IL-1β) and amplifies local inflammatory signaling [15,16]. In parallel, ATP-mediated pathways facilitate dendritic-cell maturation and enhance cross-presentation of tumor-associated antigens to cytotoxic T lymphocytes [15,17].

Surface exposure of calreticulin represents another possible hallmark of IRE-induced immunogenic cell death. Following electroporation-induced cellular stress, calreticulin translocates from the endoplasmic reticulum to the tumor cell membrane, where it functions as an “eat me” signal, promoting phagocytosis by dendritic cells and macrophages. This process enhances tumor-antigen uptake and supports subsequent activation of adaptive immune responses [15,19].

Heat-shock proteins released during IRE-induced cellular stress further contribute to antitumor immunity. These proteins can function as endogenous chaperones for tumor-associated antigens and facilitate their uptake by antigen-presenting cells through interaction with scavenger receptors and major histocompatibility complex (MHC)-associated pathways [15,16]. Such mechanisms ultimately contribute to improved antigen processing and activation of tumor-specific T lymphocytes [15,17].

Compared with thermal ablation modalities, IRE may therefore offer an immunological advantage by simultaneously inducing DAMP release and preserving tumor-associated antigenicity [15,19]. Thermal techniques frequently induce protein coagulation and denaturation, thereby limiting effective antigen presentation [15,16]. In contrast, non-thermal electroporation maintains conditions favorable for antigen recognition and immune priming, supporting its proposed role as in-situ tumor vaccination [15].

Stromal and Vascular Remodeling of the Tumor Microenvironment

In addition to its direct cytotoxic effects, irreversible electroporation (IRE) appears capable of modifying stromal and vascular components of the tumor microenvironment [11,15]. Unlike thermal ablation modalities, IRE largely preserves the extracellular collagen scaffold while selectively disrupting tumor-cell membranes [11,15]. This selective tissue preservation may have important implications for immune-cell trafficking, local perfusion, and responsiveness to systemic therapies.

Several studies suggest that IRE can partially alleviate stromal-mediated immunosuppression. Zhao et al. demonstrated that IRE reduced stromal resistance while preserving tumor-restraining collagen architecture in murine PDAC models [20]. Treatment was associated with increased infiltration of CD8+ cytotoxic T lymphocytes without marked accumulation of suppressive immune populations [20]. These findings suggest that selective stromal remodeling may improve immune access to tumor tissue while maintaining the structural integrity of the surrounding microenvironment.

The stromal compartment additionally functions as an active source of immunosuppressive cytokines and signaling pathways. Cancer-associated fibroblasts, extracellular matrix proteins, and tumor-associated macrophages collectively impair dendritic cell maturation and suppress cytotoxic lymphocyte activity by secreting TGF-β, IL-6, CXCL12, and other mediators [9–12]. By partially disrupting these stromal interactions, IRE may facilitate development of a more immunologically permissive tumor microenvironment [11,20].

IRE may also improve local vascular permeability and tissue perfusion [11,21]. Improved perfusion could enhance penetration of systemic therapies and facilitate trafficking of immune effector cells into previously inaccessible tumor regions. This is particularly relevant in PDAC, where vascular compression and poor perfusion are major barriers to drug delivery and immune-cell infiltration [10,11].

Hypoxia represents another important contributor to immune suppression and tumor progression in PDAC [10–12]. Dense stromal architecture and vascular compression impair oxygen diffusion and stabilize hypoxia-inducible transcription factors, promoting angiogenesis, metabolic adaptation, and immune evasion [10]. By reducing stromal compression and altering local vascular dynamics, IRE may possibly help alleviate hypoxia-mediated immune resistance [11,20].

Overall, IRE appears to exert multidimensional effects on the tumor microenvironment. Its non-thermal mechanism enables selective tumor-cell ablation simultaneously preserving surrounding stromal and vascular architecture. This may facilitate immune cell trafficking, tissue perfusion, and the delivery of systemic therapies [11,13,15].

Immune Effector Activation and Immune Memory Responses

Increasing evidence suggests that irreversible electroporation (IRE) may promote activation of adaptive antitumor immunity and generation of immune memory responses [17,20]. Several preclinical studies have demonstrated enhanced infiltration of CD8+ cytotoxic T cells following IRE treatment [17,20].

He et al. observed increased intra-tumoral CD8+ T-cell populations in both orthotopic and subcutaneous PDAC models, accompanied by suppression of tumor growth and delayed progression of untreated lesions [17]. These findings suggest that IRE may generate not only local, but also systemic antitumor immune effects.

This adaptive immune activation appears closely linked to dendritic cell function. Through increased release of tumor-associated antigens and DAMPs following electroporation-induced cell death, antigen-presenting cells become more effective at priming tumor-specific T lymphocytes [15,17]. Supporting this, Zhao et al. demonstrated enhanced dendritic cell activation and reduced stromal-mediated immune resistance following IRE treatment [20]. These findings therefore suggest that IRE may facilitate more effective communication between innate and adaptive immune pathways within the tumor microenvironment [15,17,20].

Beyond immediate cytotoxic immune activation, increasing attention has been directed toward the potential role of IRE in immune-memory formation. He et al. demonstrated increased populations of memory

T cells following IRE together with evidence suggestive of an abscopal effect in PDAC models [17]. Because recurrence rates in conventionally treated patients remain high even after apparently successful local therapy, the possibility that IRE may contribute to long-term tumor-specific immune surveillance is of considerable translational interest [14,17].

Recent studies additionally highlight the role of CD4+ T-cell responses following IRE. Wu et al. demonstrated that IRE promoted the differentiation of CD4+ T cells into interferon-γ-producing Th1 and Th17 phenotypes by activating type-2 conventional dendritic cells (cDC2s). These effects were associated with increased antigen presentation and amplification of antitumor immune signaling pathways. Importantly, immune activation was further enhanced when IRE was combined with PD-L1 blockade, suggesting that electroporation may improve responsiveness to checkpoint inhibition even in tumors characterized by deficient MHC-I expression [22].

Collectively, current evidence supports the concept of IRE as a potential immune-sensitizing intervention rather than solely a local ablative technique. By enhancing antigen presentation, promoting cytotoxic lymphocyte infiltration, and facilitating adaptive immune activation, IRE may improve responsiveness to systemic immunotherapy in PDAC [11,17,20]. Nevertheless, most currently available evidence derives from murine models while prospective clinical studies evaluating long-term survival outcomes and durable immune responses remain limited [11,17]. In addition, the optimal sequencing of IRE and immunotherapy, ideal electroporation parameters, and patient-selection criteria have yet to be clearly established [11].

Current Clinical Evidence for IRE in PDAC

Clinical evidence supporting irreversible electroporation (IRE) in pancreatic ductal adenocarcinoma remains most developed in locally advanced pancreatic cancer (LAPC), where the technique has primarily been evaluated as an adjunct to systemic therapy rather than as a stand-alone intervention. In a prospective multi-institutional assessment from the AHPBA pancreatic registry involving 152 patients with LAPC treated with IRE following induction therapy, morbidity and mortality rates were 18% and 2%, respectively, while severe adverse events occurred in 13% of patients. Median time to progression, progression-free survival, and overall survival from diagnosis were 27.3, 22.8, and 30.7 months, respectively, suggesting that IRE may be feasible and associated with encouraging survival outcomes in carefully selected patients undergoing multimodal treatment [24].

Additional prospective data from Japan similarly supported the practicality and safety of both open and percutaneous approaches in LAPC. Sugimoto et al. reported a median overall survival of 24 months from diagnosis with no 90-day mortality, although several major complications were observed, emphasizing the importance of procedural expertise and careful patient selection [25].

More recent real-world evidence from the DIRECT registry further supports the procedural applicability of IRE after induction chemotherapy. In this multicenter observational study, patients with stage III PDAC treated with IRE plus standard of care had 90-day mortality rates similar to those receiving standard therapy alone. Initial findings suggested that incorporation of IRE into multimodal management may not substantially increase early treatment-related morbidity or mortality when performed in experienced centers [26].

Clinical studies combining IRE with immunotherapy provide particularly relevant translational support for the proposed immune-sensitizing role of electroporation. In a phase 1b trial evaluating concurrent nivolumab and IRE in locally advanced pancreatic adenocarcinoma, no dose-limiting toxicities were observed, and nivolumab-related adverse events occurred in only one patient. Importantly, the preclinical component of the same study demonstrated increased PD-L1 expression following IRE, supporting the biological rationale for combining electroporation with immune checkpoint blockade [27].

Retrospective studies similarly suggest that IRE-based combination strategies may improve outcomes when paired with immune-directed therapies. Ma et al. demonstrated that IRE combined with chemotherapy and PD-1/PD-L1 blockade was associated with prolonged overall survival and progression-free survival compared with IRE plus chemotherapy alone, while maintaining comparable rates of treatment-related adverse events [28]. More recently, a propensity score-matched retrospective analysis reported significantly improved survival outcomes in LAPC patients treated with IRE combined with anti-PD-1 immunotherapy compared with IRE alone, without increased treatment-related mortality or major complications [29].

Other immune-oriented approaches have also been explored. Pan et al. reported that IRE combined with natural killer cell therapy enhanced lymphocyte activity and reduced CA19-9 levels in patients with locally advanced pancreatic cancer, although no significant improvement in overall survival was observed [30].

Overall, currently available clinical evidence suggests that IRE is technically feasible and may provide clinically meaningful benefit in selected LAPC patients, particularly when integrated with systemic chemotherapy and immunotherapy. However, most existing studies remain retrospective, single-arm, or early-phase investigations. Therefore, prospective randomized trials with standardized IRE protocols, comprehensive immune monitoring, and long-term survival analyses remain necessary before IRE-based immunomodulatory strategies can be incorporated into routine clinical practice.

Discussion and Future Directions

The current literature suggests that IRE may exert clinically relevant effects beyond local tumor ablation by reshaping several components of the PDAC tumor microenvironment. Mechanistically, IRE appears capable of inducing immunogenic cell death, promoting DAMP release, enhancing antigen presentation, increasing cytotoxic T-cell infiltration, and reducing selected immunosuppressive features of the tumor milieu [15–20]. These effects provide a plausible biological rationale for combining IRE with systemic immunotherapy, particularly immune checkpoint blockade, in a malignancy that is otherwise highly resistant to immunotherapeutic approaches [7,8,11].

However, translating these findings into routine clinical practice remains limited by several important challenges. First, much of the strongest mechanistic evidence derives from preclinical models. Although murine PDAC models are valuable for studying immune activation, macrophage polarization, and T-cell infiltration, they do not fully reproduce the anatomical, stromal, vascular, and immunological complexity of human PDAC [17,18,20]. Human pancreatic tumors are larger, more heterogeneous, and frequently located near major vascular, biliary, and gastrointestinal structures. These anatomical constraints may influence ablation geometry, procedural safety, immune activation, and treatment reproducibility.

Second, IRE protocols remain heterogeneous across studies. Parameters such as electrode number and spacing, pulse amplitude, pulse duration, pulse number, treatment approach, and perioperative systemic therapy vary considerably between preclinical and clinical investigations [24–26]. This variation complicates direct comparison between studies and limits the ability to define optimal technical parameters. Future research should therefore prioritize protocol standardization, ideally supported by real-time imaging, treatment-planning software, and computational modeling of electric-field distribution.

Third, the timing of immunotherapy relative to IRE remains insufficiently defined. The post-IRE inflammatory response may create a transient therapeutic window characterized by DAMP release, enhanced antigen presentation, improved immune-cell trafficking, and increased checkpoint ligand expression [15,17,27]. This period may represent an optimal opportunity for immune checkpoint blockade or other systemic therapies. However, the duration, peak intensity, and interpatient variability of this window remain unclear. Prospective studies incorporating serial immune profiling, cytokine analysis, circulating tumor DNA assessment, and tumor biopsies could help identify the most effective sequencing strategies.

Fourth, although early clinical studies are encouraging, the current evidence base remains insufficient to establish a definitive survival benefit. Registry studies and retrospective analyses suggest that IRE may be feasible and may improve outcomes in selected LAPC patients, particularly when combined with chemotherapy or immunotherapy [24,26,28,29]. Nevertheless, these studies are vulnerable to selection bias, institutional variability, differences in systemic therapy, and inconsistent follow-up. Randomized controlled trials comparing standard systemic therapy with and without IRE are therefore essential.

Future trials should also include comprehensive immune monitoring as a predefined endpoint. In addition to conventional outcomes such as overall survival, progression-free survival, local control, and adverse events, studies should also evaluate CD8+ T-cell infiltration, Treg and MDSC populations, macrophage polarization, dendritic cell activation, PD-L1 expression, cytokine profiles, and markers of immune memory [17,18,20,22,27]. Such analyses would clarify whether the immunological effects observed in preclinical studies are reproducible in human PDAC and whether they correlate with clinical outcomes.

Patient selection will also be critical. IRE is unlikely to benefit all patients with PDAC equally. The greatest potential may lie in carefully selected patients with LAPC who have stable disease after induction chemotherapy, limited metastatic risk, favorable performance status, and tumors anatomically suitable for safe ablation [24–26]. Biomarkers capable of predicting response to IRE or IRE-immunotherapy combinations would therefore represent an important step toward personalized treatment.

Overall, future research should move beyond demonstrating feasibility and focus on defining which patients benefit, which technical parameters are optimal, when immunotherapy should be administered, and which biomarkers best predict durable response. If these questions can be answered through prospective and standardized clinical studies, IRE may become an important component of multimodal treatment strategies aimed at converting immunologically resistant PDAC into a more therapeutically responsive disease.

Conclusions

Irreversible electroporation represents a promising local treatment modality with potential systemic immunomodulatory effects in pancreatic ductal adenocarcinoma. Current evidence suggests that IRE may remodel the PDAC tumor microenvironment by inducing immunogenic cell death, enhancing antigen presentation, remodeling the stroma, and increasing infiltration of cytotoxic immune cells [15–20]. Collectively, these effects may partially overcome the immunosuppressive phenotype characteristic of PDAC and provide a biological rationale for combining IRE with immune checkpoint blockade or other systemic immunotherapies [11,20,22,27–29].

Clinical data indicate that IRE is feasible in selected patients with locally advanced pancreatic cancer and may be associated with encouraging survival outcomes when integrated into multimodal treatment strategies [24–26]. Early-phase and retrospective studies further suggest that combining IRE with immunotherapy may improve antitumor immune activation and survival outcomes without clearly increasing severe treatment-related toxicity [27–29]. However, these findings remain preliminary and must be interpreted cautiously, as much of the evidence is derived from preclinical models, registry studies, retrospective analyses, and small clinical cohorts.

Therefore, while IRE appears to be a promising immune-sensitizing strategy in PDAC, it cannot yet be considered an established standard of care for immunomodulation. Further prospective randomized trials are required to define its long-term efficacy, safety profile, optimal technical parameters, ideal sequencing with systemic therapies, and most appropriate patient-selection criteria.

With rigorous clinical validation, IRE may become an important component of multimodal strategies to improve immune responsiveness in one of the most treatment-resistant malignancies in oncology.

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive special funding.

Conflict of Interest Statement: The authors declare no conflict of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process: In preparing this work, the authors used ChatGPT by OpenAI to improve language, readability, and text formatting. Following the use of this tool, the authors thoroughly reviewed and edited the content as necessary and accept full responsibility for the final version and all substantive content of the publication.

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