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REVIEW ARTICLE

A REVIEW OF TUMOUR ABLATION APPLICATORS AND THEIR ROLE IN IRREVERSIBLE ELECTROPORATION THERAPY

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Abstract: Electroporation is a phenomenon involving the formation of pores in cell membranes under the influence of short high-voltage electric pulses. Depending on the pulse parameters, it can be either reversible or irreversible. Reversible electroporation (RE) is widely used in biology and medicine, including in electrochemotherapy (ECT) and gene electrotransfer (GET). In contrast, irreversible electroporation (IRE) is an innovative, non-thermal method of tumour ablation, based on the permanent disruption of cell membranes leading to cell death – primarily through programmed apoptosis rather than necrosis. IRE is distinct from conventional ablation techniques that rely on energy sources such as radiofrequency, microwaves, laser light, or cryoablation, as it does not utilize thermal effects. This facilitates the precise removal of cancerous lesions located in proximity to temperature-sensitive structures, such as blood vessels, bile ducts, or nerves. The effectiveness of IRE therapy is contingent the design and configuration of applicators, which are responsible for delivering electric pulses to the tissue. The objective of this study is to provide a comprehensive review the current technological solutions employed in applicators designed for IRE, with particular emphasis on the construction of these applicators, types of electrodes used, spatial arrangements, material properties, and other operational parameters. The paper sets out to present and compare the available types of applicators used both clinically and experimentally, highlighting their impact on the effectiveness of ablation procedures. Special attention is given to understanding the biological and physical foundations of the electroporation phenomenon as the basis of this groundbreaking cancer treatment method.

Keywords: Tumor Ablation, Irreversible Electroporation, IRE, Electrode Design, Ablation Applicators, Electroporation Therapy

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INTRODUCTION

Electroporation, as a method of creation of pores in cell membranes using short, high-voltage pulses, has been known since the mid-20th century [1]. The medical application of electroporation began in 1982 with the pioneering work of Neumann and colleagues, who utilised pulsed electric fields to temporarily permeabilise cell membranes, thereby enabling the delivery of foreign DNA into cells [42].

Reversible electroporation (RE) is a process occurring under the influence of high voltage electric pulses with specific parameters, leading to the formation of pores in the cell membrane with diameters of approximately 1–10 nm, which reseal within a few minutes. The increase in membrane permeability, pore formation, and induced biological effects are contingent on parameters such as pulse amplitude, number, and duration. RE has been used to introduce water soluble molecules into cells (electrochemotherapy). Furthermore, it enabled the delivery of DNA into cells (gene electrotransfer), as well as transdermal drug delivery [13].

Ablation is a medical method that involves the deliberate destruction of tissue to achieve a therapeutic effect. Its use extends to oncology, as well as in cardiology, ophthalmology, otolaryngology, gynaecology, and gastroenterology [1,2, 6, 44,70, 72].

Thermal ablation in oncology is a well-established and widely used method for treating tumours of the liver, kidneys, lungs, and other organs when a patient is unwilling or unable to undergo surgery [67]. Planned thermal tissue destruction primarily involves the utilisation of microwave and radiofrequency energy, laser light, localised freezing (cryoablation) and high intensity focused ultrasound (HIFU) [15]. Radiofrequency ablation (RFA) is currently the most commonly used technique. It has shown to have a high level of reliability in the treatment of hepatocellular carcinomas (HCCs) up to 5 cm in size, liver metastases up to 3 cm, and some extrahepatic tumours, including those that develop in the lungs, kidneys and bones [55]. Microwave ablation (MWA), a more recently introduced thermal ablation technique, operates at a higher frequency than RFA. However, the distribution of microwave energy is more difficult to control, which may result in unintended damage to surrounding tissues [55]. Argon-based cryoablation is primarily used to destroy tumours in the kidneys, lungs, and bones [4]. Laser ablation (LA) is primarily employed in the treatment of hepatocellular tumours, however, its clinical acceptance is relatively limited due to the technical complexity of the procedure [45]. The effectiveness of thermal ablation ranges from 80% to 90%, however, depending on the location of the tumour, there is a risk of thermal injury to surrounding tissues and organs that are not the target of the procedure.

Irreversible electroporation (IRE) is defined as the process in which a strong electric stimulus is applied to a cell, resulting in the loss of homeostatic balance and subsequent cell, which can occur within a time frame ranging from a few minutes to several hours. As indicated by reports from the late 1990s, this process not only has the potential to result in necrosis but also the initiation of apoptosis, which is a form of programmed cell death. This constituted the initial indication that electroporation could be useful as a non-thermal ablation technique [13]. IRE was initially applied for non-thermal bacterial inactivation, such as in water and food sterilization [56]. Numerous subsequent and ongoing studies have explored its applications in oncology (e.g., non-thermal ablation of tumours in the liver, kidneys, lungs, skin, brain), cardiology (e.g., treatment of arrhythmias, particularly atrial fibrillation), as well as in dermatology, otolaryngology, gynaecology, gastroenterology, and ophthalmology. IRE operates by applying controlled, high-voltage electric fields (typically 500–3000 V/cm) to tumour tissues, thereby inducing the formation of nanopores in the cell membranes. If the pulses are sufficiently strong, the resultant damage is irreversible, triggering apoptosis without inducing thermal effects. In contrast to RFA and MWA, IRE has been shown to preserve the extracellular matrix, blood vessels, connective tissue, and nerves. This preservation helps prevent complications such as bleeding, infection, or loss of organ function, making IRE particularly valuable for tumours located near critical anatomical structures [62,63]. A key factor influencing the effectiveness of IRE therapy is the applicator used to deliver the electrical pulses [3]. The design, geometry, and materials of these applicators affect the electric field distribution, which directly determines the extent and precision of ablation [9]. High conductivity materials such as stainless steel and titanium ensure efficient energy transfer, while flexible materials like nitinol enable adaptable electrode shapes. Furthermore, innovative coatings including nanoparticle-based and polymeric layers are being explored to improve biocompatibility and reduce tissue adhesion [7,17,27,40].

This review aims to provide a comprehensive overview of applicators used in IRE therapy, focusing on their construction, material composition, and technological development. It is imperative to comprehend these factors in order to optimise the precision, safety, and effectiveness of tumour ablation procedures using IRE.

IRREVERSIBLE ELECTROPORATION IN TUMOR ABLATION

Irreversible electroporation (IRE) is a minimally invasive, non-thermal technique that is increasingly utilised in tumour ablation, particularly in cases where the lesion is in close proximity to critical structures. While IRE preserves extracellular matrix and vascular integrity, clinical implementation is encumbered by several challenges, including treating large or irregular tumours, procedure complexity and high equipment costs. A comprehensive understanding of both its advantages and limitations is imperative for the optimisation of its therapeutic applications [69].

The advantages of IRE include its ability to target tissues with high precision, minimize collateral thermal damage and allow rapid post-procedural recovery. These features render it particularly suitable for tumours in anatomically challenging locations where conventional thermal ablation techniques (e.g., radiofrequency or microwave ablation) carry elevated risks [33]. It is imperative to consider the limitations and challenges inherent in this process. IRE is generally less effective for large or irregularly shaped tumours, as achieving complete coverage may require multiple electrode placements [76]. The procedure necessitates meticulous pre-procedural planning and imaging guidance to ensure optimal electric field distribution. Furthermore, IRE equipment is costly, and the procedures are typically performed under general anaesthesia. Potential complications include transient pain, muscle contractions, and, when applied near the heart, arrhythmias [28]. Understanding both the benefits and limitations of IRE is crucial for selecting appropriate clinical scenarios and maximising therapeutic outcomes.

Liver Cancer

Liver cancer is the sixth most prevalent form of cancer on a global scale, with 749,000 new diagnoses annually. It is the third leading cause of cancer-related deaths, responsible for 692,000 fatalities, comprising approximately 7% of all cancer cases [58]. IRE has been shown to offer a promising solution for liver tumours, in particular those located in close proximity of vital anatomical structures such as blood vessels or bile ducts, where the efficiency of traditional thermal techniques is limited. A meta-analysis of 6 studies involving 807 patients and 1115 tumour lesions reported a complete ablation rate of 86% (95% CI: 81%–90%) [73]. Complication rates were deemed to be acceptable, with the majority being mild; complications occurred in 23% of patients (95% CI: 17%–28%), and severe events, such as biliary or intestinal fistulas, were rare [73].

Pancreatic Cancer

Pancreatic cancer is the seventh most common cause of cancer-related deaths on a global scale, accounting for 432,242 fatalities in 2018. Its incidence is rising, and survival rates have shown little improvement [29]. Findings of clinical studies indicate that IRE is an effective treatment for patients with locally advanced pancreatic cancer (LAPC). A meta-analysis of three studies involving 3,862 patients showed significantly improved overall survival (HR = 0.46; 95% CI: 0.28–0.74) and progression-free survival (HR = 0.38; 95% CI: 0.24–0.60) for those treated with IRE versus standard therapies [66]. Combination therapies are garnering increased attention. A retrospective study demonstrated increased survival rates in LAPC patients treated with IRE, chemotherapy, and PD-1/PD-L1 inhibitors, compared to those receiving IRE and chemotherapy only [28]. Animal models have revealed increased infiltration of CD8+ lymphocytes and macrophages post-IRE, suggesting synergy with immune oncological treatments [31]. IRE represents a valuable therapeutic option for LAPC, especially when used with chemotherapy and immunotherapy. Further studies are needed to clarify long-term outcomes and risks.

Prostate Cancer

According to the World Health Organization (WHO), prostate cancer was the third most commonly diagnosed cancer in 2020. The incidence of the condition varies is subject to significant regional variations, ranging from 6.3 to 83.4 cases per 100,000 individuals [57]. An analysis of 471 IRE procedures across various stages of prostate cancer with over six years of follow-up revealed a 90% recurrence-free survival rate. Urinary continence was preserved in all patients, with only 3% experiencing severe erectile dysfunction after 12 months [19].

A systematic review of 14 studies involving 899 patients found tumour recurrence rates within the ablation zone ranged from 0% to 38.9%, and outside the zone from 3.6% to 28%. At 12

months post treatment, urinary continence was restored to baseline in 58% of patients, with slight deterioration in 25% of patients. Erectile function improved from a baseline of 44%–75% to 55%–100%, demonstrating functional benefits [53].

IRE offers a favourable balance between oncologic control and preservation of urinary and sexual function, making it suitable for localized prostate cancer. However, further research in the form of randomised trials is necessary in order to compare the outcomes of the treatment to radical prostatectomy and radiation therapy [32].

Kidney Cancer

Kidney cancer is the thirteenth most prevalent form of cancer in terms of global incidence, accounting for 2.4% of cases with over 330,000 diagnoses annually [59]. The exploration of IRE as a treatment small renal masses (SRMs) is an area of increasing interest, particularly in cases where conventional methods, such as partial nephrectomy or thermal ablation, are contraindicated. Despite the fact that IRE boasts certain advantages, including minimal invasiveness, preservation of surrounding structures and better renal function retention, the available oncological data remain limited. The outcomes reported, such as local recurrence-free survival (LRFS) and overall survival (OS), are generally comparable or slightly inferior to standard thermal techniques (e.g., RFA, cryoablation) [21]. The majority of studies consist of small cohorts, for instance, a systematic review of 10 studies including 83 patients reported transient haematuria (11 patients) and asymptomatic perirenal hematomas (7 patients) as the most common adverse events, with no 30-day mortality and 62 of 63 patients discharged within 24 hours. Imaging follow-up of 55 patients indicated a complete response in 78% [21]. Given the limited sample sizes and short follow-up periods documented in the majority of reports, IRE is currently recommended only for highly selected cases, including patients with tumours adjacent to critical structures, those deemed unfit for surgery or when thermal ablation is contraindicated. In order to achieve a more precise definition of the role of IRE in renal cancer treatment, it is necessary to conduct larger, prospective, and preferably randomised studies.

In all the tumour locations discussed, the choice of ablation technique is determined by the patient's clinical condition and current therapeutic standards. In the treatment of liver and kidney cancers, the prevailing methods remain RFA, MWA, and cryoablation, which have been shown to yield high rates of local tumour control, particularly for lesions measuring <3–4 cm. In pancreatic cancer, thermal techniques have limited applicability due to temperature associated risks, whereas in prostate cancer HIFU and cryoablation are gaining popularity within focal therapy. Against this background, IRE stands out for its capacity to effectively treat tumours located in close proximity of structures susceptible to temperature-induced injury, such vessels, bile ducts and nerves. In the majority of comparisons,

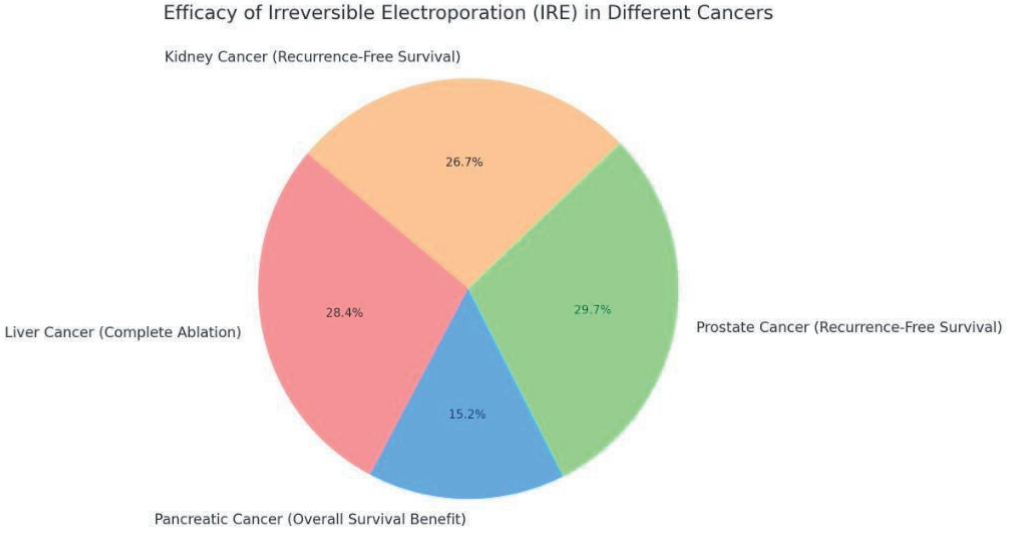

Fig. 1. Effectiveness of Irreversible Electroporation (IRE) in the treatment of cancers in different locations. The data are derived from clinical studies on liver, pancreatic, prostate, and kidney cancers. The values represent complete ablation rates, overall survival, and recurrence-free survival from selected studies.

IRE has demonstrated efficacy comparable to that of thermal methods, however, its safety profile is clearly more favourable in anatomically challenging locations where thermal damage is a concern. For this reason, IRE serves as a complementary rather than competing modality to thermal ablation and is primarily selected when conventional thermal techniques are contraindicated.

TYPES OF APPLICATORS USED IN IRREVERSIBLE ELECTROPORATION

The choice of applicator is of fundamental importance in achieving uniform electric field distribution during IRE, which is essential for effective tumour ablation while sparing healthy tissues. Various applicators have been developed to address different anatomical locations and tumour sizes (Figure 2).

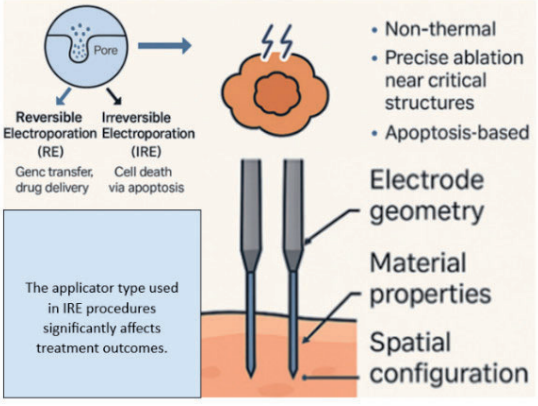

Fig. 2. Mechanism of Electroporation and Factors Affecting IRE Efficacy. The diagram illustrates the difference between reversible (RE) and irreversible electroporation (IRE), highlighting IRE's main advantages: non-thermal action, precise ablation near critical structures, and apoptosis induction. Key factors influencing IRE effectiveness include electrode geometry, material properties, and spatial configuration of the applicator.

Table 1. summarizes the main types of IRE applicators, with an emphasis on their design, materials, and functional advantages. Needle electrodes are the most commonly used due to their versatility, allowing precise tumour insertion under imaging guidance and effective membrane disruption. In comparison, plate electrodes are better suited for superficial or flat organ tumours, providing a uniform electric field across the target area. Multi-electrode arrays facilitate the treatment of large or irregularly shaped tumours, with flexible arrangements ensuring consistent energy distribution and optional temperature monitoring for safety. Finally, flexible or nitinol based electrodes offer enhanced manoeuvrability in difficult-to-access regions, with shape-memory properties that maintain electrode integrity while adapting to anatomical constraints. Building on these established applicator types, ongoing innovations in materials, electrode configurations, and integration with imaging technologies are further expanding the reach, precision, and safety of IRE. The subsequent section presents a comprehensive literature review examining how different applicator types influence the efficacy of IRE in treating tumours located in anatomically challenging regions, aiming to identify best practices and guide the development of next generation applicator technologies.

Among the applicator types discussed, needle based electrodes (including the multi-needle NanoKnife system) represent the only solution that is fully established in clinical routine. Conversely, plate electrodes, flexible nitinol-based applicators, and the majority of multi-electrode array concepts are used predominantly in preclinical studies or early clinical feasibility trials. The significance of these distinctions lies in their ability to facilitate comprehension of the technologies that have demonstrated clinical efficiency and those that remain in a state of experimental development.

Tab. 1. Types of IRE applicators and their characteristics.

Type of Applicator	Description	Materials	Key Features / Advantages
Needle Electrodes [16,59]	Most common IRE devices; straight or slightly curved needles inserted directly into tumour tissue.	Stainless steel, titanium	Percutaneous or laparoscopic insertion; imaging-guided; high voltage pulses induce irreversible membrane disruption; advanced designs include multi-faceted or expandable tips; real time imaging integration; improved spatial control.
Plate Electrodes [61]	Two flat plates placed on either side of the tumour. Ideal for superficial or flat-organ tumours.	Titanium, stainless steel	Creates homogeneous electric field; even energy distribution; can be used externally or internally for deeper tumours.
Multi-Electrode Arrays [38]	Multiple electrodes arranged in grids or custom configurations for large or irregular tumours.	Flexible, biocompatible (e.g., titanium)	Ensures consistent electric field distribution; used in open or laparoscopic surgery; some include temperature sensors to prevent thermal injury.
Flexible / Nitinol Based Electrodes [73]	Electrodes with enhanced flexibility for difficult to access regions.	Nitinol (nickel-titanium alloy)	Shape memory properties allow bending and returning to original shape; improves manoeuvrability while maintaining integrity.

MATERIAL AND METHODS

A comprehensive review of the scientific literature available in the PubMed database was conducted to identify publications that substantiate the clinical applications and significance of irreversible electroporation (IRE) technology in oncology therapy. The objective of this review was to collect substantial scientific evidence pertaining to the efficacy and safety of IRE in cancer treatment. In order to gain a deeper technical understanding of the design and operational principles of applicators used in IRE procedures, the scope of the search was expanded to encompass a variety of online sources, including manufacturers' websites, technical publications, user reports and patent descriptions. This multifaceted approach enabled a more comprehensive overview of current technological solutions.

PubMed Database Search

In order to identify relevant scientific publications focusing on applicators used in tumour ablation via irreversible electroporation (IRE), the following search query was applied in the PubMed database:

(((“Applicators for Tumour Ablation”) AND (“Tumour Ablation”)) AND (“Irreversible Electroporation”)) OR (“IRE ablation”)

As at 27 February 2025, this query yielded 630 publications. The application of filters served to restrict the results to studies published within the last decade and which were available in full-text format free of charge, narrowing the results to 361 articles. These articles were then screened specifically for discussions about applicators used in IRE technology. The inclusion criteria were:

- Explicit focus on IRE applicators with detailed information on their design and use.
- Provision of technical aspects relating to how applicators contribute to the effectiveness and safety of tumour ablation.
- Oncology related applications involving IRE technology.

Exclusion criteria included:

- Studies on IRE use outside oncology (e.g., non-tumour treatments).

Following a rigorous screening process, 11 publications were selected for detailed analysis, having met all the specified criteria. These studies provided valuable insights into the materials used in IRE applicators and their impact on procedure effectiveness and safety in oncology. Table 2. summarizes experimental, preclinical, and clinical studies investigating the use of IRE in the treatment of various cancer types. The reviewed studies utilised a variety of electrode configurations and parameters, most commonly the NanoKnife system, to ablate tumours in organs such as the liver, pancreas, prostate, and kidneys. IRE demonstrated particular advantages in the treatment of tumours located in close proximity of blood vessels and other critical anatomical structures, offering precise ablation with reduced thermal damage compared to conventional techniques, such as RFA. However, it has been reported that the procedure is both time-consuming and costly. A number of studies explored novel electrode materials and nanotechnology-based enhancements (e.g., folate conjugated nanocrystals, magnetoelectric nanoparticles), highlighting the potential of IRE as a safe, selective and minimally invasive cancer treatment that warrants further large-scale clinical validation.

The majority of the studies included in this review evaluate applicators already implemented in clinical practice, particularly commercially available needle electrodes, such as the NanoKnife system. A smaller subset of publications concerns novel electrode geometries or material innovations, which are currently limited to preclinical or early phase clinical evaluation. It should be noted that while systems such as NanoKnife represent fully clinically established platforms, several of the investigated electrode types (e.g., nanoparticle enhanced electrodes, bipolar novel designs, or functionalized nanocrystal-assisted systems) remain experimental and have yet to be adopted in routine clinical settings.

Analysis of Publication and Citation Trends in the Web of Science Core Collection

A supplementary search was performed in the Web of Science Core Collection using the term “irreversible electroporation”. Surprisingly, this search yielded only a single record, which was a non-research, industry focused report from Clarivate describing medical technologies predicted to impact clinical care in 2024 [10]. It was determined that this record did not constitute primary scientific literature and did not include data relevant to IRE applicator design, it was excluded from further analysis. This finding underscores a limitation of WoS indexing in relation to this subject area, given that a significant number of seminal IRE studies are indexed in PubMed but are absent from the WoS Core Collection.

Tab. 2. Summary of Studies on Irreversible Electroporation (IRE) Applications in Cancer Therapy.

Article	Technology Used	Applicator	Area of Application	Technical Parameters	Applicator Materials	Results/Relevance for IRE
Liu, B. [36]	IRE vs. RFA	NanoKnife	Liver cancers	Electric field: 1500 V/cm; Pulse length: 90 µs; Pulses per cycle: 70; Active electrode length: 1 cm	NA	IRE showed high efficacy in ablation of tumours located in close proximity of vessels, with fewer complications compared to RFA, but the procedure was more time-consuming and expensive.
Hsiao, CY. [23]	IRE	NanoKnife	Pancreatic cancer	Voltage: 1500–3000 V/cm; Pulse duration: 70–90 µs; Number of pulses: 90; Needle tip length: 0.5–4 cm; Electrode spacing: 1.3–2.5 cm	19G needles with echogenic tips	Review highlights theoretical advantages of IRE for pancreatic tumours, particularly in close proximity of critical structures, but lacks large scale clinical validation
Spiliopoulos, S.[64]	IRE	NanoKnife, IRE Gold	Pancreatic cancer (stage II/III)	Voltage: 1400-3000 V/cm; 90 pulses per cycle (70-90 µs); Target current: 20-50 A; Electrode distance: 7–24 mm	NA	Potentially precise ablation; promising for tumours in close proximity of vessels; requires further validation
George, AK. [18]	IRE	NanoKnife	Prostate cancer	Voltage: 1500–3000 V; Pulse duration: 100–150 µs; 90–150 pulses; Pulse frequency: 1–3 Hz; Range: 3–5 cm	NA	Preliminary data suggest feasibility and safety; oncological outcomes pending
Ong, S. [44]	IRE	Monopolar 19G needle electrodes	Prostate cancer	90 pulses; Pulse length: 70 µs; Current: 20–40 A; Electric field: 1200–1800 V/cm	NA	Narrative review highlights IRE as promising for low and intermediate risk prostate cancer; further clinical validation needed
Wang, Z.[68]	IRE	NanoKnife	Renal cell carcinoma	Active electrode length: 1–2 cm; 3–4 electrodes; 70–90 pulses; Pulse duration: 70–90 µs; Voltage: 2200–3000 V	NA	Safe and effective for RCC, preserves healthy tissue
Lim, B. [35]	IRE (preclinical beagle model)	Bipolar electrode (platinum center, stainless steel tips)	Prostate cancer	Voltage: 500–700 V; Current: 1.75–2.22 A; Min. electric field: 800 V/cm	Platinum, stainless steel	Effective and safe bipolar electrode for prostate IRE with lower voltage and fewer complications in preclinical model
Jeon, SM. [27]	IRE	Needle electrode, 21G diameter	Liver and pancreas cancer	Voltage: 1.5 kV/cm; Pulse duration: 100 µs; 60 pulses	Stainless steel coated with polydopamine nanoparticles	Polydopamine nanoparticle coated electrodes enhance thermal effects and improve ablation efficacy in liver and pancreatic cancers.
Colacino, KR. [11]	IRE + CNC-FA	Folate conjugated cellulose nanocrystals	Cancer cells	Electric field: 500–600 V/cm; Incubation 10–20 min	CNC-FA	Folate conjugated cellulose nanocrystals (CNC-FA) enhance selectivity and cytotoxic efficacy of IRE in folate receptor positive cancer cells
Bryant, JM. [5]	IRE + MENP	Magnetoelectric nanoparticles	Pancreatic adenocarcinoma	External magnetic field: 2 kOe for 30 min during MRI	CoFe2O4 core, BaTiO3 shell	Non-invasive selective cancer destruction using nanotechnology and magnetic field; promising for precise pancreatic cancer treatment
Scheffer, HJ.[61]	IRE	NanoKnife needle electrodes	Liver tumours	Pulse: 1500 V/cm, 90 µs; Total 100 pulses; Overlapping ablations for larger tumours	Needle shaped, 20 mm active tip	Effective ablation demonstrated in colorectal liver metastases in a single arm phase II clinical trial (COLDFIRE-2), showing promise for treating larger liver tumours with overlapping pulses

Supplementary Analysis of Online Sources: Technical and Practical Overview of IRE Applicators (2020–2025)

To complement the systematic review of scientific literature (PubMed), an extended search targeting technical and practical publications on IRE applicator designs was conducted (Table 3). These sources provide detailed engineering insights not always covered in clinical studies. The studies reviewed in Table 3. present a wide range of electrode designs and technologies used in electroporation procedures, all aimed at improving electric field uniformity, safety, ablation efficiency and minimizing tissue damage. Complex multi-electrode systems, such as MPPE and BP4T/BP8T, facilitate the generation of multidirectional electric fields enhanced better control over the treated volume. Operating at voltages of up to 3000 V, these devices allow effective treatment of larger tumour areas while limiting thermal effects. Electrodes with controlled tissue contact, including the wet balloon-based wIRE and magnetically

Tab. 3. Summary of Electrode Designs and Pulse Generation Systems Used for Irreversible Electroporation (IRE).

Article	Applicator Name	Type & Features	Material	Electrode Specs	Pulse Generator & Parameters	Notes
López, A. [37]	MPPE (Multi--Electrode Pulsed Electroporation)	Multi-electrode array allowing multidirectional fields; square & round electrodes; cells 0.5–1.5 cm (opt. 0.75 cm)	Stainless steel & composites	Electrode spacing: 8 mm	Multi-channel pulse generator; up to 800 V, 100 µs pulses, 100 ms intervals	Improved uniformity & effectiveness; less invasive; treats larger areas
Sheehan, MC. [62]	wIRE (Wet Electrode IRE)	Electrode on balloon catheter; saline column for energy delivery; non-contact ablation	Medical grade stainless steel	2.5 mm diameter, 10 mm length; balloon 5F	Not specified	Inserted via gastroscope or guidewire; reduces tissue damage risk
Hogenes, AM. [22]	Monopolar electrode (AngioDynamics)	19G monopolar needle with advanced insulation for current control	Stainless steel	Active needle length 1.5 cm; inter electrode distance 1.5 cm	BTX Gemini X2 (Harvard Apparatus)	Enhanced current predictability; reduced hot spot risk
Zhao, Y. [75]	BP4T & BP8T electrodes	Bipolar electrodes with tines producing large, spherical ablation zones with low thermal damage	Metal + insulation	Inter electrode distances: 5, 10 mm	Amplitude 1500–3000 V; number of pulses 60 or 300	More energy-efficient, suitable for larger tumours
Ren, F. [54]	MAE (Magnetically Anchored Electrode)	Disc shaped electrodes anchored magnetically inside stomach on flexible gastric tube	Stainless steel, $Nd_2Fe_{14}B$ magnets, photopolymer insulation	Disc electrodes: 8 mm diameter, 0.03 mm thick; magnets 3.0 mm & 9.8 mm high	BTX ECM 830; 500 V, 100 µs, 99 pulses, 1 Hz	Stable anchoring without pressure; improved positional stability
Izzo, F. [26]	Expandable needle electrodes	5-needle (20° angle) and 4-needle designs; polymer insulated stainless steel needles; adjustable depth	Stainless steel + polymer	Needle diameter <0.7 mm; penetration adjustable	Cliniporator Vitae; 80–120 pulses; 100 µs; 5 kHz	Selective deployment for volume control; laparoscopic and endoscopic applications
Pelaez, F. [51]	Metal mesh electrode	Disk shaped mesh electrodes integrated with porous biomaterial scaffold; PCL coating for biocompatibility	304 stainless steel + PCL coating	Mesh aperture ~0.35 mm, wire diameter 0.16 mm	BTX ECM 830; 1500–2000 V/cm	Uniform electric field in scaffold; designed for DTC capture
Lee, GW. [34]	Nanopore Needle Electrode (nEP)	3D needle with nanopore membrane (100 nm pores) enabling controlled molecule delivery and electroporation	Platinum plating on titanium	2.7 mm between electrodes; lateral membrane opening	BTX ECM 830; bulk EP: 200 V, 20 ms ×4; nEP: 40 V, 2 ms ×99	Precise molecular delivery with minimal tissue damage

anchored MAE systems, offer stable and minimally invasive positioning, reducing the risk of mechanical injury and proving particularly useful in endoscopic or anatomically challenging sites. Monopolar and needle-based designs, such as those manufactured by AngioDynamics and Izzo, offer precise control of penetration depth and current distribution, thereby minimising the occurrence of electrical “hot spots” and are particularly well suited for laparoscopic or percutaneous interventions. The integration of electroporation functionality with biocompatibility and molecular delivery capabilities is achieved through the use of advanced materials and microstructured electrodes, including metal mesh systems coated with PCL and nanoporous needle electrodes (nEP). These innovations enable uniform electric fields, controlled molecular transport, and reduced collateral damage, thus representing a significant step forward in the precision and versatility of electroporation-based therapies.

Among the technical solutions reviewed, only standard monopolar and multi-needle percutaneous electrodes have been approved and are currently widely used in clinical IRE procedures. Balloon-based wet electrodes (wIRE), magnetically anchored electrodes (MAE), expandable laparoscopic arrays and microstructured or nanoporous electrodes remain in the research or prototype stage, with applications limited to laboratory settings or early feasibility studies. As such, their clinical use will depend on future validation regarding safety, reliability and integration with existing IRE pulse generators.

Overview of Representative Patents Related to IRE Applicator Technology

To complement the scientific literature review, a targeted search of the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO), and the World Intellectual Property

Tab. 4. Representative patents related to IRE applicator technology.

Patent number	Year	Office	Title	Category	Relevance to IRE applicators
US 10,905,492 B2 [46]	2021	USPTO	Techniques for irreversible electroporation using a single-pole tine style internal device communicating with an external surface electrode	Multi-needle / expandable arrays; minimally invasive systems; feedback control	Describes deployable tine electrodes allowing adjustable spacing and larger ablation zones. Includes embodiments with impedance based feedback and versions suitable for minimally invasive access.
US 8,992,517 B2 [48]	2015	USPTO	Irreversible electroporation to treat aberrant cell masses	Multi-needle arrays; imaging-guided designs	Covers multi-needle electrode configurations optimized for soft tissue tumour ablation. Includes MRI and CT compatible needle arrangements.
US 9,867,652 B2 [49]	2018	USPTO	Irreversible electroporation using tissue vasculature to treat aberrant cell masses or create tissue scaffolds	Materials / coatings; field optimization	Describes electrode systems optimized for anatomical structures, including improved surface durability and conductivity enhancing treatments.
WO 2016164930 A1 [50]	2016	WIPO	System and method for irreversible electroporation with thermally controlled electrodes	Temperature controlled electrodes; materials engineering	Introduces thermal regulation sensors integrated into IRE electrodes to prevent overheating, along with improved material solutions to reduce carbonization.
US 6,567,694 B2 [47]	2003	USPTO	Needle electrodes for mediated delivery of drugs and genes	Imaging compatible electrodes; minimally invasive arrays	Early electroporation needle-array design featuring image visible, echogenic needle construction. Forms conceptual basis for modern image guided IRE applicators.

Organization (WIPO) databases was conducted to identify representative patents related to irreversible electroporation (IRE) applicators. Rather than providing an exhaustive patent landscape, the objective of this overview was to highlight major technological directions that have shaped the development of IRE delivery systems. Table 4 presents representative patents related to the development of irreversible electroporation (IRE) applicators. These patents illustrate major technological directions, including multi-needle and expandable electrode arrays, improved electrode materials, temperature controlled systems, imaging guided designs and minimally invasive or endoscopic approaches. While not exhaustive, this selection demonstrates key engineering innovations that have shaped modern IRE delivery systems.

Whilst the objective of the present review was not to perform a formal patent analysis, this brief overview demonstrates the range of technological innovations that have contributed to the evolution of IRE applicators. The patent landscape confirms strong industrial activity directed at improving electrode geometry, material performance, imaging compatibility and safety monitoring all consistent with the major trends identified in the scientific literature.

DISCUSSION

As demonstrated in the reviewed literature and technical analyses, the design of the applicator is of pivotal importance to t the success of irreversible electroporation (IRE) therapy. IRE's distinctive mechanism involving the induction of irreversible nanopores in cell membranes to trigger apoptosis without thermal damage offers distinct advantages over conventional ablation methods, such as radiofrequency, microwave or cryoablation. However, achieving precise, reproducible and safe ablation depends critically on the characteristics of the electrodes and pulse delivery systems used.

Multi-electrode arrays, exemplified by MPPE and BP4T/BP8T systems, demonstrate that complex electrode geometries can generate multidirectional electric fields and enable uniform treatment of larger or irregularly shaped tumours. Their capacity to operate at high voltages, reaching up to 3000 V, enables effective ablation while minimising collateral thermal effects, which is particularly important in the vicinity of temperature-sensitive structures. In a similar manner, electrodes designed for controlled tissue contact, such as the wet balloon- based wIRE and magnetically anchored MAE, provide stable positioning and reduce mechanical tissue trauma. These innovations enhance the safety profile of IRE, particularly in endoscopic procedures or anatomically challenging sites.

Monopolar and needle-based applicators, including standard 19G needles and expandable designs, continue to be extensively utilised due to their versatility and adaptability to a variety of tumour sizes and locations. These designs offer precise control of electrode penetration depth and

current distribution, reducing the risk of "hot spots" and improving overall treatment homogeneity. Integration with imaging technologies, such as ultrasound, CT or MRI, further enhances placement accuracy and procedural safety.

Advancements in materials and microstructured electrodes, including metal mesh systems with PCL coatings and nanopore needle electrodes (nEP), indicate a trend aimed at combining electroporation functionality with biocompatibility and controlled molecular delivery. These designs enable precise targeting, minimize damage to surrounding tissues, and open avenues for synergistic approaches, such as drug delivery or immunomodulation. Furthermore, the use of flexible materials, such as nitinol, enables applicators to navigate complex anatomical pathways while preserving their structural integrity and functional capabilities.

Despite these technological advancements, several challenges remain. The clinical implementation of IRE necessitates meticulous consideration of tumour size, geometry and proximity to critical structures, as electric field distribution is highly dependent on electrode configuration and tissue conductivity. Moreover, high-voltage pulse generation, device cost and length of the procedure continue to represent practical limitations. Future research efforts should focus on optimising applicator design, standardising treatment protocols and conducting large scale clinical trials to validate long term outcomes and safety. The reviewed studies underscore that the evolution of electrode designs from simple needle electrodes to advanced multi-electrode arrays and nanopore systems has significantly enhanced the precision, safety, and versatility of IRE therapy. Continued innovation in materials, geometry and integration with imaging and molecular delivery techniques is likely to expand the clinical applicability of IRE, establishing it as a reliable and minimally invasive alternative for the treatment of tumours in anatomically sensitive locations.

Despite the evident benefits of IRE in the treatment of tumours in proximity of temperature-sensitive structures, it is imperative to recognise its limitations and the relative risks associated with conventional thermal techniques. Thermal ablation methods such as RFA, MWA, cryoablation and HIFU are associated with procedure related complications in 3–10% of cases, depending on the location and size of the tumour. The majority of these adverse events are minor or moderate in nature, including post-ablation syndrome, transient pain and self-limiting bleeding. Clinically significant or severe complications, including thermal injury to bile ducts, bowel perforation, or damage to adjacent neurovascular bundles, occur far less frequently typically in <1–2% of procedures. However, their impact can be substantial, occasionally requiring surgical or endoscopic intervention [12,24, 30].

Notwithstanding the risks associated with such events, thermal ablation techniques generally provide excellent oncological outcomes for tumours located at a safe distance from critical structures, often achieving complete ablation rates equal to or superior to those reported for IRE. In contrast, IRE has been shown to offer comparable oncological efficacy specifically in anatomically challenging sites, while markedly reducing the incidence of temperature-related injury. Thus, IRE does not necessarily demonstrate superiority thermal ablation in terms of tumour control. Rather, it shifts the risk-benefit balance in favour of safety when conventional methods would otherwise carry a non-negligible probability of severe complication. Consequently, IRE is best understood as a technique that enables treatment in clinical scenarios where thermal ablation is feasible only with an elevated risk of critical adverse events, rather than as a universal alternative to established thermal modalities.

CONCLUSION

Irreversible electroporation (IRE) is a promising non-thermal ablation technique that has been shown to preserve critical structures while effectively treating tumours in challenging anatomical locations. The design and configuration of applicators including multi-electrode arrays, needle and monopolar systems, and advanced microstructured electrodes directly influence treatment precision, safety and efficacy. Innovations in materials, electrode geometry and integration with imaging and molecular delivery technologies have significantly enhanced the versatility and clinical potential of IRE. Continued research and optimization of applicator designs, along with large scale clinical validation, are essential to fully actualise IRE's potential as a minimally invasive, precise and safe modality for cancer therapy.

AUTHORS' DECLARATION

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