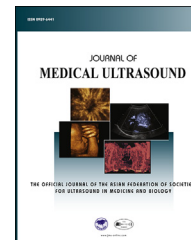


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REVIEW ARTICLE

Irreversible Electroporation: A Novel Ultrasound-guided Modality for Non- thermal Tumor Ablation



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Abstract Ultrasound-guided tumor ablation techniques have been proven to be highly effective and minimally invasive in the treatment of many diseases. Traditional approaches to ablation include microwave and radiofrequency techniques, cryotherapy, and high-intensity focused ultrasound. However, these methods are prone to heat-sink effects that can diminish the effectiveness of treatment and damage adjacent structures, such as bile ducts, blood vessels, the gallbladder, or bowel. Irreversible electroporation (IRE) is a non-thermal ablation modality that induces cell apoptosis through the application of high-voltage current. IRE is not limited by many of the limitation which affects conventional tumor ablation techniques, and is particularly useful in treating sensitive areas of the body. The article reviews the basics of ultrasound-guided technology, including its clinical applications and effectiveness in the treatment of tumors.

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Introduction

Basic rationale

Irreversible electroporation (IRE) is a novel, non-thermal tumor ablation modality [1,2] that delivers ultra-short high-voltage electrical impulses to a target area through fine antennae. The resultant strong external electric field causes electroporation (i.e. causes permeable nanoscale

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pores to form in the cell membrane) [3–6]. This phenomenon has previously been used in the laboratory to promote intracellular gene delivery. Electroporation can be reversible or irreversible, depending on the electric voltage and pulse length that are applied (Fig. 1) [7]. Lipid bilayer cell membranes are vital cellular structures which regulate intracellular and extracellular solute transport. When the intensity of the induced electric field (determined by the voltage and duration of the electric pulse) exceeds a particular threshold, the permeable pores on the cell membrane are opened permanently. This causes the membrane to lose its physiological function by preventing it from returning to a state of homeostasis, which in-turn leads to cell apoptosis and the clearing away of cell debris by the host immune system [2–4]. Potential damage to surrounding healthy tissue is minimized by preventing exposure to extreme cold or heat. Despite the recent advent of IRE, numerous clinical studies have already demonstrated its efficacy as an alternative approach to the treatment of tumors in sensitive areas of the body [8].

Ablation systems and devices

The NanoKnife® IRE System (AngioDynamics, Latham, NY) is an IRE-based ablation system in wide clinical use [9]. As shown in Fig. 2, this system includes a generator and multiple monopolar antennas. IRE ablation should be administered under continuous vital sign monitoring and, to ensure that excitation of the motor neural end-plate does not induce muscle spasms during electroporation, patients should be held in a supine position under general anesthesia and total muscle paralysis [10,11]. Prior to electroporation, imaging guidance techniques (e.g. ultrasound or computed tomography) are used to help position between two to and six antennas, which are placed within the target area by via aseptic manipulation (Fig. 3).

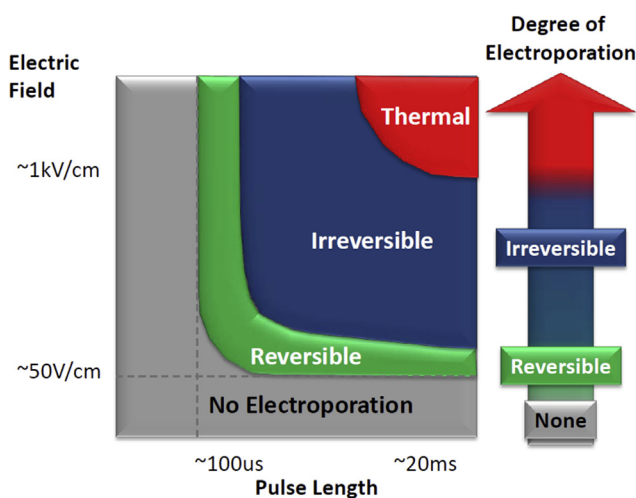


Figure 1 The reversibility of electroporation depends on the intensity of the electric field and the pulse length. Higher voltages and longer pulses cause irreversible electroporation; however, the excessive delivery of electric current can result in local heating rather than electroporation.



Figure 2 The IRE generator includes an electric power supply, a computer, and 6 output ports that are connected to antennae for the delivery of electric current.

Of imaging guidance techniques, ultrasound is particularly effective at providing a clear field in which structures surrounding the tumor can be identified. The percutaneous approach to IRE is minimally invasive and is commonly used in liver tumor ablation; however, this approach is not well suited to sites which are located deeper in the abdomen, such as the pancreas, due to a degraded ultrasound window. In these cases, the laparoscopic approach is generally preferable; however laparoscopy may also be technically feasible in highly-selected patients. Nonetheless, intra-operative ultrasound guidance is still necessary when IRE is performed using a surgical approach.

The location and size of ablation zone could be estimated by the generator after inputting the information including antenna number, electric power and antenna location (Fig. 4).

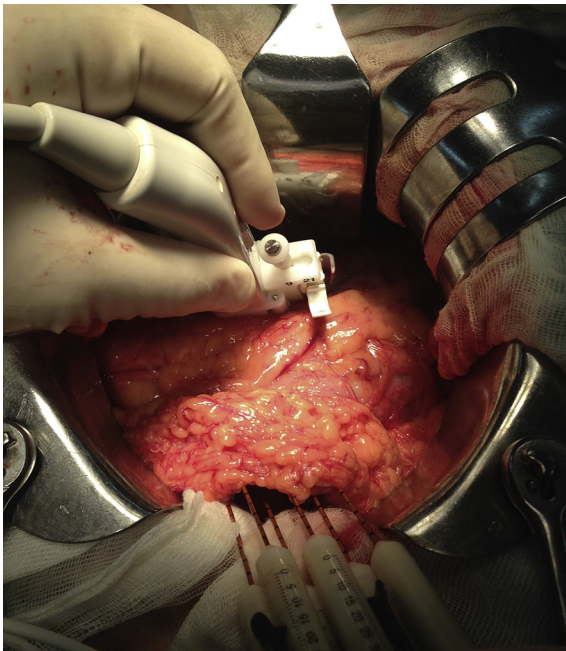


Figure 3 Under ultrasound-guidance, between 2 and 6 antenna are placed in parallel pairs within the target ablation area under laparotomic guidance. Pancreatic tumors and the course of ablation can be monitored using ultrasound.

The antenna used for IRE is a 19 gauge needle with an active tip and that can be adjusted to the length between 0.5 and 4 cm. The tip includes an echogenic marker, which allows the antenna to be visible under ultrasound examination (Fig. 5). Following antenna placement, ten test

pulses are delivered to the target area, and the tissue response to IRE is observed. If the tissue response is satisfactory without abrupt elevation of delivered electric current, then another 80 IRE ablation pulses are administered. Conversely, if the response of the tissue is not satisfactory, the voltage, antenna tip length, and/or distance between antennas can be adjusted in order to improve the delivery of energy (optimal energy delivery is approximately 25–35 amps). During the IRE treatment, cardiac synchronizer is very important, the risk of cardiac arrhythmia can be minimized by administering pulses within the refractory phase of the heartbeat, under the guidance of a cardiac synchronizer [12]. Typically, 90 pulses (with a voltage of 1500–3000 V/cm) are administered between each pair of antennas, and the pulse length is set at 70–90 μ s [13]. The number of pairs depends on the number of antenna being used. The time required for ablation varies according to the type of tissue that is being treated and the number of antennas that are being used. Throughout the entire procedure, body temperature, urine output, blood pressure, oxygen saturation, end-tidal CO₂, and EKG should be closely monitored [10,13]. Continuous ultrasound monitoring of the ablation site is also useful to detect the formation of microbubbles and vessel patency. To enable the complete ablation of tumors which exceed the length of the active tips, operators can pull the antennae back. Following IRE treatment, the antennas can be removed directly, and track bleeding is self-limited via local compression.

The success of treatment can be evaluated according to the elevation of delivered amperage response to decreased local resistance in the ablation zone. Ivorra and Rubinsky were the first to propose that a reduction in local resistance

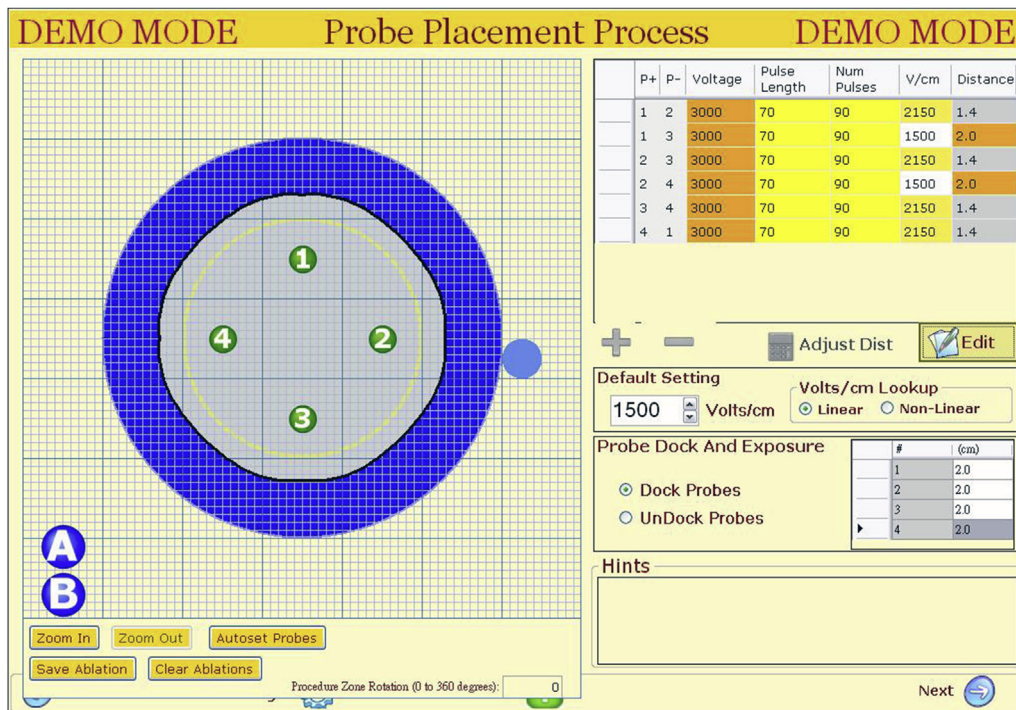


Figure 4 Software can be used to simulate the location and size of the ablation area that will surround the tumor, parameters which are determined according to the number and relative locations of antennas. Conversely, the distance between antennas and the strength of the pulses (voltage) are determined by the size and shape of the ablation zone, as estimated using software.

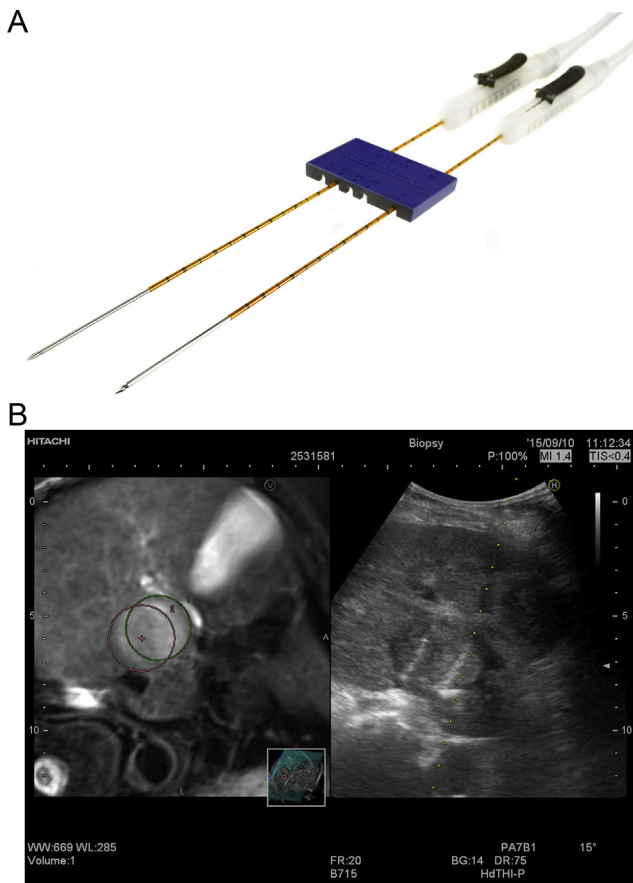


Figure 5 (A) The 19 gauge unipolar antenna is between 15 – 25 cm in length, and the tip is coated with an echogenic material. Electric current is delivered from parallel antennas and forms an electric field around the tip of the antenna, resulting in ablation within the area. (B) Under ultrasound guidance, the antenna is visible and the distance between antennas could be measured to estimate the ablation size.

is indicative of successful IRE [14], wherein the increase in electrical conductivity can be attributed to the leakage of ions into the extracellular matrix through perforations in the membrane.

After the IRE procedure is completed, patients are monitored in the recovery room while the effects of general anesthesia wear off and are then sent back to the general ward. The length of hospital stay varies according to approach type and the site of treatment. Regular monitoring of complete blood cell count, muscle enzymes, and liver and renal function is recommended for several days after the procedure. In most cases, patients can be discharged within one week, and post-operative antibiotics are not required.

Clinical efficacy

The safety of IRE in treating tumors adjacent to the kidney, pancreas, prostate, and liver has been demonstrated in both animal models and human subjects. Systemic adverse effects are rare, and damage caused to adjacent areas, including biliary tracts, the urethra, pancreas, bowel wall,

and blood vessels, is within acceptable limits. Indeed, in 2011, Thomson presented a report on the clinical safety of IRE in which he collated 38 cases involving various forms of cancer, including cancers of the lung, liver, and kidney [15]. Findings from the work confirmed that both side effects and ablation effects of IRE treatment on the blood vessels located within the vicinity of tumors were acceptable [15–18]. The US-FDA and CE has approved IRE ablation for clinical use [9].

By 2017, hundreds of medical centers had administered IRE to treat tumors in the pancreas, liver, kidney, lung, and prostate. Theoretically, IRE can be used to treat all solid tumors; however, the application of IRE has thus far generally been limited to tumors of the liver, pancreas, prostate, and kidneys. Nonetheless, several studies have demonstrated the feasibility and safety of IRE in treating locally advanced cancers in critical areas [5,7,17–22]. For example, IRE has been used in the treatment of cancers in the thyroid, breast, lung, and bones; however, its use in treating these types of cancers has not been widespread. Indeed, IRE has been found to be most effective in treating locally advanced pancreas and liver cancers that occur close to critical structures, including blood vessels and the biliary tract.

One 2014 review considered the IRE treatment of 221 patients (325 tumors) in 16 studies and reported no major adverse events. Rather, that study only noted a few minor complications in the liver and 3 complications in the pancreas (2 bile leaks and 1 case of portal vein thrombosis) [5]. Martin et al. reported on 200 patients who underwent IRE treatment for locally advanced (stage III) pancreatic adenocarcinoma [23]. They found that 37% of patients experienced complications, and that the median complication grade was 2 (range 1–5). Furthermore, evidence from both animal studies and human subjects suggests that IRE can be safely used in the treatment of renal tumors, the damage to the renal parenchyma and ductal structure is limited [15,21,22,24]. The efficacy of IRE treatment in treating liver and pancreas cancers is also evident from clinical data. For example, one systemic review of 129 patients who underwent IRE for hepatic tumors reported that the complete remission rate at 3 months was 67–100% for tumors larger than 3 cm and 93–100% for tumors smaller than 3 cm [5]. Another study reported on the application of chemotherapy and radiation therapy in conjunction with IRE for the ablative control of primary tumors in locally advanced (stage III) pancreatic cancer [23]. A total of 200 patients who underwent IRE alone or surgery plus IRE for marginal accentuation presented a median overall survival time of 24 months, which was nearly double that of the control group [23]. Two prospective trials (phase I and II) to assess the efficacy of IRE in the treatment of renal tumors are currently in the process of enrolling patients [25,26].

In 2014, Silk published a paper indicating that, in treating metastatic liver tumors, IRE had a negligible impact on bile ducts within a distance of 1 cm [27]. In other studies, hepatobiliary functional index (including hepatic enzyme and bilirubin levels) only underwent short-term changes, returning to normal within a week. The short-term changes in hepatobiliary function that were observed can be attributed to damage in the

surrounding liver cells. Researchers have also posited that the elevation of transient hepatic enzyme levels is caused by the escape of intracellular water following IRE treatment, which collects around bile ducts to produce edematous swelling [28]. Other safety indices, such as renal function and blood cell count, did not present significant changes.

The percutaneous approach to IRE is generally adopted for the treatment of liver tumors due to its minimally invasive nature (Fig. 6). Narayanan reported good clinical results for both percutaneous and CT-guided application of IRE to liver tumors (PFS = 11.6 months); however, other researchers [29,15] have noted that percutaneous ablation results in higher local recurrence rates than does surgical ablation. For example, Cannon [30] and Silk [27] reported that local recurrence rates associated with percutaneous and CT-guided IRE were 40–50%. Conversely, Kingham et al. [29] reported a local recurrence rate of only 6% and a complete ablation rate of 98% in applying surgical IRE to liver tumors. Similar results were also obtained when IRE ablation was applied to treat pancreatic cancer.

Limitations and complications

Under normal conditions, the electric current used in IRE treatment results in general muscle contraction, which can cause the antenna location to change and thereby induce muscle damage. Furthermore, if muscles frequently contract during the procedure, rhabdomyolysis and acute kidney injury can result. Therefore, patients must receive general anesthesia and undergo complete muscle paralysis prior to the administration of IRE [3]. Patients who are unable to tolerate general anesthesia are absolutely contraindicated to IRE treatment. The risk of arrhythmia induced by the electric current can be life-threatening if cardiac output is lost [3,12]. Fortunately, this risk can be moderated through the application of a cardiac synchronizer, which ensures that the electric pulse is synchronized with the refractory phase of every heartbeat. Nonetheless, patients presenting with cardiovascular comorbidities, such

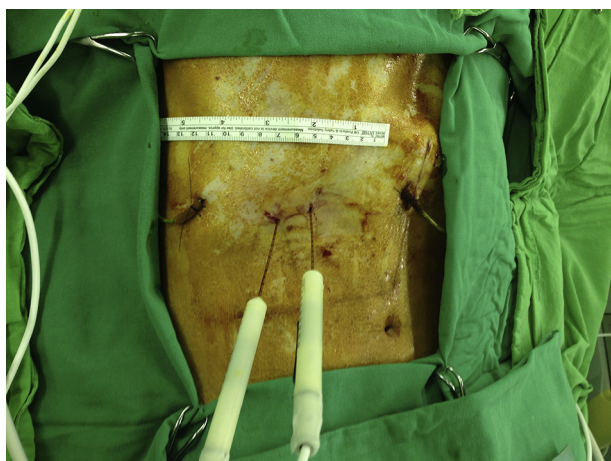


Figure 6 Percutaneous application of IRE guided using ultrasound or CT. The distance between antennas should be maintained at 1.3–2.5 cm to ensure optimal IRE effects.

as cardiac arrhythmia, coronary artery disease, or recent myocardial infarction, are still contraindicated for IRE due to the high risk of symptomatic arrhythmia.

The elevation of systolic blood pressure to 20–30 mmHg under IRE stimulation is very common but self-limited. This effect is caused when electric stimulation or muscular stretching of the arteries leads to the release of catecholamine from the nerve end-plate [13]. Blood pressure always returns to normal levels following the cessation of IRE treatment. In cases where anesthesiologists deem elevated blood pressure to be problematic, medical control is also encouraged. However, patients with a history of poorly controlled hypertension are also contraindicated for IRE. In addition, patients with metallic implants, such as a pacemaker or intraluminal stent, do not qualify for IRE treatment, as the metal in these devices would provide an alternate path for the electric current due to its lower electrical resistance. This could in-turn increase local temperatures around the implants and thereby results in thermal injury.

Complications associated with IRE ablation are often related to effects of electrical pulses and can include cardiovascular problems, pneumothorax and severe muscle contractions. (However, muscle contractions can be minimized through the administration of muscle relaxants). Complications at the site of ablation, including bleeding, abscess formation, damage to adjacent bile ducts, vascular thrombosis, and damage to local organs (e.g. pancreatitis), are often associated with injuries that occur during the insertion of antennae or with the thermal effects of overly high current [5]. In addition, post-procedural pain has been noted less frequently for IRE treatment than for thermal ablation techniques, such as RFA and MWA. In most situations, these effects are mild and can be relieved by oral medications [5]. Finally, the occurrence of metabolic acidosis and/or electrolyte imbalance is encountered most often in patients with impaired renal function or a large ablation area. In these cases, electroporation can cause electrolytes to leak outside the cell, which tends to elevate the concentrations of potassium and chloride. This effect is very similar to tumor lysis syndrome following chemotherapy and can be relieved by adequate hydration. Nonetheless, according to Common Terminology Criteria for Adverse Events (version 3.0), most IRE complications are grade I or II (i.e. minor complications) [5].

Conclusions

IRE is a non-thermal ablation modality that features numerous advantages over conventional ablation techniques, particularly in treating tumors which are located adjacent to vital structures. Under ultrasound guidance, IRE is time-saving and effective. A growing number of clinical studies are reporting encouraging results following IRE treatment. Compared with traditional ablative modalities, IRE is higher technique-demanded in aspect of image-guidance and generator manipulation. Nonetheless, controversies concerning the indication and patient selection of IRE abound, and the efficacy and long-term effects of this technique have thus far only been reported by a small number of experts. Further studies that employ larger

cohorts of specific patient groups and longer follow-up times are required to conclusively establish IRE as a reliable treatment modality.

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