# Technological Breakthroughs in Irreversible Electroporation: The Future of Non-Thermal Ablation

Fady Bassem Fayek[1], Emily Hashem[1], Laxman Singanamala[1], Mina S. Makary[2]

[1]Sidney Kimmel Medical College, Thomas Jefferson University, [2]Ohio State University Wexner Medical Center

## Background

- Irreversible Electroporation (IRE) is a nonthermal ablation technique that uses pulsed high-voltage electrical energy to disrupt the lipid bilayer of tumor cells' membranes by creating nanopores, leading to cell death[1].
- Using electrical energy instead of heat allows ablation near heat-labile structures. Additionally, IRE eliminates the heat sink effect, which carries heat away from the desired ablation site via blood flow[2].
- IRE studies are currently in the early clinical stage for tumors of the pancreas, liver, prostate, and kidney.

## Results

### Pancreatic Cancer

- Used in locally advanced pancreatic cancer (stage II or III, T4N1M0) with a maximum of three positive regional lymph nodes, tumor size ≤5 cm, in patients who are not radical resection candidates or refuse surgery[3].
- Recent trends have shown good potential of IRE in combination with chemotherapy and immunotherapy.
  - Retrospective study showed combination of IRE with anti-PD1 immunotherapy showed an overall survival of 35.03 months for locally advanced pancreatic cancer compared to 15.87 months for IRE alone[4].
  - IRE has been found to expedite and enable better chemotherapy delivery to tumors[3].
- IRE has shown an anti-tumor immune response, particularly through the preservation of tumor antigens with non-thermal ablation. There is evidence of increased influx of CD8+ T cells and macrophages after IRE treatment[5].

### Liver Cancer

- Meta-analysis by Cribbs et al. showed an 84% complete response rate for IRE compared to 68% for Transarterial Chemoembolization in early-stage hepatocellular carcinoma[6].
- Due to the plethora of ablation techniques, IRE is considered for special circumstances in which the tumor is <5cm and <1cm from main bile ducts, intestine, or vasculature[7].
- In animal studies, IRE was found to increase peri-ablation zone infiltration of CD8+ T cells and macrophages as well as down-regulate local and splenic immunosuppression through the inhibition of Treg and PD-1+ T cells[8].

### Prostate cancer

- Used for low-to-intermediate risk prostate cancer (PSA ≤15 ng/mL, Gleason score ≤3+4, clinical stage ≤T2c, and MRI lesion size ≤20 mm)[9].
- PRESERVE Trial evaluated the effectiveness of IRE in intermediate-risk prostate cancer. After a year, 84% of biopsies met the Delphi Criteria for clinical significance of prostate cancer, and 64% of biopsies outside the ablation target were negative[10].
- Electrical properties between healthy and tumor tissue are found to be significantly different, requiring tailoring of local electric fields. There is a need for algorithmic models to predict local tissue electrical field parameters; current predictive models have not undergone validation in clinical practice[11].

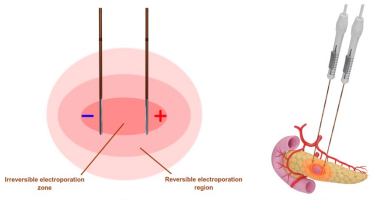


**Fig. 1**[1]. Schematic adopted from Mansur et al showing the (A) application of IRE probes to tumors, creating strong electric fields that disrupt the lipid bilayer of tumor cells. (B) Representation of IRE probes on a pancreatic tumor.

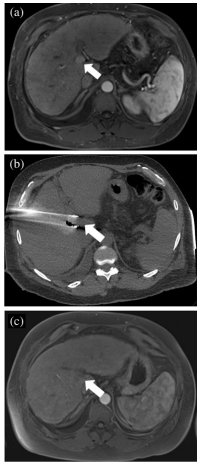


**Fig. 2**[7].Schematic adopted from Yun et. al. showing (a) a mass near the hepatic hilum. (b)Intraprocedural image showing IRE ablation of liver mass. (c) Three months follow-up after ablation.

### Renal cancer

- Used for small-to-intermediate renal masses (typically cT1a, ≤4 cm)[12].
- IRE has allowed tumors in unfavorable locations, including the center of the kidney and near the renal pelvis or hilar vessels, to be treated while limiting procedural complications[7].
- Retrospective study by Dai et al. showed IRE to have an initial treatment success rate of 91.7%, a local recurrence-free survival of 81.4%, and 92.3% overall survival without any procedural complications[8].
  - Lower recurrence-free survival than conventional thermal ablation techniques[8].

## Technological Advancements

- High Frequency IRE (H-FIRE) is an advancement of IRE that replaces unipolar 100 µs pulses with bipolar pulses with shorter periods ranging from 0.25–5.0 µs. This eliminates the impedance differences among tissues, particularly between healthy and cancerous tissue. Unlike IRE, H-FIRE does not need anesthesia to prevent involuntary muscle contractions and cardiac synchronization to prevent arrhythmias[14].
- Nanosecond Pulsed Electric Fields (nsPEF) uses high voltage bursts of electrical energy at periods ranging from 100-500ns. nsPEF has proven to be effective not only in penetrating cell membranes but also in organelles[15]. In addition to the negation of muscular anesthesia and cardiac synchronization, nsPEF induces cell death via multiple mechanisms simultaneously and has been found to induce a potent immune response via an array of mechanisms, including both adaptive and innate immunity[16].

## Limitations

- Limited number of randomized control trials.
- Risk of incomplete ablation and consequent recurrence associated with suboptimal probe placement[17].
- Volume limitation on tumor sizes due to significant field strength decay as the distance from electrodes increases[15].
- Despite being shown to induce an anti-tumor immune response, incomplete ablation preserves the tumor's immunosuppression hubs that can dampen the effects of recruited immune cells[15].
- Requirement of neuromuscular blockade and cardiac synchronization[14].

## Conclusion

IRE has proven to be a promising ablation technique for multiple cancers, providing an overarching benefit of killing tumors near heat-sensitive structures. There are concerns regarding IRE's efficacy, which is dependent on tumor sizes and probe placement- these are strong determining factors of whether complete ablation is achieved. Two novel electroporation-based therapies are H-FIRE and nsPEF, which are promising alternatives to IRE, having the benefits of overall improved efficacy and reduced side effects. An increase in the number of randomized control trials is required before IRE can be validated as a cornerstone ablation technique.

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