CLINICAL STUDY

Irreversible Electroporation for Nonthermal Tumor Ablation in the Clinical Setting: A Systematic Review of Safety and Efficacy

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ABSTRACT

Purpose: To provide an overview of current clinical results of irreversible electroporation (IRE), a novel, nonthermal tumor ablation technique that uses electric pulses to induce cell death, while preserving structural integrity of bile ducts and vessels.

Methods: All in-human literature on IRE reporting safety or efficacy or both was included. All adverse events were recorded. Tumor response on follow-up imaging from 3 months onward was evaluated.

Results: In 16 studies, 221 patients had 325 tumors treated in liver (n = 129), pancreas (n = 69), kidney (n = 14), lung (n = 6), lesser pelvis (n = 1), and lymph node (n = 2). No major adverse events during IRE were reported. IRE caused only minor complications in the liver; however, three major complications were reported in the pancreas (bile leak [n = 2], portal vein thrombosis [n = 1]). Complete response at 3 months was 67%–100% for hepatic tumors (93%–100% for tumors < 3 cm). Pancreatic IRE combined with surgery led to prolonged survival compared with control patients (20 mo vs 13 mo) and significant pain reduction.

Conclusions: In cases where other techniques are unsuitable, IRE is a promising modality for the ablation of tumors near bile ducts and blood vessels. This articles gives an extensive overview of the available evidence, which is limited in terms of quality and quantity. With the limitations of the evidence in mind, IRE of central liver tumors seems relatively safe without major complications, whereas complications after pancreatic IRE appear more severe. The available limited results for tumor control are generally good. Overall, the future of IRE for difficult-to-reach tumors appears promising.

ABBREVIATIONS

CTCAE = Common Terminology Criteria of Adverse Events, HCC = hepatocellular carcinoma, IRE = irreversible electroporation

In the past 2 decades, image-guided ablation for focal tumor treatment has received substantial attention when surgical options are precluded. The rapid development of ablative devices has led to a continuous expansion of treatment options, and tumor ablation has become accepted as a valuable adjunct to traditional surgical, chemotherapeutic, and radiation regimens (1). Different ablative techniques for the treatment of unresectable tumors include percutaneous ethanol injection; stereotactic ablative radiotherapy; and thermal ablation such as cryoablation, laser interstitial thermotherapy, high-intensity focused ultrasound, microwave ablation, and radiofrequency (RF) ablation.

Irreversible electroporation (IRE) is a new treatment method with certain advantages over the existing ablative techniques that has gained widespread attention. With IRE, cell death is induced with electric energy. Under image guidance, electrodes are placed around the tumor, and through multiple short high-voltage electric pulses, the

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None of the authors have identified a conflict of interest.

Appendices A and B are available online at *www.jvir.org*.

J Vasc Interv Radiol 2014; XX:▮▮▮–▮▮▮

http://dx.doi.org/10.1016/j.jvir.2014.01.028

existing cell membrane potential is disturbed (Fig 1a–i). As a consequence, nanoscale defects appear in the lipid bilayer of the cell membrane. Depending on the amplitude and duration of the pulses, the permeability of the cell membrane is reversible, after which the cell survives, or irreversible, after which the cell dies through loss of homeostasis (2). Although IRE is believed to destroy all cells within the ablation zone effectively, the nonthermal nature of IRE results in relative preservation of the extracellular matrix. As a result, the structural integrity of inlaying and adjacent tissue structures such as vessels and bile ducts remains intact. Additionally, treatment effect should not be impeded by heat sink (2).

Numerous animal studies have investigated these hypotheses. The integrity of portal triad structures, bowel wall, pancreatic duct, and urinary collecting system is guarded, owing to sparing of the collagen scaffold, followed by regeneration (3–11). After IRE around peripheral nerves, preservation of endoneural architecture and proliferation of Schwann cells may enable axonal regeneration with recovery of full function (12,13). Most importantly, complete cell death has been confirmed throughout the ablation zone within hours after IRE (14) as well as significant tumor reduction of hepatic and pancreatic cancer xenografts in mice (8,15).

With these distinctive characteristics, IRE may be suitable for the treatment of tumors ineligible for surgical resection or thermal ablation because of unfavorable location. However, the local application of an excessive electric field is a potential hazard because the pulses could induce cardiac arrhythmias and severe muscle contractions (16). In the last 2 years, a growing experience with IRE in humans has been reported in the literature. To investigate how the theoretical advantages of IRE are reflected in clinical practice, we performed a systematic review. Objectives were safety and efficacy in terms of complications, tumor response, survival, and symptom reduction. The analyzed data should inform clinicians on the current position of IRE in interventional oncology as well as its indications for clinical use and should provide researchers a compass for future clinical studies.

MATERIALS AND METHODS

This review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews (17). The reviewers agreed to the terminology suggested by the Society of Interventional Radiology (SIR) in "Image-Guided Tumor Ablation: Standardization of Terminology and Reporting Criteria" (18).

Search Strategy

A comprehensive systematic review of the literature published until November 2013 was performed using EMBASE and MEDLINE (PubMed). Studies found in alternative ways were also checked for eligibility. Medical Subject Headings search terms and key words used in the search were "irreversible electroporation (IRE)," "electroporation," "electropermeabilization," and "electrocoagulation."

Inclusion and Exclusion Criteria

Studies were included if they met all of the following criteria: (*a*) human subject(s), (*b*) who underwent IRE, (*c*) of primary or secondary tumors, (*d*) investigating safety or efficacy or both. Exclusion criteria were as follows: (*a*) review or meta-analysis, (*b*) abstract only. Studies of all designs published in English, French, and German were included. Two reviewers (K.N. and H.J.S.) independently performed literature search, article inclusion, data extraction, and quality assessment. When necessary, the corresponding author was contacted to prevent analysis of overlapping study results.

Quality Assessment

The Quality Assessment Tool for Quantitative Studies checklist was used to assess the quality of the included studies in terms of study design, risk of bias, confounders, blinding, data collection methods, and withdrawals and dropouts (http://ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf). Although a dedicated assessment tool for case reports does not exist, this checklist includes valuable criteria that apply to case reports as well. The level of evidence of each article was scored according to the system for assigning level of evidence from the Centre for Evidence-Based Medicine (Oxford, United Kingdom) (19). The levels of evidence range from 1 (strong evidence) to 5 (weak evidence). Discrepancies were resolved by consensus.

Data Extraction

From each article, the clinical indication for IRE was noted. Other baseline characteristics were treated organ and tumor type, previous treatments, ablation approach, and additional surgical procedures.

For safety assessment, all adverse events during IRE, including events related to the direct application of a strong electric field, events related to electrode placement, or any other adverse event, were recorded as well as all adverse events occurring during follow-up. When mentioned by the original authors, complications were divided in IRE-related and not IRE-related and graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 3.0 (20). CTCAE grade $\geq$ 3 was considered a major complication. When complication grades were not mentioned by the authors, the reviewers addressed a grade only if it could be clearly derived from the text, which meant that treatment as well as outcome after treatment were explicitly stated (eg, if the authors stated "resolving spontaneously" or "requiring chest drainage"). If uncertainty remained, no grade was addressed.

Despite a lack of consensus on a standard follow-up interval regimen for imaging, a period of at least 3 months is