



Review article

IRREVERSIBLE ELECTROPORATION FOR CANCER TREATMENT: A REVIEW

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ABSTRACT

Introduction: Prostate, pancreatic and liver cancers are a major cause of death in Europe and including Bulgaria. Some methods for treatment include the use of electric current to create pores in the cells' membranes, and can be used in combination with other techniques, while an electric field with enough strength causes irreversible electroporation (IRE) and is a separate technique.

Material and methods: Search was conducted for scientific articles about electroporation and IRE.

Results: Most important parameters reported in scientific articles are electric field distribution, tissue characteristics and interaction, electric pulse settings. Articles that report patient outcomes suggest several possible advantages of – retaining urinary and sexual functions, possible increase of overall survival rate, low rate of serious adverse events and promising results when applied with chemotherapy. However, there are some studies that do not corroborate these results. The technique is also used for the treatment of renal cancer, and there are researches indicating a potential for use in ovarian, cervical and breast cancer.

Conclusion: Studies suggest the IRE method is safe and feasible for the treatment of prostate cancer, pancreatic cancer and liver cancer, but improvements in the protocols is needed to prevent a decrease of quality of life.

Keywords: electroporation, irreversible electroporation, electroporation therapies,

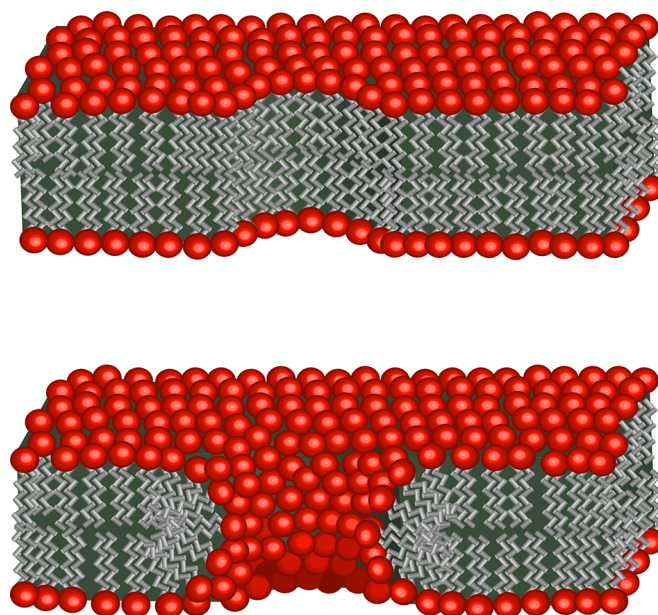
INTRODUCTION

Prostate cancer is the most diagnosed cancer in men in most European countries, including Bulgaria and prostate cancer, pancreas cancer and liver cancers are the reason for more than 300 000 deaths per annum only in Europe [1].

Therefore, different approaches for the treatment of the above cancers are researched and applied. It was determined that electric fields with strength above a given threshold cause increase in the permeability of biological membranes, and the method of creation of such pores is called electroporation [2, 3]. The earliest research in the field of electroporation can be dated back to the 1950s [4].

A model of electroporation is shown in Fig. 1. The bilayer is partially permeable, but with applying of an electric pulse, there appear hydrophobic pores (up) which later stabilize in hydrophilic pores (below).

Fig. 1. Diagram of possible lipid arrangements at the edge of a pore through a lipid bilayer. (Author: MDougM, Public domain, via Wikimedia Commons [Internet])



An early theory was the aqueous pore theory, but even the exact mechanism still remains not fully clear the electroporation method had been increasingly researched for applications in medicine since the 1980s [4, 5]. Early results from such research were techniques that create temporary pores – for example, electrochemotherapy that allows for smaller chemotherapeutic doses, and electrogene transfer that is still mostly in the research field and allows for DNA introduction, but it was in 2005 when the IRE was considered a separate method that uses stronger electric pulses with the goal of cells death and with the advantages of being non-thermal method and not damaging the surrounding cells and tissues but general anaesthesia is required and IRE should be avoided near metallic implants [2, 4, 6]. A recent article [7], however, calculated that the temperature increase is negligible for a distance between a stent and an electrode is 1 cm and usual IRE pulse settings.

MATERIALS AND METHODS:

Search in scientific databases for articles on electroporation and IRE. Then it was performed an analysis of the article's data on the use of electroporation and IRE, electric pulse specifications and treatment of various cancers, advantages and disadvantages of the technique.

RESULTS

Specifications and models

There are studies to evaluate the tissue characteristics – lipid bilayer thickness, conductivity and dielectric permittivity, pores energy and radius, water and membrane dielectric constants, electrodes specifications, etc. and/or to create electric field models, thermal models and/or electroporation models based on these specifications [4, 8-14]. Model of electrical pulses interference between IRE and pacemakers [15] had been researched, and authors reported that when the pacemaker pulse is at the same time as the electroporation pulse, there is a certain effect on the former, therefore, the best option is delivery of properly synchronized pulses from the electroporator, and that the pacemaker pulse has heating effect on the IRE electrodes and space close to their tips that is most significant if there is a contact between the pacemaker and an electrode but no other significant effects had been reported. There are software applications developed to simulate and/or educate on electroporation and its electric field [16-19].

An article [20] describes a general structure of an electroporation device with basic units – power control, high voltage charge block, pulse generator, electrode switch, trigger and user interface, and also how to achieve a good pulse shape without high cost equipment

The authors described that the user interface is to

adjust the parameters and provide them to the power unit, then the power unit executes the procedure using a field programmable gate array to perform control and store energy in the capacitors of the high voltage block, then release the energy and measure the parameters using the pulse generator block following the operator signal given with the trigger. Additionally, pulse length control measures are taken against pulses delivered due to a failure. Finally, the electrode switch serves to select the electrode switching order [20].

NanoKnife™ by AngioDynamics is yet the only commercial IRE device, and its specifications are up to 3000 V, up to 100 pulses and a maximum pulse duration of 100 ms [21]. Therefore, several studies [22-25] used NanoKnife™ in their research, while one [26] reported the use of a generator supplied by AngioDynamics.

Treatments

An early study [26] on IRE on hepatocellular carcinoma (HCC) performed on humans described the technique performed percutaneously on 11 patients with 18 lesions and reported despite there had been major organs near the lesion, there not been observed major complications or death related to the performed IRE. The authors, however, reported five lesions had been incompletely ablated and required further treatment, also, one patient was treated for metastatic disease, one patient needed a transplant, and one patient died on the 17th month. The pulses parameters were sets of 90 pulses, pulse duration 70 is and field strength more than 1000 V/cm.

The same IRE settings on pulses number and duration were used in a study by Valerio *et al.* [22] reporting results for 34 patients in a two-centre study on prostate cancer, the electric current was selected between 20 and 40 A and electrodes were positioned not more than 2 cm apart. Authors reported complications, if any, were only mild to moderate, furthermore, on 24 followed-up patients, authors reported retained sexual function in 95% of 20 patients, and preservations of continence in 100% of the 24 followed-up patients while no death or metastasis was reported.

A prospective study on IRE on 19 patients with prostate cancer [23] reported that patients were discharged the same day or the next morning after the procedure. The pulses were with the same settings as in the above-written study [22], the result for retained erectile function was 83% and preservation of continence 100%, the adverse events were only grade 1 and 2. Further, authors reported residual cancer had not been found in 61.1% of the patients who had a biopsy.

A study [24] evaluated the quality of life after prostatic cancer treatment by IRE. NanoKnife™ was used with ECG synchronization and pulse settings 1500 V/cm, 20-40 A, 90 pulses, initially 70 is pulse duration but increased to 90 is. The authors reported the expanded pros-

tate cancer index composite sexual score declined significantly and 68% preservation of sexual function. The other aspects of quality of life had not been significantly affected.

A recent article [25] reported on whole tumour percutaneous IRE ablation on patients with HCC and with parameters set to 90 pulses, 70-90 is, 1500 V/cm and concluded on the immunological effects there had been a benefit on anti-tumour activity of the patients.

Comparison between chemotherapy together with open IRE and chemotherapy alone [27] reported that patients with chemotherapy and IRE had a higher overall survival rate than chemotherapy alone. The authors' analysis showed median overall survival longer than 24 months and a rate of 89.9% and 77.2% for the 1st and 2nd year after the chemotherapy and IRE, and 7.1 months and a rate of 18.1% and 18.1% for the 1st and 2nd year of the chemotherapy alone, and the progression-free survival had been 7.1 months when IRE used, and for chemotherapy alone - 4.9 months.

A review [21] on IRE performed on pancreatic and liver cancer reported median overall survival after IRE 4.3 – 22.6 months for pancreatic cancer, but reviewed studies included chemotherapy, radiotherapy or chemoradiotherapy before or after IRE, and 37.92 months for liver cancer in one reviewed study. The authors also reviewed the quality of life and found a significant decline reported in one study on pancreatic cancer and reported pain that affected life in another pancreatic cancer study. Furthermore, for pancreatic cancer, the review authors found that there were adverse events associated with 19.47% of the patients, overall mortality was 1.62%, and some but not all deaths and adverse events had been related to IRE. Data for liver cancer had been written 8.70% adverse events and no deaths.

An article dedicated to percutaneous pancreatic cancer treatment [6] reviewed studies with several ablation techniques – radiofrequency ablation, microwave ablation, cryoablation and IRE. The IRE review was on three studies and one case report, the case report and two studies were on percutaneous IRE, while one study was on mostly surgical procedures. In general, the article describes the IRE technique as safe and feasible in the reviewed studies – pancreatic ductal adenocarcinoma. The overall survival reported in one of the reviewed studies was 17.9 months.

An article by Aycock and Davalos [4] reviewed several studies and described the advantages of this method, which are possible better preservation of sexual and urinary function in the treatment of prostate cancer, the increased potential survival rate for pancreatic cancer in patients with unresectable disease and a possibility to perform IRE for HCC in unresectable disease patients with small tumours.

Another article on IRE in locally advanced pancreatic cancer [28] reviewed 19 clinical studies published between 2013 and 2020. The two studies with the most patients reported median overall survival of 24.9 months and 30 months, and the other studies – between 10 and 27 months. It should be noted that different methods had been used in the different studies, patients in some studies underwent chemotherapy and/or chemoradiotherapy, and tumour sizes were different. Severe complication in studies that provided such information usually between 0% and 25%, with only one study, 42%.

IRE can be used for the treatment of renal tumours, and a review by Zondervan *et al.* [29] on seven studies stated that IRE seems feasible and safe, but further investigations are needed.

Although articles and researches are often dedicated to IRE used mostly for prostate, pancreas and liver cancer, a recent article [30] considers the use of IRE for ovarian cancer, cervical cancer and breast cancer, however, despite promising results performed in vitro or on animals in most of the reviewed studies the number of clinical trials is still limited.

CONCLUSION:

There are a number of studies that suggest IRE is a safe and feasible technique for the treatment of prostate, pancreas, liver and renal cancer. Different models and simulators of the electroporation had been developed to facilitate research in the field to develop technique and protocols aimed at maintaining patients' quality of life, increasing overall survival and keeping a relatively low percentage of adverse events. Further research can reveal more specific details and facilitate better application protocols.

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