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Journal of Clinical Research and Reports
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Research Article

Irreversible Electroporation of Carcinoma of the Prostate Gland with a Focus on Localized Carcinoma of the Prostate Gland: A Review and Update

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Received date: February 28, 2022; **Accepted date:** March 16, 2022; **Published date:** March 28, 2022

Citation: Anthony K. G Venyo, (2022). Irreversible Electroporation of Carcinoma of the Prostate Gland with a Focus on Localized Carcinoma of the Prostate Gland: A Review and Update. *J Clinical Research and Reports*, 10(5); DOI:10.31579/2690-1919/239

Abstract

Even though adenocarcinoma of the prostate gland could be lethal in its advanced stage, adenocarcinoma of the prostate gland can be effectively treated when the carcinoma is localized to the prostate gland and when the localized adenocarcinoma is a low-risk or intermediate-risk localized adenocarcinoma of the prostate gland. it is localized. Traditionally, radical prostatectomy (RP) or radical radiotherapy (RT) in the form of either external beam radiotherapy or brachytherapy were utilized to treat all men who have localized adenocarcinoma of the prostate gland as treatment of curative intent. Nevertheless, Radical prostatectomy and radical radiotherapy do tend to be associated with significant risks of post-treatment side effects. Some patients who have localized prostate cancer may not be medically fit as a result of their comorbidities to undergo radical prostatectomy or radical radiotherapy to their prostate cancers. Over recent years a number of less-invasive treatment options are being utilized for the treatment of some localized adenocarcinomas of the prostate gland and some of the treatment options include: Cryotherapy of prostate Cancer; Radiofrequency ablation of prostate cancer, High Intensity Focused Ultrasound Treatment of Prostate Cancer and Irreversible Electroporation of prostate cancer as focal ablation or whole gland ablation. Focal therapy has emerged as a potential form of treatment that can achieve similar oncological outcomes to radical treatment while preserving functional outcomes and decreasing rates of adverse effects. Irreversible electroporation (IRE) is one such form of focal therapy which utilizes pulsatile electrical currents to ablate tissue. This modality of treatment is still in an early research phase, with studies showing that IRE is a safe procedure that can offer good short-term oncological outcomes whilst carrying a lower risk of poor functional outcomes. Irreversible Electroporation (IRE) is a new radiology image-guided tissue ablation which does induce cell death through very short but strong electric fields. IRE had been demonstrated to have preserving properties towards vessels, nerves, as well as the extra-cellular matrix. For this reason, IRE could represent an ideal treatment option for adenocarcinoma where other treatment options including radical prostatectomy and radical radiotherapy tend to unselectively destroy that encompass the prostate cancer and inducing side effects including urinary incontinence as well as sexual dysfunction / impotence. Some results of studies in which IRE had been utilized for the treatment of curative intent of localized low-risk and intermediate-risk adenocarcinomas of the prostate gland had indicated complete efficacy of IRE to the standard of radical prostatectomy and standard radical radiotherapy with regard to the 5-year tumour recurrence rate as well as better preservation of genitourinary function which did prove the safety as well as suitability of IRE for the treatment of localized low-risk and intermediate risk adenocarcinoma of the prostate gland. Some data pertaining to IRE besides focal treatment of early adenocarcinoma of the prostate gland had shown that IRE besides focal treatment of early prostate cancer could also be utilized for whole prostate gland ablations in patients who develop recurrent prostate cancer as well as a problem-solving treatment for the control of local tumour within the prostate gland that are not amenable to surgery or radiotherapy anymore. Some studies had demonstrated comparable short-term and medium-term functional outcomes functional outcomes with radical prostatectomy and radical radiotherapy but following longer surveillance assessments those underwent IRE were found tom have superior genitourinary function in that a number of the sexual dysfunction and urinary incontinence had resolved but with regard to the oncology outcome repeat follow-up biopsy of the prostate had demonstrated a higher positive tumour biopsy upon pathology examination for which either further IRE, or radical radiotherapy, or radical prostatectomy was required as subsequent treatment of curative intent in that radical prostatectomy of curative intent had superior medium-term to long-term outcome in comparison with IRE. IRE can also be utilized to treat locally recurrent prostate cancer following: (a) radical radiotherapy and (b) following the finding of persistent or locally recurrent adenocarcinoma of the prostate gland pursuant the undertaking of IRE as treatment of curative intent of localized adenocarcinoma of the prostate gland. Following failure of IRE treatment for localized adenocarcinoma

of the prostate, the persistent carcinoma of the prostate gland could also be treated by means of radical prostatectomy, or radical radiotherapy or any other minimally invasive treatment of curative intent including cryotherapy, radiofrequency ablation of the prostate and high intensity focused ultrasound treatment. Considering that IRE tends to be associated with good short-term and medium-term outcome which also tends to be generally superior to the outcome following radiotherapy as well as radical prostatectomy, and the fact that the medium-term to long-term oncology outcome tends to be good but the oncology outcome following radical prostatectomy as well as radiotherapy would tend to be a bit superior to IRE, it could be suggested that patients who have low-risk and intermediate-risk localized adenocarcinoma who prefer to maintain their genitourinary function could be offered IRE as first line treatment of curative intent which should be followed up with regular frequent assessments which would enable early identification of treatment failures at an early stage. The individuals who are found to have IRE failure could then be offered radical prostatectomy or radical radiotherapy as second line treatment of curative intent. Finally, there is need for a global multi-centre trial of IRE in the treatment of curative intent of localized low-risk, intermediate-risk, as well as high risk groups and those who have high risk group localized prostate cancer could be offered adjuvant therapy and all these treatments should be compared with radical radiotherapy and radical prostatectomy with a long period of follow-up to enable a consensus opinion to be established as well as guidelines to be formulated.

Key Words: adenocarcinoma of prostate; localized; low-risk; intermediate-risk; medium-risk; radical prostatectomy; radical radiotherapy; irreversible electroporation; oncology outcome; functional outcome; serum prostate-specific antigen; prostate biopsy; computed tomography scan; magnetic resonance imaging scan; recurrent tumor; failure of irreversible electroporation; survival

Introduction

Carcinoma of the prostate gland can be localized carcinoma of the prostate gland, locally advanced carcinoma of the prostate gland or metastatic carcinoma of the prostate gland. It has been iterated that carcinoma of the prostate gland has continued to be one of the commonest diagnosed carcinomas in men as well as a leading cause of cancer deaths in men globally [1,2]. It has also been documented that even though carcinoma of the prostate gland could be lethal in its advanced stage, carcinoma of the prostate gland could be treated effectively when it is localized to the prostate gland [1]. Traditionally radical prostatectomy (RP) or radical radiotherapy (RT) either in the form of external beam radiotherapy or brachytherapy were utilized for the treatment of all men who have localized prostate cancer, irrespective of their risk [1]. Nevertheless, notwithstanding their improved survival benefits, radical prostatectomy (RP) and radical radiotherapy (RP) have tended to be associated significant risks of post-treatment side effects / complications and the two commonest of these complications tend to include urinary incontinence (UI) and erectile dysfunction (ED). [ong 0000]. It has been iterated that over the preceding decade, a change in the treatment of very low-risk as well as low-risk adenocarcinoma of the prostate gland, as well as an increasing interest in new techniques for the treatment of intermediate-risk localized adenocarcinoma of the prostate gland has emerged [1]. it has also been iterated that very low-risk and low-risk adenocarcinoma of the prostate gland does tend to be associated with an unlikely chance of developing metastasis as well as a very low-risk of mortality [2]. In view of the aforementioned facts, new guidelines, do now recommend treatment of such very low-risk group and low-risk groups of localized prostate cancer by means of active surveillance to delay or mitigate the need to undertake radical prostatectomy (RP) or radical radiotherapy [1,3]. Likewise, it has been iterated that some evidence had indicated that intermediate-risk group of localized-adenocarcinoma of the prostate gland tend to be associated with oncology outcomes that are close to the oncology outcomes of low-risk localized adenocarcinoma of the prostate gland [1,4]. Nevertheless, the risk for the development is stated to be still relevant and does warrant some form of therapy [1]. It has been documented those different types of focal therapy to the prostate gland are currently being utilized on trial basis for these men [1].

It has been explained that by focusing treatment upon a specific area of the prostate gland, the aim of focal treatment is to achieve similar oncology outcomes to radical treatment while preserving functional outcomes as well as decreasing the rates of adverse effects [1]. Irreversible electroporation (IRE) is a new focal therapy option which utilizes pulsatile electrical currents to ablate tissue. Animal and human models had been utilized to confirm that IRE could induce cell death but at the same time preserving important encompassing structures [5].

The mechanism in which IRE does this is said to be via the destabilization of the cell membrane, which then causes the alteration of membrane shape and the formation of nanopores. It has been iterated that the excessive permeability of these cells does tend to disrupt the osmotic balance, and this leads to irreversible damage and the process of apoptosis [1,6]. It has been documented that the IRE technique has now been refined in order to administer electrical pulses at levels to prompt cell death whilst keeping the procedure below harmful thermal thresholds [1,5]. It has been pointed out that with regard to important structures such as blood vessels, IRE has been demonstrated to decrease smooth muscle cells but maintain the connective tissue matrix [1,7]. Hence, it has been utilized effectively within liver lesions where damage to bile ducts and hepatic vessels are lethal [1,8,9]. It has been pointed out that with regard to men who have adenocarcinoma of the prostate gland, preservation of the neurovascular bundles adjacent to the gland could emanate in the preservation of continence and erectile function, which would therefore increase or improve the quality of life of the patient [1].

It has been pointed out that initial trials for localized adenocarcinoma of prostate gland patients had demonstrated promising results with regard to both oncology and functional outcomes; nevertheless, more information on the clinical performance of IRE is required before clinicians could integrate IRE into their routine clinical practice [1]. Even though IRE is being utilized in some research and academic centers within many developed countries, it would be envisaged that many clinicians globally may not be familiar with utilization of IRE in the treatment of many lesions within the body including localized adenocarcinoma of the prostate gland. Considering that IRE has only be utilized in the treatment of prostate cancer, it would be envisaged that perhaps the short-term and perhaps the intermediate-term outcome of IRE for the treatment of prostate cancer would be known and the long-term outcome of IRE in the treatment localized adenocarcinoma would not be known yet. Before a consensus is made globally regarding the utilization as well as timing and indications for utilizing prostate cancer is made it would be important to summate the outcome of IRE in the treatment of carcinomas of the prostate gland that have been reported in various journals in order to be sure about the outcome of treatment of prostate cancer with IRE. The ensuing article of IRE in the treatment of prostate cancer is divided into three parts: (A) Overview that has defined Irreversible electroporation as well as described various lesions of the body that have been treated by IRE, (B) Miscellaneous Narrations and Discussions Related to Utilization

of IRE in Research Work Focusing on Animal Studies And (C) Utilization of Irreversible Electroporation OF Prostate Cancer IN Human Beings and In Few Animals.

Aims

To Review and Update the Literature on Irreversible Electroporation in The Treatment of Various Lesions of The BODY In General and with a Focus of Localized Adenocarcinoma of the Prostate Gland.

Methods

Various Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Irreversible Electroporation; Irreversible Electroporation of Prostate Cancer; Irreversible Electroporation of Adenocarcinoma of Prostate; Irreversible Electroporation of Carcinoma of Prostate; Irreversible Electroporation of Localized Prostate Cancer. One hundred and six (106) references were identified which were used to write the review and update of the literature on Irreversible Electroporation in General And Irreversible Electroporation of Prostate Cancer which has been divided into three parts: (A) Overview that has defined Irreversible electroporation as well as described various lesions of the body that have been treated by IRE, (B) Miscellaneous Narrations And Discussions Related to Utilization of IRE in Research Work Focusing On Animal Studies And (C) Utilization of Irreversible Electroporation OF Prostate Cancer IN Human Beings and In Few Animals.

Overview

Definition / general statements

Irreversible electroporation (IRE) is a terminology that is utilized for soft tissue ablation technique which utilizes short but strong electrical fields in order to create permanent and thus lethal nanopores within the cell membrane, and to disrupt cellular homeostasis [10]. The resulting cell death does emanate from induced apoptosis or necrosis which has been induced by either membrane disruption or secondary breakdown of the membrane as an emanation of transmembrane transfer of electrolytes and adenosine triphosphate [10,14]. It has been stated that the main utilization of IRE does lie upon tumour ablation within regions where precision and conservation of the extracellular matrix, blood flow and nerves are of importance [10]. The first generation of IRE for clinical utilization, in the form of the NanoKnife System, became commercially available for research purposes in 2009, and this was mainly for the surgical ablation of soft tissue tumours [10,15].

It has additionally been iterated that ablation of cancerous tissue ablation by means of IRE does appear to demonstrate significant cancer specific immunological responses that are currently being evaluated alone and in combination with cancer immunotherapy [10,16-19].

History

With regard to the history of Irreversible electroporation (IRE). It has been iterated that the first observations of the effects of IRE was reported in 1898. [10] [20] Nollet did report the first systematic observations of the appearance of red spots upon animal and human skin that had been exposed to electric sparks [10, 21]. Nevertheless, the use of IRE for modern medicine did begin in 1982 with the seminal work of Neumann and colleagues. [10] [22] Pulsed electric fields were utilized to temporarily permeabilize cell membranes in order to deliver foreign DNA into cells. Within the ensuing decade, the combination of high-voltage pulsed electric fields with the chemotherapeutic drug bleomycin and with DNA had yielded new clinical applications including: electrochemotherapy as well as gene electro-transfer. [10,23-27] It has been iterated that utilization of irreversible electroporation (IRE) for therapeutic purposes was first suggested by Davalos, Mit, as well as Rubinsky [10] [28].

[A] Mechanism of Irreversible electroporation

Irreversible electroporation is said to utilize ultra-short pulsed but very strong electrical fields, micropores and nanopores are induced in the phospholipid bilayers which form the outer cell membranes. [10] It has been iterated those two types of damage can occur following irreversible electroporation and these include: [10]

(a) Reversible electroporation (RE): Temporary and limited pathways for molecular transport through nanopores are formed; nevertheless, after the end of the electric pulse, the transport ceases as well as the cells do remain viable. [10] Medical applications of reversible electroporation include: local introduction of intracellular cytotoxic pharmaceuticals such as bleomycin (electroporation and electrochemotherapy) [10].

(b) Irreversible electroporation (IRE): Following a certain degree of damage to the cell membranes by electroporation, the leakage of intracellular contents tends to be too severe or the resealing of the cellular membrane tends to be too slow, leaving healthy and/or cancerous cells irreversibly damaged. The cells die by either apoptosis or by means of cell-internally induced necrotic pathways, which is unique to this ablation technique. [10].

It has been iterated that that even though the ablation method is generally accepted to be apoptosis, some findings seem to contradict a pure apoptotic cell death, which has made the exact process by which IRE causes cell death unclear [10,14,29] Nevertheless, all studies do agree that the cell death is an induced cell death in which the cells dying over a varying time period of hours to days and does not rely on local extreme heating and melting of tissue by means of high energy deposition like most ablation technologies [10].

When an electrical field of greater than 0.5 V/nm [30] is applied to the resting trans-membrane potential, it has been promulgated that water does enter the cell during this dielectric breakdown. Hydrophilic pores tend to be formed. [31,32] It has been iterated that a molecular dynamics simulation by Tarek [33] had demonstrated this proposed pore formation in two steps as follows: [34]

1. Pursuant to the application of an electrical field, water molecules line up in single file and they do penetrate the hydrophobic centre of the bilayer lipid membrane.
2. These water channels do continue to grow with regard to length and diameter and expand into water-filled pores, at which point they tend to be stabilized by the lipid head groups which move from the membrane-water interface to the middle of the bilayer.

It has been postulated that as the applied electrical field increases, the greater is the perturbation of the phospholipid head groups, which in turn increases the number of water- filled pores [10,35]. It has been documented the entire electroporation process could occur within a few nanoseconds. [10,33] It has been iterated that the average sizes of nanopores are likely cell-type specific. In swine livers, they average around 340-360 nm, as found using SEM [10,34]. A secondary promulgated mode of cell death was postulated to be from a breakdown of the membrane ensuing transmembrane transfer of electrolytes and adenosine triphosphate [10,13]. Other effects like heat [10,36] or electrolysis [10,37,38] were also demonstrated to play a pivotal role with regard to the currently clinically applied IRE pulse protocols.

Potential Advantages and Disadvantages of Irreversible Electroporation (IRE)

Advantages of Irreversible Electroporation (IRE) Some of the advantages of IRE have been summates as the ensuing: [10]

a. Tissue selectivity - conservation of vital structures within the treatment field. Its capability of preserving vital structures within the IRE-ablated zone. It has been iterated that in all IRE ablated liver tissues, critical structures, including the hepatic arteries, hepatic veins, portal veins and intrahepatic bile ducts were all preserved.

b. Within IRE, the cell death is stated to be mediated by apoptosis. Structures that mainly consist of proteins like vascular elastic and collagenous structures, and peri-cellular matrix proteins tend not to be affected by the currents. Vital and scaffolding structures including structures like large blood vessels, urethra or intrahepatic bile ducts, tend to be conserved [39]. The electrically insulating myelin layer, encompassing nerve fibers, does protect nerve bundles from the IRE effects to a certain degree. It has been stated that it is not completely understood up to what point the nerves stay unaffected or can regenerate [10,40].

c. Sharp ablation zone margins- It has been stated that the transition zone between the reversible electroporated area and the irreversible electroporated area has been accepted to be only a few cell layers. On the other hand, the transition areas as in radiation or thermal based ablation techniques are understood to be non-existent. It has additionally been stated that the absence of the heat sink effect, which has been a cause of many problems as well as treatment failures, is advantageous and does increase the predictability of the treatment field, as well as it has been iterated that geometrically, rather complex treatment fields tend to be enabled by the multi-electrode concept [10,41].

d. Absence of thermally induced necrosis - It has been summated that the short pulse lengths relative to the time between the pulses does prevent joule heating of the tissue. Thus, by design, no necrotic cell damage is to be expected with the exception of perhaps in association with very close proximity to the needle. In view of this, irreversible electroporation (IRE) does not have any typical short-term and long-term side-effects associated with necrosis [7,10,42].

e. Short treatment time – It has been iterated that a typical IRE treatment does tend to last less than 5 minutes and that this does not include the possibly complicated electrode placement which could require utilization of many electrodes and re-position of the electrodes during the procedure [10].

f. Real time monitoring – It has been stated that the IRE treatment volume could be to a certain degree be visualized, both during and pursuant to the IRE treatment. It has additionally been stated that possible radiology imaging visualization methods include: ultrasound scan, magnetic resonance imaging (MRI) scan, and computed tomography (CT) scan [10,41].

g. Immunological response – It has been stated that irreversible electroporation (IRE) does appear to provoke a stronger immunology response in comparison with other ablation methods [10,18] which is at the moment being studied for utilization in conjunction with cancer immunotherapy options [10,16].

Disadvantages of Irreversible Electroporation (IRE)

Strong muscle contractions – It has been documented that the strong electric fields that are created by Irreversible Electroporation (IRE), due to the direct stimulation of the neuromuscular junction, do cause strong muscle contractions that require special anesthesia and paralysis of the entire body [10,43].

a. Incomplete ablation within targeted tumours – It has been stated that the originally threshold for Irreversible electroporation (IRE) of cells was approximately 600 V/cm with 8 pulses, a pulse duration of 100 μs, as well as a frequency of 10 Hz. [10,11]. It has been stated that Qin and associates., subsequently discovered that even at 1,300 V/cm with 99 pulses, a pulse duration of 100 μs, and 10 Hz, there were still islands of viable tumour cells within the ablated zones [10,44]. This discovery has been stated to suggest that tumour tissue might respond differently to Irreversible Electroporation (IRE) in comparison with healthy parenchyma. The mechanism of cell death pursuant to Irreversible Electroporation (IRE) is stated to rely upon cellular apoptosis, which does emanate from pore formation within the cellular membrane. Tumour cells, that are known to be resistant to apoptotic pathways, could require higher thresholds of energy to be adequately treated. Nevertheless, the recurrence rates that was found in clinical studies do suggest a rather low recurrence rate and often superior overall survival rates in comparison with other ablation treatment options [10,45,46].

b. Local environment – It has been iterated that the electric fields of Irreversible Electroporation (IRE) tend to be strongly influenced by the conductivity of the local environment. [Wikipedia10] The presence of metal, for example with biliary stents, could emanate in variances in energy deposition. [Wikipedia 10] Various organs, including the kidneys, are also subject to irregular ablation zones, as a result of the increased conductivity of urine [10,47].

Utilization of Irreversible Electroporation in Medical Practice

A number of electrodes, in the form of long needles, tend to be placed encompassing the target volume. The point of penetration for the electrodes is chosen based upon the anatomical conditions [10]. Radiology imaging is important for the placement and this could be achieved by means of ultrasound scan, magnetic resonance imaging (MRI) scan or computed tomography (CT) scan [10]. The needles are then connected to the Irreversible Electroporation (IRE)-generator, which then does proceed to sequentially build up a potential difference between two electrodes. The geometry of the Irreversible Electroporation (IRE)-treatment field tends to be calculated in real time and it could be influenced by the user [10]. Depending upon the treatment-field and the number of electrodes that are utilized, the ablation tends to take between 1 minute and 10 minutes [10]. In general muscle relaxants tend to be administered, in view of the fact that even under general anesthesia, strong muscle contractions tend to be induced by excitation of the motor end-plate [10].

Typical parameters (1st generation IRE system):

The ensuing summations have been made regarding the typical parameters of 1st generation irreversible electroporation (IRE) system: [10]

- Number of pulses per treatment: 90
- Pulse length: 100μs
- Intermission between pulses: 100 to 1000ms
- Field strength: 1500 volt/cm

- Current: ca. 50 A (tissue- and geometry dependent)
- Max ablation volume using two electrodes: 4 × 3 × 2 cm^3

It has been iterated that the shortly pulsed, strong electrical fields tend to be induced via thin, sterile, disposable electrodes. [Wikipedia 10] The potential differences tend to be calculated as well as applied through a computer system between these electrodes in accordance to a previously planned treatment field [10].

One specific device that is utilized for the Irreversible Electroporation (IRE) procedure is the NanoKnife system which was manufactured by AngioDynamics, that received FDA 510k clearance on October 24, 2011 [48].

The NanoKnife system did also receive an Investigational Device Exemption (IDE) from the FDA which enables AngioDynamics to conduct clinical trials utilizing this device [48]. The Nanoknife system is said to transmit a low-energy direct current from a generator to electrode probes that inserted/placed within the target tissues for the surgical ablation of soft tissue [10]. It has been stated that in 2011, AngioDynamics apparently did receive an FDA warning letter for promoting the device for indications for which it had not received approval [10,49].

It has also been documented that in 2013, the United Kingdom National Institute for Health and Clinical Excellence (NICE) had issued a guidance that the safety and efficacy of utilization of irreversible electroporation (IRE) of the treatment of various types of cancer had not yet been established [10,50]. Current evidence related to the safety and efficacy of irreversible electroporation for treating primary lung cancer and metastases in the lung is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.

It has been iterated that newer generations of Electroporation-based ablation systems are being developed specifically in order to address the shortcomings of the first generation of Irreversible Electroporation (IRE); however, as of June 2020, none of the technologies were available as a medical device to be utilized. [10,38**,**51,52]

Clinical data

It has been iterated that potential organ systems, in which Irreversible Electroporation (IRE) could be of significant impact due to its properties include: the pancreas, the liver, the prostate gland.

Hepatic (liver) irreversible electroporation (IRE) is stated to appear to be safe, even when performed near vessels and bile ducts [10,53,54] with an overall complication rate of 16%, with majority of the complications being needle related (pneumothorax and hemorrhage). The COLDFIRE-2 trial which included 50 patients did show 76% local tumour progression-free survival after 1 year of follow-up [55]. However; no studies had been undertaken which hade compared Irreversible Electroporation (IRE) to other ablative treatment options; nevertheless; thermal ablations procedures had been reported to be associated with a higher efficacy in that matter with about 96% progression free survival. In view of this, Geboers et al. [45] did conclude that Irreversible Electroporation (IRE) should at the moment only be performed for only truly unresectable and tumours that are considered to be non-ablatable. It has been documented that the overall survival rates in studies related to utilization Irreversible Electroporation (IRE) for cancer of the pancreas do provide an encouraging non-variable end-point and do show an additive beneficial effect of Irreversible Electroporation (IRE) in comparison with the standard-of care chemotherapeutic treatment with FOLFIRINOX which entailed a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) (median OS, 12–14months) [56,57]. Nevertheless; Irreversible Electroporation (IRE) does appear to be more effective in conjunction with systemic therapy and it has not been suggested as first-line treatment option of choice [58]. It has additionally been iterated that even though Irreversible Electroporation (IRE) does make adjuvant tumour mass reduction treatment for LAPC possible for the first time, IRE does remain, in its current state, a high risk and high side effect associated treatment procedure which is justified only due to the high mortality and the lack of alternative treatments [10].

Prostate

It has been iterated that the concept of treating carcinoma of the prostate gland with utilization of Irreversible Electroporation (IRE) was first promulgated by Gary Onik and Boris Rubinsky in 2007 [10,59]. It has been iterated that Carcinomas of the prostate gland tend to be frequently found near sensitive structures which might be permanently damaged by thermal treatments or radiotherapy [10]. With regard to carcinomas of the prostate gland, it has been iterated that the applicability of surgical treatment methods has often been limited by accessibility and precision [10]. It has also been stated that surgery also tends to be associated with a long period of healing time and a high rate of side effects. [10,60].

It had been conjectured that with utilization of Irreversible Electroporation (IRE), the urethra, bladder, rectum and neurovascular bundle and lower urinary sphincter could potentially be included within the treatment field without creating permanent-damage [10].

It has been pointed out that Irreversible Electroporation (IRE) has been utilized for the treatment of carcinoma of the prostate gland since 2011, and that IRE treatment of carcinoma of the prostate gland has partly in been in the form of clinical trials, compassionate care or individualized treatment approach. [10] It has additionally been pointed out that like for all other ablation treatment options, and also most conventional methods of treatment of prostate cancer, no studies had utilized a randomized multi-centre approach or targeted cancer-specific mortality as end-point [10]. Other summating iterations that had been made regarding treatment of carcinoma including the use of IRE include the following:

- Cancer-specific mortality or overall survival had proven to be notoriously hard to assess for carcinoma of the prostate gland, in view of the fact that the treatment trials do need more than a decade and usually many treatment types tend to be undertaken during the years which does make treatment specific survival advantages difficult to quantify.
- In view of this, the results of ablation-based treatments and focal treatments in general usually utilize local tumour recurrences and functional outcome including quality of life as endpoint.
- In this regard, the clinical results that had been undertaken so far had demonstrated encouraging results and had uniformly stated IRE as a safe as well as effective treatment option at least for focal ablation; nevertheless, further studies are required.
- The largest cohort of treatment study which was reported by Guenther et al [61].

that was associated with up to 6-year follow-up has been limited as a heterogeneous retrospective analysis and no prospective clinical trial, was undertaken.

- Therefore, despite that many hospitals within Europe had been undertaking the IRE treatment method for prostate cancer for many years with one private clinic even listing more than one thousand treatments as of June 2020, [62].

IRE for carcinoma of the prostate gland is at the moment not recommended in treatment guidelines [10].

Kidney

While nephron-sparing surgery has been regarded as the gold standard treatment option for small, malignant renal masses, ablative treatment options are also regarded as viable options in patients who have been assessed and found to be poor surgical candidates to undergo nephron-sparing surgery. Radiofrequency ablation (RFA) of kidney lesions and cryoablation of kidney lesions have been utilized since the 1990s; nevertheless, in lesions that are found to be larger than 3 cm, the efficacy of RFA and cryotherapy of kidney lesions is said to be limited [10]. It has been iterated that the newer ablation options of treatment including: IRE, microwave ablation (MWA), as well as high-intensity focused ultrasound, could help overcome the challenges related to the size of the kidney tumour [10,63].

It has been stated that the first human studies that had been undertaken had proven the safety of IRE for the ablation of kidney masses; nevertheless, the effectiveness of IRE based upon histopathology examination features of an ablated kidney tumour in human beings is yet to be known or confirmed [10]. Wagstaff and associates., had set out to investigate the safety and effectiveness of IRE ablation of kidney tumour masses and to evaluate the efficacy of ablation with utilization of MIR and contrast-enhanced ultrasound imaging. It has been pointed out that in accordance with the prospective protocol that was designed by the authors, the treated patients would later on undergo radical nephrectomy in order to assess the success of IRE ablation [64]. It has been pointed out that later phase 2 prospective trials had demonstrated good results in terms of safety and feasibility [64,65] for small kidney tumour masses but the cohort was limited in numbers and these cohorts had included 7 patients and 10 patients respectively; In view of this, it has been iterated that the efficacy of IRE had not yet been established sufficiently [10]. It has additionally been stated that IRE does appear to be safe for small kidney masses that measure up to 4 cm [10]. Nevertheless; the consensus opinion is that current evidence on utilization of IRE to treat kidney tumour masses is still not adequate in quality and quantity for a consensus opinion to be established regarding the safety and efficacy of utilizing IRE to treat kidney tumour masses [45].

Lung

It has been iterated that in a prospective, single-arm, multi-centre, phase II clinical trial, the safety and efficacy of IRE upon lung cancers had been evaluated and that the trial had included patients who had primary and secondary lung malignancies as well as preserved pulmonary (lung) functions. It was reported that the expected effectiveness of IRE in the treatment of malignancies of the lung had not been met during interim analysis of the results and the trial had been stopped prematurely. It was also reported that the complications of IRE of the lung had included: pneumothorax in 11 out of 23 patients, alveolar hemorrhage not resulting in significant haemoptysis, and needle tract seeding was found in 3 cases that amounted to 13% of the cases. Disease progression was noticed in 14 out of the 23 patients that amounted to 61% of the patients. Stable disease was observed in 1 patient which amounted 4% of the patients, partial remission of the tumour was observed in 1 patient which amounted to 4% of the patients and complete remission was found in 7 patients which amounted to 30% of the patients. The authors did conclude that IRE is not effective for the treatment of lung cancers/malignancies [66].

Likewise, some authors reported that they had found similarly poor treatment outcomes in their studies [67,68].

It has been pointed out that a major obstacle of IRE in the treatment of lung lesions is the difficulty in positioning of the electrodes; placing the probes in parallel alignment is made challenging by the interposition of ribs. Furthermore, the planned and actual ablation zones within the lung tend to be dramatically different because of the differences in conductivity between the tumour, lung parenchyma, as well as air [10,69].

Coronary arteries

It has been iterated that Maor and associates had illustrated the safety and efficiency of IRE as an ablation option of treatment for smooth muscle cells within the walls of large vessels in rat model [70].

In view of this IRE has been postulated as representing a preventive treatment for coronary artery re-stenosis pursuant to percutaneous coronary intervention procedure [10].

Pulmonary veins

It has been pointed out that many studies on animals had illustrated the safety and efficiency of IRE as a non-thermal ablation option of treatment for pulmonary veins with regard to the treatment of atrial fibrillation [10]. The advantages of IREs' in comparison with radiofrequency ablation (RFA) and cryoablation do include: Well defined ablation area and the lack of peripheral thermal damage. In view of this, IRE has been promulgated as a part of novel option of treatment for atrial fibrillation (AF) [10,71].

Other organs

It has furthermore been iterated that IRE had also been investigated within ex-vivo human eye models for the treatment of uveal melanoma [10,72], as well as in thyroid cancer [10,73].

It has been pointed out that successful IRE ablations in animal tumour models had been undertaken for lung, [10,74,75] brain, [10,74,76,77], heart, [10,78] skin, [10,79,80] bone, [10,81,82] head and neck cancer [10,83], as well as blood vessels. [10,84]

[B] Miscellaneous studies on Irreversible electroporation of various organs in animals

Rubinsky et al. [11] made the following summations related irreversible electroporation:

- Irreversible electroporation (IRE) is a new tissue ablation technique in which micro to millisecond electrical pulses tend to be delivered to undesirable tissue in order to produce cell necrosis via irreversible cell membrane permeabilization.
- IRE does affect only the cell membrane and no other structure within the tissue.

Rubinsky et al. [11] undertook a study which was aimed to study their IRE tissue ablation methodology in the pig liver, to provide first experience results on long term histopathology of IRE ablated tissue, as well as to discuss the clinical implications of the findings. The study consisted of the following: a) the designing of an IRE ablation protocol via a mathematical analysis of the electrical field during electroporation; b) utilization of ultrasound scan to position the electroporation electrodes within the predetermined locations and subsequently to monitor the process; c) application of the predetermined electroporation pulses; d) the undertaking of histopathology examination on the IRE treated samples for up to two weeks pursuant to the procedure; and e) correlation of the mathematical analysis, ultrasound scan data, and histology. Rubinsky et al. [11] observed that electroporation does affect tissue in a way that could be imaged in real time with ultrasound scan, which should facilitate real time control of the electroporation during clinical applications. Rubinsky et al. [11] observed cell ablation to the margin of the treated lesion with several cells thickness resolution. There did appear to be complete ablation to the margin of blood vessels without compromising the functionality of the blood vessels, which had indicated that IRE is a promising method for the treatment of tumours that are near blood vessels which has been a significant challenge with current ablation methods. Consistent with the mechanism of action of IRE on the cell membrane only, Rubinsky et al. [11] demonstrated that the structure of bile ducts, blood vessels, and connective tissues had remained intact with IRE. Rubinsky et al. [11] stated the following:

- They had reported extremely rapid resolution of lesions, within two weeks, which was consistent with retention of vasculature.
- They had also documented tentative evidence for an immunological response to the ablated tissue.
- They had lastly demonstrated that mathematical predictions with the Laplace equation could be utilized in treatment planning.
- The IRE tissue ablation technique, as characterized in their report, might become an important new tool in the surgeon's armamentarium.

Au et al. [85] stated that Irreversible electroporation (IRE) is a new ablation technique which tends to induce permanent membrane permeability and cell death and that they were interested in ultrasound B-mode and elastography in order to monitor IRE ablation within the liver. With regard to methods, Au et al. [85] reported that Yorkshire pigs had undergone IRE ablation of the liver and they were imaged with ultrasound B-mode and elastography. Histopathology evaluation of cell death by triphenyltetrazolium chloride and haematoxylin and eosin staining was undertaken. Au et al. [85] summarized the results as follows:

- Elastography demonstrated that liver that is ablated by IRE had exhibited increased tissue stiffness with a peak strain ratio of 2.22.
- The IRE lesion did have a discrete border without bubble artifact, and the size of the lesion size significantly correlated with area of cell death upon histology examination of the specimen.
- IRE ablation was not affected by presence of large blood vessels or bile ducts.

Au et al. [85] made the following conclusions:

- IRE ablation had led to increased tissue stiffness which was detectable by elastography and which was indicative of cell death.
- Elastography could complement B-mode ultrasonography to monitor IRE ablation of the liver.

Lee et al. [86] evaluated the effectiveness of irreversible electroporation (IRE) in hepatic (liver) tissue ablation and the radiology-pathology correlation of IRE-induced cell death. With regard to the materials and methods of their study, Lee et al. [86] reported that pursuant to an approval of the animal research committee, 16 Yorkshire pigs had undergone ultrasonography (US)-guided IRE of normal liver. A total of 55 ablation zones were created, that were imaged with US, magnetic resonance (MR) imaging, and computed tomography (CT) and evaluated with immunohistochemical analysis of the tissues were undertaken, including haematoxylin-eosin (H-E), Von Kossa, and von Willibrand factor (vWF) staining as well as terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Lee et aal. [86] summarized the results as follows:

- During macroscopy section examination of the specimens, the mean diameter of the ablation zones was 33.5 mm + or - 3.0 (standard deviation) and this was achieved in 6.9 minutes (mean total procedure time per ablation), with a mean difference of 2.5 mm + or - 3.6 between US and gross section measurements (r = 0.804).
- No complications were observed in any of the 16 animals.
- The IRE ablation zones were well characterized with based upon US, CT, and MR radiology imaging, and real-time monitoring was feasible with US. H-E, Von Kossa, and vWF staining which demonstrated complete cell death, with a sharply demarcated treatment area.
- The bile ducts and vessels had been completely preserved.
- Areas of complete cell death had exhibited positive staining for apoptotic markers (TUNEL, BCL-2 oncoprotein), which had suggested involvement of the apoptotic process in the pathophysiology of cell death that was caused by IRE.

Lee et al. [86] made the ensuing conclusions:

- In an animal model, IRE treatment did prove to be a fast, safe, and potent ablative method, which had caused complete tissue death by means of apoptosis.
- Cell death was demonstrated with full preservation of the peri-ablative zone structures, that included blood vessels, bile ducts, and neighbouring nonablated tissues.

Duuki-Jacobs et al. [87] stated that Irreversible electroporation (IRE) is a new technique for tumour cell ablation which had been reported to involve non-thermal-based energy utilizing high voltage at short microsecond pulse lengths. They also stated that In vivo assessment of the thermal energy generated during IRE had not been undertaken and that Thermal injury could be predicted utilizing a critical temperature model. The aim of their study was to assess the potential for thermal injury during IRE in an in vivo porcine model. With regard to the methods, Duuki-Jacobs et al. [87] reported the following: In vivo continuous temperature assessments of 86 different IRE procedures were undertaken on porcine liver, pancreas, kidney and retroperitoneal tissue. They measured issue temperature continuously throughout IRE procedure by means of two thermocouples that were placed at set distances of 0·5 cm or less, and 1 cm from the IRE probes within the treatment field. They defined thermal injury as a tissue temperature of 54°C that lasted at least 10 seconds. They evaluated tissue type, pulse length, probe exposure length, number of probes and retreatment for associations with thermal injury. Additionally, IRE ablation was undertaken with metal clips or metal stents in the ablation field in order to determine their effect upon thermal injury. Duuki-Jacobs et al. [87] summarized the results as follows:

- They had generated an increase in tissue temperature above the animals' baseline temperature (median 36·0°C) during IRE in all tissues that were studied, with the greatest increase found at the thermocouple placed within 0·5 cm in all instances.
- Upon univariable and multivariable analysis, ablation in kidney tissue with a maximum temperature of 62·8°C, ablation with a pulse length setting of 100 µs with a maximum temperature of 54·7°C, probe exposure of at least 3·0 cm with a maximum temperature of 52·0°C, and ablation with metal within the ablation field with a maximum temperature of 65·3°C were all associated with a significant risk of thermal injury.

Duuki-Jacobs et al. [87] made the following conclusions:

- IRE could generate thermal energy, as well as even thermal injury, based upon the type of tissue, probe exposure lengths, pulse lengths and proximity to metal.
- Awareness of the placement of the probe regarding proximity to critical structures as well as probe exposure length and pulse length are required to ensure safety and prevent thermal injury.
- A probe exposure of 2·5 cm or less for liver IRE, and 1·5 cm or less for pancreas, with maximum pulse length of 90 µs would

result in safe and non-thermal energy delivery with spacing of 1·5-2·3 cm between probe pairs.

Sugimoto et al. [88] undertook a study **t**o assess various ultrasound (US) scan findings, including B-mode, shear-wave elastography (SWE), and contrast-enhanced US, in accurately assessing ablation margins pursuant to irreversible electroporation (IRE) based upon radiology-pathology examination feature correlation, and to compare these findings between IRE and radiofrequency (RF) ablation. With regard to the materials and methods of their study, Sugimoto et al. [88] reported that IRE was undertaken on nine (9) and radiofrequency ablation (RF ablation) on three (3) in vivo in three pig livers. Each ablation zone was imaged radiologically by each method immediately after the procedure and 90 minutes subsequently. They evaluated the ablation zones based upon gross pathological and histopathology findings within samples that were obtained from the animals that were euthanized 2 hours pursuant to the last ablation. They compared the characteristics and dimensions of the histologically ablation zones were qualitatively and quantitatively against each US finding. Sugimoto et al. [88] summarized the results as follows:

- In B-mode US at 90 minutes pursuant to the IRE, the ablation zones had appeared as hyperechoic areas with a peripheral hyperechoic rim, which showed excellent correlation ($r(2) = 0.905$, $P < .0001$) with the gross pathology examination findings.
- SWE demonstrated that tissue stiffness in the IRE ablation zones had increased over time.
- Contrast-enhanced US demonstrated the IRE ablation zones as hypo-vascular areas within the portal phase, and had shown the highest correlation [$r(2)=0.923$, $P< .0001$] with gross pathology examination findings.
- The RF ablation zones were clearly demonstrated by B-mode US.
- SWE did show that tissue stiffness pursuant to RF ablation was higher in comparison with pursuant to IRE.
- Contrast-enhanced US demonstrated RF ablation zones as avascular areas.

Sugimoto et al. [88] concluded that RE and RF ablation zones could be most accurately predicted by portal-phase contrast-enhanced US measurements which has been obtained immediately after the ablation.

Appelbaum et al. [89] undertook a study in order to characterize ultrasonographic (US) findings pursuant to irreversible electroporation (IRE) in order to determine the utility of these findings in the accurate assessment of ablation margins. With regard to the materials and methods of their study, Sugimoto et al. [89] stated the following: Their institutional animal care and use committee approval of the study was obtained. IRE ablation totalling 58) was performed in vivo in 16 pig livers by utilizing two 18-gauge electroporation electrodes with 2-cm tip exposure, 1.5- or 2.0-cm interelectrode spacing, and an electroporation generator. Energy deposition was applied at 2250-3000 V (pulse length, 50-100 µsec; pulse repetition, 50-100). Ablations were undertaken under the guidance of ultrasound (US) scan. Images had been obtained during ablation and at defined intervals from 1 minute to 2 hours pursuant to the procedure. Zones of ablation were examined during Macroscopic and histopathology examination of samples that had been obtained from the animals which had been sacrificed 2 hours to 3 hours following the IRE procedures. The dimensions of the histopathology necrosis zone and ultrasound (US) findings were compared and subjected to statistical analysis, with the inclusion of a "Student" t-test and multiple linear regression.

Appelbaum et al. [89] summarized the results as follows:

- Within 20-50 pulse repetitions of IRE energy, the ablation zone had appeared as a hypo-echoic area with well-demarcated margins.
- During the next 8 minutes to 15 minutes, this zone decreased in size from 3.4 cm ± 0.5 to 2.5 cm ± 0.4 and it became progressively more iso-echoic.
- Subsequently, a peripheral hyper-echoic rim that measured 2 mm to 7 mm, with a mean of 4 mm ± 1mm encompassing the isoechoic zone had developed 25 minutes to 90 minutes, with a mean of 41 minutes ± 19 minutes following the IRE.
- The final length of the treatment zone, including the rim, increased to 3.3 cm ± 0.6.
- The final dimensions of the outer margin of this rim had provided greatest accuracy (1.7 mm ± 0.2) and tightest correlation [$r(2) = 0.89$] with macroscopic (gross) pathology examination findings.
- Histopathology examination demonstrated widened sinusoidal spaces which had progressively filled with spatially distributed haemorrhagic infiltrate upon a bed of hepatocytes with pyknotic nuclei throughout the treatment zone.

Appelbaum et al. [89] made the following conclusions:

- Ultra-sound (US) scan findings in the acute period following IRE are dynamic and they evolve.
- The ablation zone could be best predicted by measurement of the external hyper-echoic rim that forms 90 minutes to 120 minutes pursuant to the ablation. This rim is possibly attributable to evolving haemorrhagic infiltration via widened sinusoids.

Appelbaum et al. [90] undertook a study to prospectively ascertain the optimal parameters with which to achieve defined large target zones of coagulation by utilizing irreversible electroporation (IRE) with four-electrode arrays and the time that is needed to achieve this treatment effect in an in vivo animal model. With regard to the materials and methods, Appelbaum et al. [90] reported the following:

- Their study was approved by the animal care and use committee.
- Ultrasonography (US)-guided IRE ablation that totalled 90 was undertaken in vivo in 69 pig livers with an array of four electrodes (18 gauge) and an electroporation generator.
- Cardiac-gated 100-µsec IRE pulses had been applied sequentially between the six sets of electrode pairs at 2250-3000 V.
- Multiple algorithms of energy deposition and electrode configuration had been studied, which included interelectrode spacing (1.5-2.5 cm), number of IRE pulses applied consecutively to each electrode pair (10, 20, 50, and 100), and number of times per cycle each electrode pair was activated (one to 10).
- They measured the resultant zones of treatment with ultrasound (US) scan 1.5 hours to 3 hours following the IRE and this was confirmed at macroscopic (gross) and histopathology examination.
- They compared data and ablation times in order to ascertain the optimal algorithms with which to achieve 4-7-cm areas of treatment effect in the shortest time possible.

- Additionally, the IRE current that was applied was correlated with the ablation size.
- They analysed the data by utilising analysis of variance with multiple comparisons, t tests, or nonparametric statistics.

Appelbaum et al. [90] summarized the results as follows:

- For 2.5-cm spacing, the ablation diameter was increased by increasing either the overall time of energy application or the number of cycles of 20 pulses ($P < .01$ for both).
- The application of IRE of less than four cycles (or continuous IRE application of 100 pulses) did not emanate in contiguous ablation.
- Nevertheless, sequentially increasing the number of cycles of IRE from four to 10 increased both the electrical current that was applied (from 14.4 A ± 0.4 to 17.6 A ± 0.7, $P = .0004$) and ablation diameter (from 5.6 cm ± 0.3 to 6.6 cm ± 0.3, $P = .001$).
- Even though division of application into cycles had not altered the coagulation at 2.0- and 1.5-cm spacing, application of energy to diagonal electrode pairs had increased the coagulation. Hence, one 100-pulse cycle (11.0 minutes ± 1.4) did produce 4.8 cm ± 0.3 of ablation for 2.0-cm spacing with diagonal pairs but only 4.1 cm ± 0.3 of ablation without diagonal pairs (7.5 minutes ± 1.0, $P < .03$ for both).

Appelbaum et al. [90] made the ensuing conclusions:

- With four-electrode arrays, IRE could create large contiguous zones of treatment effect within clinically acceptable ablation times; the parameters could be tailored in order to achieve a wide range of ablation sizes.
- Cyclical deposition of IRE application is beneficial, especially, for larger inter-probe spacing, most likely as a result of alterations of electrical conductivity which occur pursuant to successive applications of IRE energy.

Faroja et al. [91] undertook a study in order to ascertain whether high-dose irreversible electroporation (IRE) ablation does induce thermal effects in normal liver tissue. With regard to materials and methods, Faroja et al. [91] stated the following: They had obtained animal care and use committee approval was preceding their experiments. IRE ablation that totalled 78 was undertaken by a single four-person team in vivo in 22 porcine livers by through the application of electric current to two 1.3-cm-diameter circular flat-plate electrodes that were spaced 1 cm apart. Cardiac-gated IRE pulses that ranged between 40 and 360 were systematically applied at varying voltages betwenn1500 volts and 2900 volts. They measured End temperatures at the ablation zone centre which were correlated with ablation time, energy parameters, and resultant treatment effect as was determined at macroscopic (gross) pathology and histopathology examination. Faroja et al. [91] then monitored temperatures at the centre as well as the periphery of four ablations that were created by the use of a four-electrode IRE array (3000 V, 90 pulses per electrode pair). Faroja et al. [91] analysed the data by utilising multivariate analysis of variance with multiple comparisons and/or paired t tests and regression analysis, as appropriate. Faroja et al. [91] summarised the results as follows:

- Temperature rose above the 34°C baseline following the IRE in all flat-plate experiments and this correlated linearly ($R (2) = 0.39$) with IRE "energy dose" (product of voltage and number of pulses) as well as more tightly in univariate analysis with both voltage and number of pulses.
- Hence, the mean temperatures as high as 86°C ± 3 (standard deviation) were noted for 2500 V and 270 pulses.
- Ablations of 90 pulses or higher at 2500 V did produce temperatures of 50°C or higher and classic macroscopic (gross) and histopathology findings of thermal coagulation (pyknotic nuclei and streaming cytoplasm).
- With regard to lower IRE doses (ie, 2100 V, 90 pulses), the temperatures had remained below 45°C, and it was only IRE-associated pathology findings, for example, swollen sinusoids, dehydrated cells, and haemorrhagic infiltrate were visualised.
- For the four-electrode arrays, the temperatures had measured 54.2°C ± 6.1 at the electrode surfaces and 38.6°C ± 3.2 within the ablation zone margin.

Faroja et al. [91] made the ensuing conclusions:

- In some conditions of high intensity, IRE could produce sufficient heating in order to induce "white zone" thermal coagulation.
- While this could be useful in some settings to increase destruction of tumour, additional characterization of the thermal profile which is created with clinical electrodes and energy parameters would therefore be required in order to better comprehend the best ways to avoid unintended damage when ablating near thermally sensitive critical structures.

Wagstaff et al. [92] stated that even though tissue ablation by irreversible electroporation (IRE) had been characterized as nonthermal, the application of frequent repetitive high-intensity electric pulses does have the potential of substantially heating the targeted tissue and causing thermal damage. Wagstaff et al. [92] undertook a study to evaluate the risk of possible thermal damage by measuring temperature development and distribution during IRE of porcine kidney tissue. With regard to the methods of the study, Wagstaff et al. [92] stated the following: The animal procedures were conducted after obtaining an approved Institutional Animal Ethics Committee protocol. IRE ablation was undertaken in 8 porcine kidneys. Out of them, 4 kidneys were treated with the use of a 3-needle configuration and the remaining 4 were treated with a 4-needle configuration. All IRE ablations had consisted of 70 pulses with a length 90 µs. The pulse frequency was set at 90 pulses/min, and the pulse intensity at 1,500 V/cm with a spacing of 15 mm between the needles. They measured the temperature internally utilising 4 fiber-optic temperature probes and at the surface by using a thermal camera. Wagstaff et al. [92] summarised the results of the study as follows:

- They had measured for the 3-needle configuration, a peak temperature of 57°C (mean = 49 ± 10°C, n = 3) within the core of the ablation zone and 40°C (mean = 36 ± 3°C, n = 3) at 1cm outside of the ablation zone, from a baseline temperature of 33 ± 1°C.
- They had measured for the 4-needle configuration, a peak temperature of 79°C (mean = 62 ± 16°C, n = 3) within the core of the ablation zone and 42°C (mean = 39 ± 3°C, n = 3) at 1cm outside of the ablation zone, from a baseline of 35 ± 1°C.
- The thermal camera had recorded the peak surface temperatures within the centre of the ablation zone, reaching 31°C and 35°C for the 3- and 4-needle configuration IRE (baseline 22°C).

Wagstaff et al. [92] made the following conclusions:

- The application of repetitive high-intensity electric pulses during the process of IRE ablation in porcine kidney does cause lethal rise in temperature within the ablation zone.

- Temperature monitoring should be considered when undertaking IRE ablation near vital structures.

Agnass et al. [93] undertook a study which was aimed first to ascertain whether irreversible electroporation (IRE) is associated with heat generation in the liver and pancreas at clinical (≤1,500 V/cm) and supra-clinical (>1,500 V/cm) electroporation settings; second, and secondly to assess the risk of thermal tissue damage within and adjacent to the treated volume in highly perfused versus moderately perfused parts of both organs; as well as thirdly, to investigate the influence of perfusion and of the presence and the orientation of a metal stent on the maximal thermal elevation ($\Delta T_{Session,max}$) within the tissue during an IRE session at fixed IRE settings, and finally, to ascertain whether the maximum temperature elevation within the IRE-subjected organ during an IRE treatment (single or multiple sessions) is reflected in the organ's surface temperature. With regard to the methods of the study, Agnass et al. [93] stated the following: The aims had been investigated in 12 case studies which were undertaken in five female Landrace pigs. Many IRE settings had been applied for lateral (2), triangular (3), and rectangular (4) electrode configurations within the liver hilum, liver periphery, pancreas head, and pancreas tail. IRE series of 10-90 pulses had been applied with pulse durations which had varied from 70 µs to 90 µs and electric field strengths between 1,200 V/cm and 3,000 V/cm. In select cases, a metal stent was positioned in the bile duct at the level of the liver hilum. They measured temperatures before, during, and following the IRE in and adjacent to the treatment volumes using fibre optical temperature probes (temperature at the nucleation centres) and digital thermography (surface temperature). They assumed the occurrence of thermal damage to be at temperatures above 50 °C ($\Delta T_{Session,max} \geq 13$ °C relative to body temperature of 37 °C). They compared the temperature fluctuations at the organ surface ($\Delta T_{LocSurf}$) to the maximum temperature elevation during an IRE treatment procedure in the electroporation zone. In select cases, they applied IRE to tissue volumes surrounding the portal vein (PV) and a constricted and patent superior mesenteric vein (SMV) in order to ascertain the influence of the heatsink effect of PV and SMV on $\Delta T_{Session,max}$. Agnass et al. [93] summarised the results as follows:

- The median baseline temperature was 31.6 °C-36.3 °C. $\Delta T_{Session,max}$ which had ranged from -1.7 °C to 25.5 °C in moderately perfused parts of the liver and pancreas, and from 0.0 °C to 5.8 °C in highly perfused parts.
- The median $\Delta T_{LocSurf}$ of the liver and pancreas was found to be 1.0 °C and 10.3 °C, respectively.
- Constricting the SMV within the pancreas head yielded a 0.8 °C higher $\Delta T_{Session,max}$.
- The presence of a metal stent within the liver hilum resulted in a $\Delta T_{Session,max}$ of 19.8 °C.
- Stents that were parallel to the electrodes caused a $\Delta T_{Session,max}$ difference of 4.2 °C relative to the perpendicular orientation.

Agnass et al. [93] advised that appropriate IRE settings should be chosen based upon the tissue type and the presence of stents in order to avoid thermal damage within healthy peritumoral tissue and in order to protect anatomical structures. Agnass et al. [93] made the ensuing conclusions:

- Depending upon the IRE settings and tissue type, IRE has the capability of inducing considerable heating within the liver and pancreas which is sufficient to cause thermal tissue damage.
- More significant temperature elevations tend to be positively correlated with increasing number of electrode pairs, electric field strength, and pulse number.
- Temperature elevations could be further exacerbated by the presence and orientation of metal stents.
- Temperature elevations within the nucleation centres tend not always to be reflected in the organ's surface temperature.
- Heat sink effects that are caused by large vessels were minimal in some instances, possibly due to reduced blood flow which had been caused by anaesthesia.

Discussion

[C] Miscellaneous Narrations and Discussions Related to Some Case Reports, Case Series, And Studies Related to Irreversible Electroporation of Prostate Cancer.

Dong et al. [94] undertook clinical trials after they had obtained patients' consent and approval from the Shanghai Changhai Hospital Ethics Committee (CHEC2017-075) and Good Clinical Practices. Dong et al. [94] reported that forty patients had received therapeutic HF bipolar pulses, and their ages had ranged between 51 years and 85 years. The patients underwent treatment within Shanghai Changhai Hospital in Shanghai, China. Significantly elevated serum prostate-specific antigen level was detected in patients, and the patients then underwent multiparametric MRI to identify the suspected tumours within their prostate glands; the maximum size of the tumour in all of the patients ranged between 1 cm and 3 cm. The patients' treatment information has been illustrated in Table 1. A prostate needle biopsy was undertaken preceding the IRE procedure in order to illustrate the clinical significance of prostate cancer through histopathology examination of the specimens.

No	Number of Electrodes	Maximum Size of Tumour, cm	Number of Patients	Patients Age	Treatment Time, min
1	2	<1	3	64, 76, 79	<8
2	3	1.0-1.5	13	81, 71, 59, 71, 82, 74, 69, 59, 79, 67, 51, 58, 63	<20
3	4	1.5-2.0	10	76, 68, 73, 57, 65, 81, 84, 85, 73, 78	<30
4	5	2.0-2.5	8	68, 51, 65, 74, 68, 76, 82, 75	<40
5	6	2.5-3.0	6	75, 66, 75, 64, 72, 77	<45

Table 1: *The Patients Treatment Information*

Reproduced from: [94] Dong S, Wang H, Zhao Y, Sun Y, Yao C. First Human Trial of High-Frequency Irreversible Electroporation Therapy for Prostate Cancer. Technol Cancer Res. Treat. 2018 July 25; 17: 1533033918789692 PMCID: PMC6071159 PMID: 30045668 Doi: 10.1177/1533033818789692
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6071159/

Therapeutic Equipment

A composite steep pulse therapeutic apparatus was utilized in order to generate HF bipolar pulses, as illustrated in Figure 1A. The apparatus could produce bursts of HF bipolar pulses, constituting of individual pulses of duration which had ranged between 1 micro-seconds and 100 microseconds; the inter-burst delay was 1 second, and the rise time was less than 100 nanoseconds. The schematic of bipolar HF pulse bursts applied in the study has been illustrated in Figure 1B.

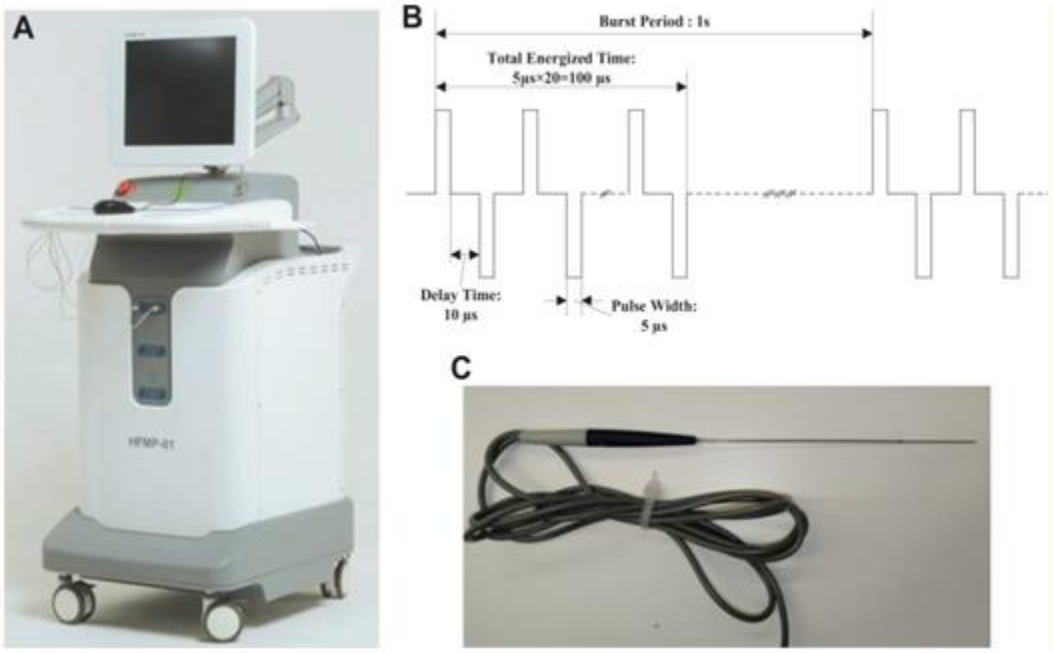

Figure 1: *The picture of (A) composite steep pulse therapeutic apparatus and (b) the schematic of HF bipolar pulses. (C) Electrodes. HF indicates high frequency.*

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6071159/

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In each trial, 2 to 6 needle electrodes had been inserted into the tumour region, and the distance between 2 electrodes was less than 2 cm. The diameter of the electrodes was 1 mm, and the exposure length was set to 1.0 to 3.0 cm (see figure 1B), depending upon the size of the tumour.

The Procedure

The patients were positioned in the dorsal lithotomy position and they were operated under aseptic conditions and under general anaesthesia. In order to provide a lower concentration of muscle relaxant to the patients, a muscle relaxant (cisatracurium besylate) at a dose of only 0.001 mg/ kg·min was injected, which was lower than the dose that is utilized during a conventional surgery (0.0015 mg/kg·min).

The therapeutic electrodes were then punctured transperineally at the margin of the cancer lesion under trans-rectal ultrasound scan-guidance, and the space between electrodes was measured utilizing the ultra-sound scan images.

High-frequency bipolar pulses were administered following determination of the position of the needle electrodes. The burst of HF bipolar pulses, which consisted of 20 pulses each of 5 microseconds, had a total energized time of 100 microseconds, with a 10-μs delay time between the positive and the negative pulses. The schematic of HF bipolar pulses is illustrated in Figure 1C. The initial voltage-to-distance ratio applied which was 1500 V/cm between the pairs of electrodes. The voltage was adjusted during the trial in order to avoid a very large pulse current greater than 40 A. Pulses were administered at a repetition rate of 1 burst/second in sets of 50 pulses, following a 10-second delay so as to avoid an increase in temperature within the tissues; the cycle was repeated for a total number of 250 bursts which were administered between each pair of electrodes. The electrodes were removed pursuant to the treatment, and the patient was catheterized through the urethra before the patient recovered from the anaesthesia.

The Therapeutic Effect Evaluation

Four weeks pursuant to the treatment, magnetic resonance imaging (MRI) scan was utilized to estimate the ablation area. Furthermore, the position of the electrodes in MRI scan image, which would be utilized to analyse the electric field threshold of ablation, was ascertained by matching the MRI scan image and the ultrasound scan image with the location of electrodes.

The efficacy of ablation at the cellular level was analysed in 8 patients who had undergone complete resection of the prostate gland after 4 weeks based upon voluntary principles. These prostate specimens were sectioned and processed for histopathology examination utilizing haematoxylin and eosin staining. Colour images of each tissue section were acquired utilizing the Aperio LV1 Digital Pathology Slide Scanner (Leica Biosystems Inc, Buffalo Grove, Illinois).

Numerical Simulations

The authors stated that it was difficult to reconstruct an accurate 3D model in view of the fact that only low-resolution MRI slices were acquired. Hence, a 2D finite element model of the prostate tissue was established utilizing COMSOL Multiphysics software (version 4.2a; COMSOL Inc, Burlington, Massachusetts). As has been illustrated in Figure 2, the ellipse does illustrate the prostate and the 3 small circles do depict the electrodes. The diameter of the needle electrode was set at 1 mm, and the electrode spacing was set according to the measured distance within the ultrasound scan image. The tumours were not considered in the model in view of the fact that the dielectric parameters of prostate cancer were not clear when HF bipolar pulses were applied.

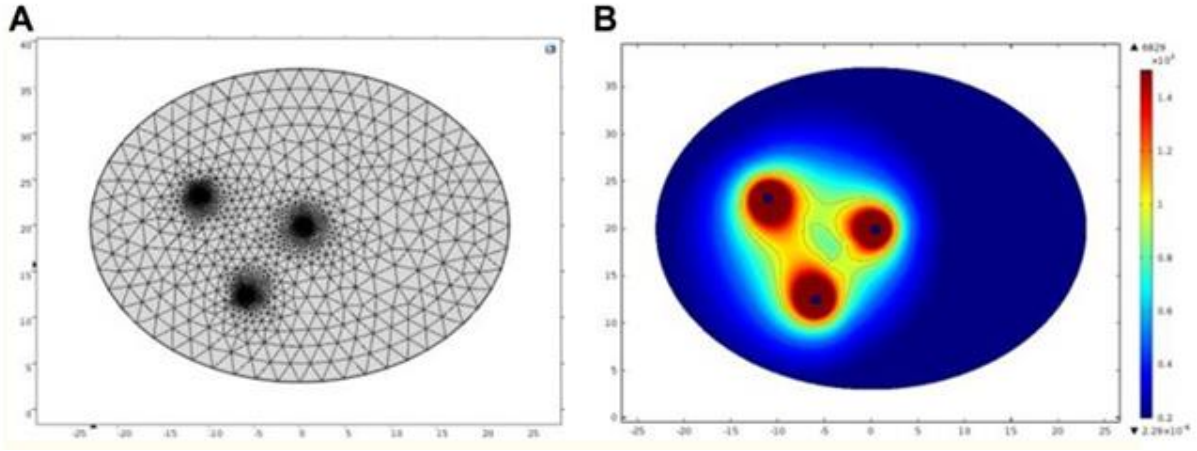

Figure 2: *Mesh model and simulation result with 3 electrodes Mesh model and simulation result with 3 electrodes. The coordinate unit is mm. The field intensity unit is V/cm. (A) Mesh model. (B). Electric field intensity simulation.*

Reproduced from: [94] Dong S, Wang H, Zhao Y, Sun Y, Yao C. First Human Trial of High-Frequency Irreversible Electroporation Therapy for Prostate Cancer. Technol Cancer Res. Treat. 2018 July 25; 17: 1533033918789692 PMCID: PMC6071159 PMID: 30045668 Doi: 10.1177/1533033818789692 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6071159/

The electric field distribution in the biological tissue was stated to be closely related to the electrical conductivity and permittivity. The electrical conductivity and permittivity changes during the process of electroporation, but the dynamic response of tissue to HF bipolar pulses had been poorly researched; hence, in the study, the static model was utilized for an initial analysis. The fundamental frequency of the burst in the study was 33.3 kHz, and the corresponding permittivity and conductivity of the prostate tissues, which could be observed from the (reference 22) were 7162.9 and 0.43292 S/m, respectively.

The Laplace equation was utilized to solve the electric field distribution within the tissue region. Within the solution domain, the electric current module was utilized to solve the following equations:

$$\nabla \cdot J = Q[Am3], \text{----------1}$$

$$J = (\sigma + \epsilon 0 \epsilon r \partial\partial t)\, E[Am2], \text{----------2}$$

$$E = -\nabla U[Vm], \text{----------3}$$

where U represents the electric potential, E represents the electric field, J represents the current density, Q represents the current source, σ represents the conductivity, ϵ_r represents the relative permittivity, and ϵ_0 represents the permittivity of free space. The boundaries encompassing 1 electrode were assigned a constant electrical potential:

$$U = U[V]. \text{----------4}$$

The boundaries of the other electrode were assigned as a relative ground:

$$U = 0[V]. \text{----------5}$$

The remaining boundaries were defined as electrical insulation:

$$n \cdot J = 0[Am], \text{----------6}$$

where n represents the normal vector to the surface and J represents the electrical current density.

The electric field distribution with iso-contours could be computed utilizing COMSOL software through electric field simulation. The electric field lethality threshold could be determined preliminarily by comparing the calculated electric field intensity contours and the ablation zone in MRI section as well as finding the electric field intensity closest to the ablation boundary.

Results

Dong et al. [94] summarized the results as follows:

- The number of electrodes that were utilized in the clinical trial was 2 to 6 as has been illustrated in Table 1.
- The treatment time for each patient lasted less than45 minutes, and there were no abnormalities encountered during the pulse delivery process.
- The patients' physiological indexes were monitored during treatment and these included: the heart rate, blood oxygen level, and respiration rate, and all these parameters were found to be within the normal range.
- Low-dose muscle relaxants were injected prior to the treatment; therefore, muscle contractions had not occurred during the process of treatment. This is important because any major movements that generated by the patients could potentially damage the nearby structures as a result of the movement of electrodes.
- Pursuant to the treatment, the patients felt well and they could move around after about 10 hours.
- All of the patients were discharged from the hospital on the next day after their treatments, and none of the patients had required any further hospitalization.
- After 4 weeks, the lesions were clearly visible within their MRI scans.
- As illustrated in Figure 3, the areas encompassed by the red curve, namely, the darker regions, represent the ablation areas. The areas encompassed by the blue curves are the prostate. In some of the cases, the electrode needles were positioned very close to the capsule of the prostate gland, but MRI scans demonstrated that the HF bipolar pulses had not damaged the prostate capsule. Figure 3 also demonstrated that the capsule of the prostate gland was intact, which could inhibit the metastasis of prostate cancer cells.

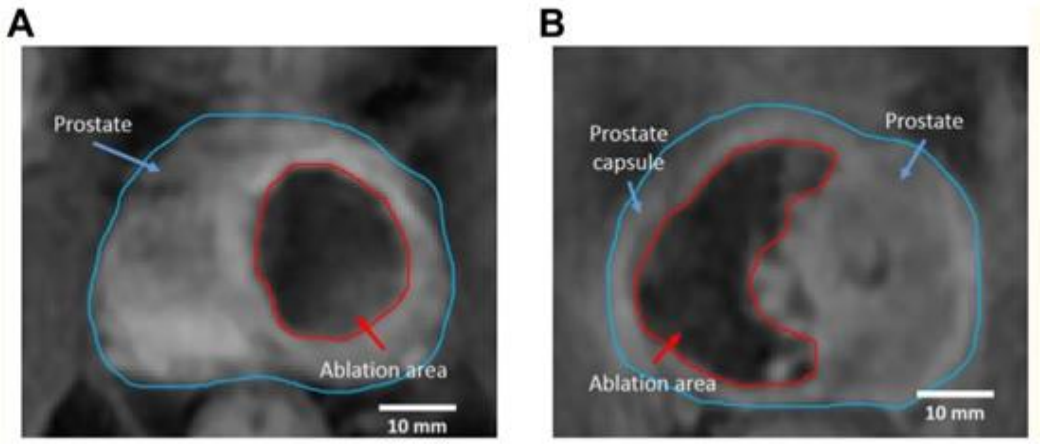

Figure 3: *In MRI scans, lesions were clearly visible and the prostate capsule was noted to be intact. The area surrounded by the red curve is the ablation area, and the area surrounded by the blue curve is the prostate. (A) MRI of one patient before treatment. (B) MRI of another patient before treatment. MRI indicates magnetic resonance imaging.*

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The location of prostate cancer was determined utilizing MRI scan preceding the treatment (see figure 4A). The therapeutic electrodes were then punctured transperineally at the margin of the cancer lesion under trans-rectal ultrasound scan-guidance (see Figure 4B). The authors pointed out that by comparing MRI scan images with ultrasound scan images facilitated the determination of the positions of the electrodes positions in MRI scans as has been demonstrated in figure 4C. The electrode needles were all positioned within the ablation area, and the tissue between the electrodes had been completely ablated. The shape of the ablation area was closely related to the position of electrodes.

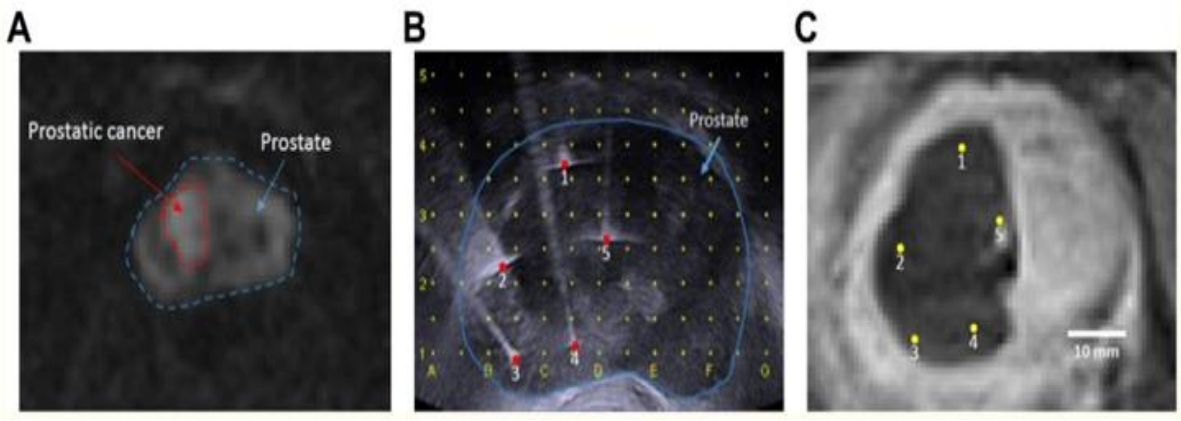

Figure 4: *The electrode position on the ultrasound images and MRI scans. The dots are the position of electrodes, and the area surrounded by the red dashes is the prostate cancer. The areas surrounded by blue dashes or blue curves are the prostate, and the dots are the position of electrodes. (A) MRI before the treatment. (B) Ultrasound image. (C) MRI after the treatment. MRI indicates magnetic resonance imaging.*

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After determining the position of electrodes in MRI scans, the contours of the electric field distributions between each pair of electrodes were drawn as shown out as illustrated in Figure 5. The authors iterated that by comparing the ablation boundaries as well as the electric field distribution allowed the preliminary ascertaining of the electric field lethality threshold with regard to the case of constant conductivity, and the average lethality threshold of the treatment protocol that was utilized in the trial was 522 ± 74 V/cm.

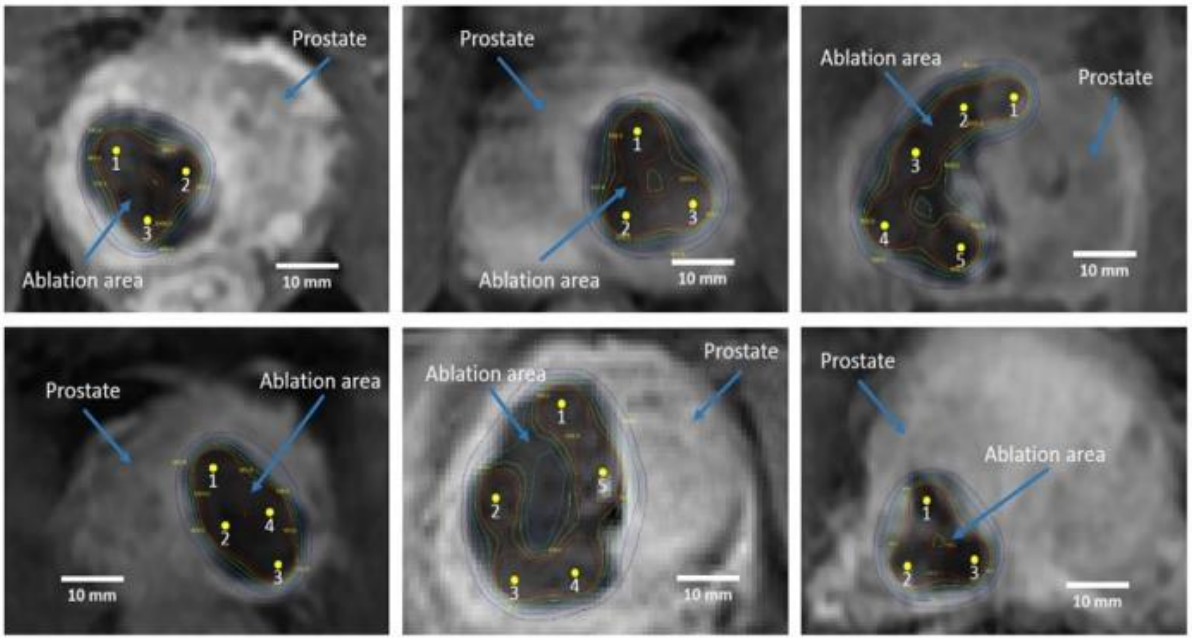

Figure 5: *The electric field distribution contours in MRI. The Color contours are the electric field intensity lines in the range of 400 to 1000 V/cm. The light gray area is the prostate and the dark gray area in the prostate is the ablation area. The yellow dots indicate the position of electrodes. MRI indicates magnetic resonance imaging.*

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Dong et al. [94] reported that the prostate glands of 8 patients were excised and utilized for histopathology examination 4 weeks pursuant to their treatment. Histopathology examination of the excised prostate demonstrated that the ablated area had diffuse necrotic glandular tissue without any obvious viable tissue within the ablated zone (see Figure 6A).

They also stated that even though Figure 6B demonstrated that large vessels within the tissue were intact, some amount of bleeding was visualised near the electrodes with the demonstration of scattered blood cells in the tissue which might have been caused capillary damage. The ablated zone had been well demarcated from the immediately adjacent unaffected parenchyma of the prostate gland as well as the transition zone between the necrotic glandular tissue in the ablation area as well as the adjacent normal glandular tissue was found to be abrupt (see Figure 6C). Furthermore, necrotic glandular tissue was observed adjacent to the urethra as illustrated in Figure 6D. Nevertheless, the integrity of the urethral structure had remained intact without any evidence of necrosis within the submucosa, even in the scenario when the urethra had been subjected to direct ablation during the safety portion of the study.

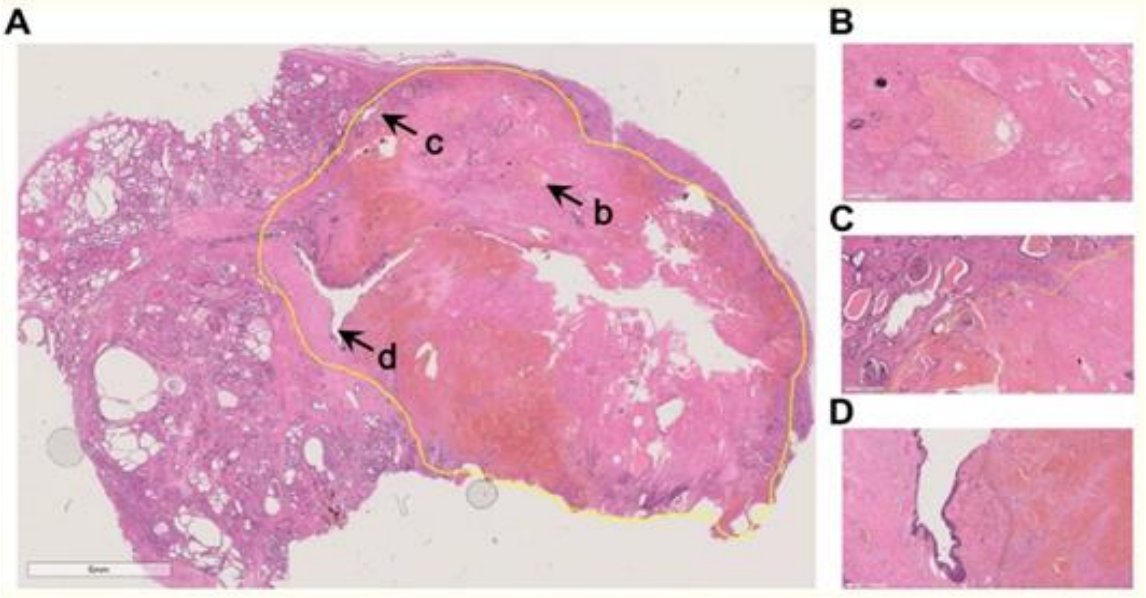

Figure 6: *H&E stain of the prostate in which the ablation is clear, there are no viable glandular tissues in the ablation area, and the urethra is intact after treatment. The yellow line is the ablation boundary. (A) H&E stain of prostate. (B) Larger vessels, (C) Ablation boundary. (D) Urethra H&E indicates haematoxylin and eosin.*

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With regard to the outcome of the treatment procedures, Dong et al. [94] reported the following:

- The patients were followed up for 6 months and in summary, the overall outcomes of their clinical treatment of patients who had prostate cancer were that 8 of 40 patients underwent radical prostatectomy 4 weeks subsequently, and 32 of the 40 patients retained their prostates.
- Sexual function was preserved in 14 patients out of 14 patients that amounted to 100%) of the 14 patients, 40 patients out of 40 patients that amounted to 100% of the 40 patients could control their micturition and they did not require any urinary pads, and None (0) of the 40 patients had urinary incontinence during surgery.
- The average duration of hospitalization of the 40 patients was 2 days, and the use time of urination was 2 to 10 days.
- Out of the 40 patients, 15 patients that amounted 37.5% of the patients had manifested with haematuria 2 weeks pursuant to their surgery (irreversible electroporation) and 5 patients that amounted to 12.5% of the patients had manifested with haematuria 4 weeks after their treatment. None of the patients had haematuria after 6 months.

Dong et al. [94] made the ensuing conclusions:

- Their study had described the first trial which had been conducted in human beings that involved the administration of HF bipolar pulses therapy for carcinoma of the prostate gland.
- HF bipolar pulse is a minimally invasive nonthermal treatment in ablation of tumour which could reduce the dose of muscle relaxant during treatment.

- In comparison with radical prostatectomy and thermal therapy, HF could preserve the NVB, urethra, and major vasculature within the prostate gland, which is beneficial for recovery of patients.
- The post-operative effect of such a treatment on their patients was very encouraging, in that sexual function was preserved in 14 patients out of 14 patients that amounted to 100% of the 14 patients, 40 patients out of 40 patients that amounted to 100% of the 40 patients could control their micturition and they and did not require utilization of urinary pads, and None (0) of the 40 patients had urinary incontinence during surgery.
- The clinical trials were conducted successfully, and they provided valuable insights relating to the treatment of prostate cancer with utilization of HF bipolar pulses, which would promote the ablation of solid tumours by IRE.

Colletini et al. [95] stated that Irreversible electroporation (IRE) is a nonthermal ablative method which is based upon the formation of nanoscale defects within cell membranes leading to cell death and that clinical experience with the technique for the treatment of prostate cancer had been limited. Collettini et al. [95] evaluated the urogenital toxicity and oncology outcome of MRI–transrectal US fusion–guided IRE of localized prostate cancer. With regard to the materials and methods of their study, Colletini et al. [95] reported that in their prospective study, men who had biopsy-proven, treatment-naive, low- to intermediate-risk carcinoma of the prostate gland with serum prostate-specific antigen [PSA] of equal to or less than 15 ng/mL; Gleason score of equal to or less than 3 + 4 = 7; clinical stage of equal to or less than T2c; lesion size at multiparametric MRI scan of equal to or less than 20 mm, had undergone focal MRI/transrectal US fusion–guided IRE between July 2014 and July 2017. The primary end point of the study was the urogenital toxicity profile of focal IRE by utilizing participant-reported questionnaires. The secondary end points of the study were biochemical, histopathology, and imaging measures of oncology control. Colletini et al. [95] undertook analyses of their data by utilising nonparametric and χ^2 test statistics. Colletini et al. [95] summarised the results as follows:

- Thirty men were included in the study and their median age was 65.5 years); their mean serum PSA level was 8.65 ng/mL and mean tumour size was 13.5 mm.
- One grade III adverse event which consisted of urethral stricture was recorded.
- The proportion of men who had erection sufficient for penetration was observed in 25 men out of 30 mean which amounted to 83.3% at baseline and 23 out of 29 which amounted to 79.3% with $P > .99$) at 12 months.
- Leak-free and pad-free continence rate was noted in 27 out of 30 men that amounted to 90% at baseline and 25 out of 29 men that amounted to 86.2% at $P > .99$ at 12 months.
- Urogenital function had remained stable at 12 months according to changes within the modified International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms, or ICIQ-MLUTS, and the International Index of Erectile Function, or IIEF-5, questionnaires ($P = .58$ and $P = .07$, respectively).
- The serum PSA level had decreased from a baseline median value of 8.65 ng/mL (interquartile range, 5–11.4 ng/mL) to 2.35 ng/mL (interquartile range, 1–3.4 ng/mL) at 12 months ($P < .001$) pursuant to the IRE procedure.
- At 6 months, 28 of 30 of the participants that amounted to 93.3% of the patients underwent post-treatment prostate biopsy.
- The rate of in-field treatment failure was found in five out of 28 patients that amounted to 17.9% of the patients as was determined with multiparametric prostate MRI and targeted biopsies of the prostate at 6 months.

Colletini et al. [95] concluded that after a median follow-up of 20 months, they had found out in their study that focal irreversible electroporation of localized carcinoma of the prostate gland was associated with low urogenital toxicity as well as promising oncology outcomes. Colletini et al. [95] made the ensuing summation as well as Key Points:

- MRI–transrectal US fusion–guided irreversible electroporation represents a safe and effective procedure for patients who have localized low- to intermediate-risk prostate cancer with promising midterm results, both with regard to urogenital toxicity and oncology control.
- Pursuant to irreversible electroporation (IRE) treatment of prostate cancer, no residual cancer was found in 23 of out of 28 patients that amounted to 82% of their study participants at 6 months after targeted prostate biopsy.
- Serum Prostate-specific antigen (PSA) levels had decreased from 8.65 ng/mL to 2.35 ng/mL at 12 months ($P < .001$) pursuant to IRE of the prostate.
- IRE of the prostate was found to be associated with a leak-free and pad-free continence rate of 96.3% and stable urogenital function at 12 months.

Guenther et al. [61] stated that Irreversible Electroporation (IRE) is a new image-guided tissue ablation technology which does induce cell death through very short but strong pulsed electric fields and that IRE had been demonstrated to have preserving properties towards vessels and nerves as well as the extracellular matrix. They also stated that the aforementioned points do make IRE an ideal candidate to utilize for the treatment of prostate cancer (PCa) where other treatment modalities frequently unselectively tend to destroy encompassing structures which induce severe side effects like incontinence or impotence. Guenther et al. [61] reported their retrospective assessment of 471 IRE treatments in 429 patients who had all grades and stages of prostate cancer (PCa) with 6-year maximum follow-up time. With regard to the material and findings in the study, Guenther et al. [61] stated the following:

- The cohort oof patients had consisted of low-risk cancers that amounted to 25, intermediate-risk cancers that amounted to 88 and high-risk cancers that totalled 312.
- All of the patients had multi-parametric magnetic resonance imaging, and 199 men had additional 3D-mapping prostate biopsy for diagnostic work-up preceding their IRE.
- The patients were treated either focally with regard to 123 patients, sub-whole-gland with regard to 154 patients, whole-gland with regard to 134 patients or for recurrent disease with regard to (63 patients after previous radical prostatectomy, radiation therapy, etc.
- Adverse effects were found to be mild in 19.7% of the patients, moderate in 3.7% of the patients and severe in 1.4% of the patients and these were never life-threatening.
- Urinary continence was noted to be preserved in all cases.

- IRE-induced erectile dysfunction had persisted in 3% of the evaluated cases 12 months pursuant to treatment.
- The mean transient IIEF-5-Score reduction was 33% within 12-month pursuant to the IRE follow-up and 15% after 12 months.
- Recurrences of the prostate cancer within the follow-up period had occurred in 10% of the treated men, 23 in or adjacent to the treatment field and 18 outside the treatment field (residuals).
- They had found that with the inclusion of residuals for worst case analysis, Kaplan Maier estimation on recurrence rate at 5 years resulted in 5.6% (CI95: 1.8-16.93) for Gleason 6, 14.6% (CI95: 8.8-23.7) for Gleason 7 and 39.5% (CI95: 23.5-61.4) for Gleason [8-10].

Guenther et al. [61] made the following conclusions:

- The results of their study had indicated comparable efficacy of IRE to standard radical prostatectomy with regard to the 5-year recurrence rates and better preservation of urogenital function, proving the safety and suitability of IRE for PCa treatment.
- The data had also demonstrated that IRE, besides focal therapy of early PCa, could also be utilized for whole-gland ablations, in patients who have PCa, and as a problem-solver for local tumour control in T4-cancers that are not amenable to surgery and radiotherapy anymore.

Ong et al. [1] made the following summating iterations related to Irreversible Electroporation of prostate Cancer:

- Even though it could be lethal in its advanced stage, carcinoma of the prostate gland could be effectively treated when it is localised.
- Traditionally, radical prostatectomy (RP) or radiotherapy (RT) were utilized to treat all men who have localised prostate cancer; nevertheless, this has significant risks of post-treatment side effects.
- Focal therapy has emerged as a potential form of treatment which could achieve similar oncology outcomes to radical treatment but at the same time preserving functional outcomes and decreasing rates of adverse effects.
- Irreversible electroporation (IRE) is one such forms of focal treatment which does use pulsatile electrical currents to ablate tissue.
- IRE modality of treatment is still in an early research phase, with studies demonstrating that IRE is a safe procedure which could offer good short-term oncology outcomes whilst carrying a lower risk of poor functional outcomes.
- They believe that based upon these results, future well-designed clinical trials would be needed to truly assess the efficacy of IRE in the treatment of men who have localised prostate cancer.

Abs

Rojo et al. [96] stated that metastatic prostate cancer within bone is difficult to treat in view of the fact that the tumour cells tend to be relatively resistant to hormonal or chemotherapies in comparison with primary prostate cancer. They also stated that Irreversible electroporation (IRE) is a minimally invasive ablation treatment procedure which has potential applications in the management of prostate cancer within bone. Nevertheless, a common limitation of IRE is recurrence of tumour, which does arise from incomplete ablation which does allow the remaining cancer cells to proliferate. Rojo et al. [96] in their study, combined IRE with radium-223 (Ra-223), a bone-seeking radionuclide which does emit short track length alpha particles and thus tends to be associated with reduced damage to the bone marrow and evaluated the impact of the combination treatment on bone-forming prostate cancer tumours. With regard to the methods of their study, Rojo et al. [96] stated that they had tested the antitumor activity of IRE and Ra-223 as single agents and in combination in vitro against three bone morphogenetic protein 4 (BMP4)-expressing prostate cancer cell lines (C4-2B–BMP4, Myc-CaP–BMP4, and TRAMP-C2–BMP4). They had also performed similar evaluation was in vivo using a bone-forming C4-2B–BMP4 tumour model in nude mice. Rojo et al. [96] summarized their results as follows:

- IRE and Ra-223 as monotherapy had inhibited prostate cancer cell proliferation in vitro, and their combination had resulted in significant reduction in cell viability in comparison with monotherapy.
- In vivo evaluation demonstrated that IRE with single-dose administration of Ra-233, in comparison with IRE alone, reduced the rate of tumour recurrence by 40% following initial apparent complete ablation and had decreased the rate of proliferation of incompletely ablated tumour as was quantified in Ki-67 staining ($53.58 \pm 16.0\%$ for IRE vs. $20.12 \pm 1.63\%$; for IRE plus Ra-223; $p = 0.004$).
- Histopathology analysis did qualitatively show the enhanced killing of tumour cells that were adjacent to bone by Ra-223 in comparison with those tumours that were treated with IRE alone.

Rojo et al. [96] made the following conclusions:

IRE in combination with Ra-223, which enhanced the destruction of cancer cells which are adjacent to bone, had resulted in reduction recurrence of tumour via through improved clearance of proliferative cells within the tumour region.

Onik et al. [59] stated that percutaneous prostate cryo-ablation had become an accepted option for the treatment for primary prostate cancer and that thermal tissue ablation based upon cold, nevertheless, does have some distinct limitations which include the following: Variable damage at the cryo lesions margin, injury to adjacent structures such as rectum, urethra and NVB (neurovascular bundle), and long procedure time due to the need to utilize multiple freeze thaw cycles, which tend to have limited the acceptance of this modality of treatment. Onik et al. [59] also iterated that Irreversible electroporation IRE, is a novel non-thermal ablation modality of treatment which utilizes short pulses of DC electric current to create irreversible pore within the cell membrane, thus, causing cell death. They additionally stated that Irreversible Electroporation, theoretically should be associated with significant advantages in ablating prostate tissue. Onik et al. [59] reported that six male dogs had their prostates treated utilizing IRE. In this study, pulses were applied using a DC generator which had delivered pulses in the microsecond range of duration, with a variable pulse interval and voltage range. The IRE probes were inserted percutaneously or trans-rectally utilizing trans-rectal ultrasound guidance. With regard to one of the dogs, the lesions were made purposely to include the rectum, urethra, and neurovascular bundle (NVB). The subjects were followed-up for 1 day to 14 days before they were sacrificed. They found out that IRE lesions within the prostate had unique characteristics in comparison with thermal lesions. The margins of the IRE lesions were very distinct in that they had a narrow zone of transition from normal to complete necrosis, there was complete destruction within the IRE lesion, and rapid resolution of the lesions with marked shrinkage within two weeks were noted. Structures such as urethra, vessels, nerves, and rectum were found not to be affected by the IRE application. The IRE lesions were found to have characteristics

which were distinctly different from thermal lesions. Onik et al. [59] were of the opinion that the differences could be very advantageous with regard to a clinical setting, improving the results and acceptance of prostate ablation.

Lim et al. [97] made the ensuing summations related to irreversible electroporation of prostate cancer.: The exposure of the prostate to high electric field strength during irreversible electroporation (IRE) has been extensively investigated. Multiple monopolar electrodes, however, have risks of organ piercing and bleeding when placing electrodes. A novel bipolar electrode made of pure platinum and stainless steel was developed for prostate cancer ablation. Voltages of 500 and 700 V were applied to the beagle prostate with this electrode to evaluate ablated tissues and their characteristics. IRE procedures were technically successful in all dogs without procedure-related complications. The current that flowed through the anode and cathode while applying 500 and 700 V were 1.75 ± 0.25 A and 2.22 ± 0.35 A, respectively. TUNEL assays showed that the estimated ablated areas when applying 500 and 700 V were 0.78 cm^2 and 1.21 cm^2, respectively. The minimum electric field strength threshold required for induction of IRE was 800 V/cm. The platinum electrode was resistant to corrosion. The IRE procedure for beagle prostates using a single bipolar electrode was technically feasible and safe. The novel bipolar electrode has great potential for treating human prostate cancer with fewer IRE-related complications.

Blazevski et al. [98] made the following summations related to Irreversible Electroporation of prostate cancer:

Whilst whole-gland radical treatment is highly effective for the control of prostate cancer, it does tend to have significant impact upon quality of life and has tended to be unnecessary 'over-treatment' in many men who are diagnosed as having prostate cancer based upon screening-detected prostate cancer. They also stated that improvements in prostate biopsy and radiology imaging had led to increased interest in partial gland ablation in order to reduce treatment-related morbidity. They additionally iterated that several energies that are utilized for focal ablation had been trialled as well as Irreversible electroporation (IRE) is a new technology which does ablate tissue by delivering direct current between electrodes. Blazevski et al. [98] undertook a narrative review which had documented the history of electroporation including its scientific basis, early data from pre-clinical animal studies, and contemporary clinical outcomes from the use of IRE in prostate cancer. With regard to the methods, Blazevski et al. [98] stated that they undertook a literature search utilizing the Medical Literature Analysis and Retrieval System Online by utilizing a number of literature search data bases in order to identify historical perspectives and current clinical data relating to IRE for prostate cancer. Blazevski et al. [98] summarized their results as follows:

- The history of electroporation and its implementation as a prostate cancer treatment was following the basic scientific principles, in vitro data, then animal studies, and now short- to medium-term clinical cohorts in humans.
- The results of IRE on more than 283 patients had been published in many papers, which had reported preserved rates of (pad-free) continence in 91% to 100% of men as well as preserved erectile function in 79% to100% of men.
- In-field recurrence rates had ranged from 0% to 33%.
- The current state of evidence for IRE for the treatment of primary and salvage carcinoma of the prostate gland cancer is considered as Idea, Development, Exploration, Assessment, Long-term follow-up (IDEAL) stage 2B.

Blazevski et al. [98] made the following conclusions:

- IRE is a novel focal ablative technology for the treatment of localised carcinoma of the prostate gland in carefully selected men.
- Published cohorts had reported encouraging short-term oncology as well as functional outcomes; nevertheless, longer-term data are required in order to validate this treatment before it could be recommended for widespread clinical utilization.

Blazevski et al. [99] stated that focal irreversible electroporation (IRE) could be utilized to treat men who have localised prostate cancer (PCa) with reduced impact on quality of life (QoL). Blaevski et al. [99] assessed the oncology and functional outcomes of IRE as treatment for localized prostate cancer. Blazevski et al. [99] reported on a prospective database of patients who had undergoing primary IRE between February 2013 and August 2018. A minimum of 12-months follow-up was available for 123 patients. The median follow-up of the patients was 36 months and the interquartile range [IQR] was between 24 months and 52 months. A total of 112 of the patients that amounted to 91% of the patients had National Comprehensive Cancer Network intermediate risk and 11 of the patients that amounted to 9% of the patients had low risk prostate cancer. A total of 12 patients that amounted to 9.8% of the patients had International Society of Urological Pathology (ISUP) grade 1, 88 patients that amounted to 71.5% of the patients had ISUP 2, and 23 patients that amounted to 18.7% of the patients had ISUP 3. The patients were treated by means of Focal IRE ablation of their localized PCa lesions. With regard to the outcome measurements and statistical analysis, Blazevski et al. [99] reported that the follow-up had involved serial serum prostate-specific antigen (PSA) level testing, multiparametric magnetic resonance imaging (mpMRI), and trans-perineal template mapping biopsy (TTMB) at 12 months pursuant to the IRE. They defined failure-free survival (FFS) as progression to whole-gland or systemic treatment or metastasis/death. Blazevski et al. [99] assessed the functional outcomes of the patients. Blazevski et al. [99] summarized the results and limitations of the study as follows:

- The median age of the patients was 68 years and the inter quarter range (IQR) had ranged between 62 years and73years.
- The median pre-operative serum PSA was 5.7ng/ml with inter-quarter range (IQR) of between 3.8–8.0ng/ml.
- Upon post-treatment TTMB, in-field recurrence was found in between 2.7% and 9.8% of the patients.
- Failure free survival (FFS) at 3 years was 96.75%, metastasis-free survival was 99%, and the overall survival was 100%.
- A total of 18 patients did require salvage treatment and of the 18 patients, 12 patients had repeat IRE; six patients had whole-gland treatment.
- The negative predictive value of mpMRI was 94% and sensitivity was 40% for detecting in-field residual disease 6 months pursuant to treatment.
- Among patients who returned their questionnaires, 80 out of 81 patients that amounted to 98.8% of patients had remained pad free and 40 patients out of 53 patients that amounted to 76% of patient did not have any change in their erectile function.

Blazevski et al. [99] concluded that focal IRE in select patients who have localised clinically significant prostate cancer (PCa) had satisfactory short-term oncology outcomes with a minimal impact on patient QoL. Blazevski et al. [99] summated their findings as follows:

- In their study, 123 patients underwent focal therapy utilizing irreversible electroporation.

- The results of pathology examination of follow-up biopsy specimens of the prostate were clear of residual disease in 90.2% to 97.3% of the patients.
- Out of the patients, 96.75% avoided whole gland treatment at 3 years,

Blazevski, et al. [100] assessed the safety, oncological and quality-of-life (QoL) outcomes of focal ablation of apical prostate cancer (PCa) lesions with utilization of irreversible electroporation (IRE). With regard to the methods of the study, patients were included in the study if they had a prostate cancer (PCa) lesion within 3 millimetres of the apical capsule which had been treated with IRE. The IRE procedure was undertaken in one institution by a one urologist. Quality of life (QoL) and functional data was collected prospectively from the patients who had given consent for the use of the Expanded Prostate Cancer Index Composite (EPIC). The oncology follow-up of the patients included 3-month serum prostate-specific antigen (PSA) levels testing, the undertaking of mpMRI at 6 months and trans-perineal biopsy at 1-year post treatment. Blazevski et al. [100] summarized the results as follows:

- A total of 50 patients had apical prostate cancer (PCa) lesions which had been treated between February 2013 and September 2018.
- The median follow-up time was 44 months.
- No Clavien–Dindo grade 3 events or higher were encountered.
- No perioperative complications were noted.
- No significant difference was found in the EPIC urinary or bowel QoL domain between baseline and at 12-months pursuant to the IRE treatment.
- One patient that amounted to 2% of the patients required the use of one pad per day for urinary incontinence 12-months pursuant to his IRE treatment.
- There was a small but significant decline in EPIC sexual QoL with a score of 65 at baseline and 59 at 12-month post-IRE treatment.
- Out of patients who were potent pre-treatment, 94% of the patients had remained potent after their IRE treatment.
- The median serum PSA nadir had decreased by 71% with the levels between 6.25 ng/mL and 1.7 ng/mL
- Only one patient that amounted to 2.5% of the patients had in-field residual disease on repeat biopsy.

Blazevski et al. [100] concluded that focal ablation utilizing IRE for prostate cancer (PCa) within the distal apex of the prostate gland does appear to be safe and feasible with acceptable early QoL and oncology outcomes.

Blazevski et al. [101] reported the feasibility, oncological and functional outcomes of salvage robot-assisted radical prostatectomy (sRARP) for recurrent prostate cancer (PCa) pursuant to irreversible electroporation (IRE). Blazevski et al. [101] undertook a retrospective analysis of patients who had undergone sRARP pursuant to IRE treatment within their institution. Blazevski et al. [101] assessed the surgical complications, oncology and functional outcomes. Blazevski et al. [101] summarized the results as follows:

- Fifteen (15) patients who had at least 12 months follow up were identified out of the 234 men who had undergone primary IRE between 2013 and 2019.
- The median and inter quarter range [IQR] age of the patients were 68 years and a range of between 62 years and 70 years.
- The median [IQR] time from focal IRE to sRARP was 42 months and 21 months to 57 months.
- There were no rectal, bladder or ureteric injuries that had emanated from the IRE procedures.
- The T stage was pT2 in 9 of the patients that amounted to 60% of the patients and pT3a in 6 patients that amounted to 40% of the patients.
- Only one patient that amounted to 7% of the patients had a positive surgical margin.
- At a median [IQR] follow-up of 22 months (16 months to 32 months), no patient had a biochemical recurrence with serum PSA greater than 0.2.
- All 15 patients were found to be continent and pad-free by 6 months and 9 patients which amounted to 60% of the patients had erections sufficient for coital activity (intercourse) with or without PDE5 inhibitors.
- No predisposing factors were identified for the prediction of erectile dysfunction following sRARP.

Blazevski et al. [101] made the following conclusions:

- With regard to patients who had recurrent or residual significant prostate cancer (PCa) after undergoing focal IRE ablation it is feasible to obtain good functional and oncological outcomes with sRARP.
- Their results had demonstrated that good outcomes could be achieved with sRARP, when respecting close monitoring post-IRE, good patient selection and surgical experience.

Blazevski et al. [102] stated that focal Therapy is an emerging option of treatment for prostate cancer (PCa), which does target individual localised cancer whilst sparing important functional as well as anatomical structures. They additionally iterated that Irreversible electroporation (IRE) represents a focal therapy modality of treatment which is based upon the process of cell membrane electroporation. Blazevski et al. [102] summated the history of IRE from initial observations to its utilization within the Urology theatre. Blazevski et al. [102] undertook a comprehensive literature search with utilization of data bases including PubMed, Medline, Google and Google Scholar utilising the ensuing words: “irreversible electroporation”, “electroporation”, “history”, and “prostate cancer”. Bazevski et al. [102] reported their results as follows: The phenomenon of Irreversible electroporation (IRE) was observed for the first time in 1754 when Nollet had applied electric sparks to human skin and had noticed the occurrence of red spots or “Lichtenbeg” figures. Subsequently it was also noticed that lighting strikes had caused different damaging effects to the damaging effects caused by thermal burns. In the 1990s, the bactericidal effects that are caused by electricity had been identified and utilized in the purification of food and water. Late in the 20th century “reversible” electroporation began to be utilized to disrupt cell membrane and to allow the transfer DNA as well as chemotherapy agents into cells. It was in the early parts of the 21st century that IRE was initially utilized as a tissue ablation methodology. The rational for utilizing IRE in order to ablate tissue is that IRE is a non-thermal energy and it has the potential to limit damage to adjacent tissues as well as structures. In 2007, Onik and associates, ablated the prostates of Beagle dogs. The first phase I-II trials of IRE in human beings were in 2010. In the subsequent years, the safety and clinical feasibility of IRE was

assessed. IRE is now utilized in many different sites around the world as a focal treatment modality under investigational conditions. Blazevski et al. [102] made the ensuing conclusions:

- IRE is now utilized within many different sites around the world.
- IRE is still an investigational technique and does require further long-term studies in order to make IRE an accepted segment of the standard of care in carcinoma of the prostate gland.

Blazevski et al. [103] stated that the undertaking of focal therapy for the treatment of prostate cancer (PCa) is increasing globally and that there is no consensus agreed protocol regarding how to monitor patients pursuant to focal therapy; nevertheless, many institutions utilise multi-parametric magnetic resonance imaging mpMRI in order to detect residual or recurrent prostate cancer (PCa). Blazenski et al. [103] undertook a study in order to ascertain the diagnostic accuracy of mpMRI to detect residual PCa pursuant to focal therapy with utilization of irreversible electroporation (IRE). With regard to the method of their study, Blazevski et al. [103] reported the following: Between February 2013 and September 2018, 170 patients had consented to undergo as well as had undergone primary irreversible electroporation (IRE). 102 of these patients were included for analysis after they undergone follow-up mpMRI at 6 months pursuant to the IRE and a trans-perineal template mapping biopsy of the prostate at 12 months pursuant to the IRE-procedure. PIRADS v2 was utilized to report outfield of interest (ROI) recurrence whilst a binary outcome (suspicious versus non-suspicious) was utilized for the infield ablative zone. Sensitivity, specificity, positive predictive value (PPV) as well as negative predictive value (NPV) of mpMRI scan was calculated in patients who had Gleason equal to or higher than 3+4 =7 and Gleason equal to or greater than 3+3 = 6 with a maximum core length equal to or longer than 4 mm on pathology examination of their follow-up post-IRE prostate biopsy specimens. The diagnostic accuracy was calculated for infield ROI, outfield ROI, as well as the whole prostate gland. Glazevski et al. [103] summarized the results as follows:

- The sensitivity, specificity, positive predictive value as well as negative predictive value (NPV) of the infield ROI were 40%, 98%, 67%, and 94% respectively, whilst the outfield ROI results were 58%, 93%, 69% and 90% respectively.
- For the whole prostate gland, the sensitivity, specificity, positive predictive value and negative predictive value (NPV) were 56%, 89%, 60% and 86% respectively.

Glazevski et al. [103] made the ensuing conclusions:

- Their data had demonstrated that follow-up mpMRI has the capability to rule out residual prostate cancer (PCa) within both the infield as well as the outfield areas.
- Nevertheless, given that 14% of residual prostate cancer (PCa) is missed by mpMRI scan repeat biopsies of the prostate gland would still be required in patients pursuant to their undergoing focal therapy.
- The limitations of their study are the low incidence of recurrence in their cohort as well as the retrospective design of their study.

Morozov et al. [104] stated that irreversible electroporation is a treatment option used for the provision of focal therapy. Morozov et al. [104] undertook a systematic review, as well as summarised data on irreversible electroporation outcomes with regard to patients who had localised prostate cancer. They undertook a literature search in from three databases and they included articles with their own data on irreversible electroporation results in patients who had localised prostate cancer. They stated that the primary outcome was procedure efficacy that was measured as the absence of cancer within the treatment area on the pathology examination findings of the follow-up prostate biopsy specimens. The secondary outcomes included the absence of prostate cancer recurrence in the treatment area on magnetic resonance imaging (MRI) scan, out-of-field recurrence, complications and functional outcomes including erectile function as well as micturition. They reported the salient points of their findings as follows:

- The in-field recurrence rate was between 0% and 39% and the out-field recurrence rate was between 6.4% and 24%.
- In all of the studies, serum PSA level had decreased: twice lower than baseline after 4 weeks and by 76% after 2 years.
- Majority of the authors had noted sexual and urinary toxicity during the first half year pursuant to surgery. Nevertheless, the functional outcomes recovered to baseline after 6 months with mild decrease in sexual function.
- The complication rates pursuant to irreversible electroporation (IRE) were 0% to 1% of Clavien–Dindo III and 5% to 20% of Clavien–Dindo I–II.

Morozov et al. [104] made the following conclusions:

- Irreversible electroporation does have promise oncology outcomes, rate of post-operative complications and minimal-to-no effects upon erectile and urinary function.
- Nevertheless, medium and long-term follow-up data on cancer-specific and recurrence-free survival were still lacking.

Scheltema et al. [105] iterated that the design, conduct, as well as completion of randomised trials for curative prostate cancer (PCa) treatments tend to be challenging. Scheltema et al. [105] undertook a study in order to evaluate the effect of robot-assisted radical prostatectomy (RARP) versus focal irreversible electroporation (IRE) upon patient-reported quality of life (QOL) as well as early oncology control utilizing propensity-scored matching. With regard to the methods of the study, Scheltema et al. [105] reported the following: Patients who had T1c to cT2b significant prostate cancer (PCa) including high-volume ISUP 1 or any 2/3 who had received unifocal irreversible electroporation (IRE) were pair-matched to patients who had undergone nerve-sparing RARP. Scheltema et al. [105] prospectively assessed the patients who had reported outcomes utilizing the Expanded Prostate cancer Index Composite (EPIC), America Urological association (AUA) Symptom Score and Short Form of Health Survey (SF-12) physical and mental components. Scheltema et al. [105] defined oncology failure as biochemical recurrence following RARP or prostate cancer positive pathology examination finding on follow-up prostate biopsy specimens. Generalized mixed-effect models were utilized to compare the results of IRE and RARP. Scheltema et al. [105] summarized the results as follows:

- 50 IRE patients had been matched to 50 RARP patients by means of propensity score.
- IRE was found to be significantly superior to RARP with regard to preservation of pad-free continence (UC0 and erections that are sufficient for sexual intercourse (ESI).
- The absolute differences were 44, 21, 13, 14% for urinary continence (UC), and 32, 46, 27, 22% for sufficient sexual intercourse (ESI) at 1.5 months, 3 months, 6 months, and 12 months after treatment procedure respectively.
- The EPIC summary scores had shown no statistically significant differences.

- Urinary symptoms were reduced for IRE patients and RARP patients at 12 months, even though IRE patients initially reported more complaints.
- IRE patients did experience more early oncology failure in comparison with RARP patients.

Scheltema et al. [105] made the ensuing conclusions:

- Their data had demonstrated the superior preservation of urinary continence and satisfactory sexual function (ESI) in comparison with RARP up to 12 months pursuant to treatment.
- Long-term oncology data would be required in order to provide ultimate proof for or against the undertaking of focal therapy like IRE.

Kizil et al. [106] evaluated early clinical and multiparametric prostate magnetic resonance imaging (mpMRI) results of irreversible electroporation (IRE) efficiency in the treatment of localized prostate cancer. With regard to the materials and method, Kizil et al. [106] stated that with regard to the patients in whom IRE was undertaken local ablation, mpMRI was utilized for the sixth month follow-up. These images were compared with the mpMRI images which had been obtained prior to the IRE procedure. Kizil et al. [106] undertook trans-perineal fusion biopsy to patients who had a diagnosis of localized prostate cancer. Kizil et al. [106] treated the eligible ones with IRE. Six of the patients had completed their 6-month follow-up period. Kizil et al. [106] compared the pre-operative serum prostate-specific antigen (PSA), international prostate symptom score, international index of erectile function (IIEF), and mpMRI of these patients with those they had obtained at the sixth month of follow-up. They evaluated the side effects that had been experienced by the patients as well. Kizil et al. [106] summarized the results as follows:

- They had 10 patients who had undergone IRE treatment.
- Six patients had completed their sixth month-follow-up and they attended for their control visits.
- At the end of 6 months, the mean decrease in the serum prostate-specific antigen (PSA) level was 73%.
- IIEF results were found not to have changed significantly.
- Upon mpMRI, diffusion restriction was observed to have disappeared except for one patient, and Prostate Imaging Reporting Data System scores were decreased.

Kizil et al. [106] made the following conclusions:

- Early clinical and mpMRI results for IRE in the focal ablative treatment of localized prostate cancer were found to be gratifying.
- As an ambulatory procedure with a low incidence of side effects, they were looking forward to ascertaining the long-term results of IRE treatment.

Conclusions and Summary

- Irreversible Electroporation (IRE) is a new radiology image-guided tissue ablation which does induce cell death through very short but strong electric fields.
- IRE had been demonstrated to have preserving properties towards vessels, nerves, as well as the extra-cellular matrix. For this reason, IRE could represent an ideal treatment option for adenocarcinoma where other treatment options including radical prostatectomy and radical radiotherapy tend to unselectively destroy that encompass the prostate cancer and inducing side effects including urinary incontinence as well as sexual dysfunction / impotence.
- Results of some studies in which IRE had been utilized for the treatment of curative intent of localized low-risk and intermediate-risk adenocarcinomas of the prostate gland had indicated complete efficacy of IRE to the standard of radical prostatectomy and standard radical radiotherapy with regard to the 5-year tumour recurrence rate as well as better preservation of genitourinary function which did prove the safety as well as suitability of IRE for the treatment of localized low-risk and intermediate risk adenocarcinoma of the prostate gland. Some data pertaining to IRE besides focal treatment of early adenocarcinoma of the prostate gland had shown that IRE besides focal treatment of early prostate cancer could also be utilized for whole prostate gland ablations in patients who develop recurrent prostate cancer as well as a problem-solving treatment for the control of local tumour within the prostate gland that are not amenable to surgery or radiotherapy anymore.
- Some studies had demonstrated comparable short-term and medium-term functional outcomes functional outcomes with radical prostatectomy and radical radiotherapy but following longer surveillance assessments those underwent IRE were found tom have superior genitourinary function in that a number of the sexual dysfunction and urinary incontinence had resolved but with regard to the oncology outcome repeat follow-up biopsy of the prostate had demonstrated a higher positive tumour biopsy upon pathology examination for which either further IRE, or radical radiotherapy, or radical prostatectomy was required as subsequent treatment of curative intent in that radical prostatectomy of curative intent had superior medium-term to long-term outcome in comparison with IRE. IRE can also be utilized to treat locally recurrent prostate cancer following: (a) radical radiotherapy and (b) following the finding of persistent or locally recurrent adenocarcinoma of the prostate gland pursuant the undertaking of IRE as treatment of curative intent of localized adenocarcinoma of the prostate gland.
- Following failure of IRE treatment for localized adenocarcinoma of the prostate, the persistent carcinoma of the prostate gland could also be treated by means of radical prostatectomy, or radical radiotherapy or any other minimally invasive treatment of curative intent including cryotherapy, radiofrequency ablation of the prostate and high intensity focussed ultrasound treatment.
- Considering that IRE tends to be associated with good short-term and medium-term outcome which also tends to be generally superior to the outcome following radiotherapy as well as radical prostatectomy, and the fact that the medium-term to long-term oncology outcome tends to be good but the oncology outcome following radical prostatectomy as well as radiotherapy would tend to be a bit superior to IRE, it could be suggested that patients who have low-risk and intermediate-risk localized adenocarcinoma who prefer to maintain their genitourinary function could be offered IRE as first line treatment of curative intent which should be followed up with regular frequent assessments which would enable early identification of treatment failures at an early stage.
- The individuals who are found to have IRE failure could then be offered radical prostatectomy or radical radiotherapy as second line treatment of curative intent.

- Finally, there is need for a global multi-centre trial of IRE in the treatment of curative intent of localized low-risk, intermediate-risk, as well as high risk groups and those who have high risk group localized prostate cancer could be offered adjuvant therapy and all these treatments should be compared with radical radiotherapy and radical prostatectomy with a long period of follow-up to enable a consensus opinion to be established as well as guidelines to be formulated.

Conflict of Interest

None

Acknowledgements

Acknowledgement to:
Dong S, Wang H, Zhao Y, Sun Y, Yao C. and Technol Cancer Res. Treat, for granting permission for reproduction of contents and figures of their journal article under Copyright © The Author(s) 2018.

References

1. Ong S, Leonardo M, Chengodu T, Bagguley D, Lawrentschuk N. (2021). Irreversible Electroporation for Prostate Cancer. Life (Basel). 2021 May 27; 11(6):490.
2. Ong X R S, Bagguley D, Yaxley J W, Azad A A, Murphy D G, Lawrentchuk N. (2020). Understanding the diagnosis of prostate cancer. Med. J. Aust. 2020; 213:424-429.
3. Mottet N, van den Bergh R, Briers E. (2019). EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Eur. Assoc. Urol. 2019; 75: 889-890
4. Wang AZ, Lebastchi AH, O'Connor LP, Ahdoot M, Mehralivand S, Yerram N, Taneja SS, George AK, Sanchez-Salas R, Ward JF, Laguna P, de la Rosette J, Pinto PA. (2021). Making a case "for" focal therapy of the prostate in intermediate risk prostate cancer: current perspective and ongoing trials. World J Urol. 2021 Mar; 39(3):729-739.
5. Davalos RV, Mir IL, Rubinsky B. (2005). Tissue ablation with irreversible electroporation. Ann Biomed Eng. (2005 Feb); 33(2):223-231.
6. Blazevski A, Scheltema MJ, Amin A, Thompson JE, Lawrentschuk N, Stricker PD. (2020). Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment. BJU Int. 2020 Mar; 125(3):369-378.
7. Edd JF, Horowitz L, Davalos RV, Mir LM, Rubinsky B. (2006). In vivo results of a new focal tissue ablation technique: irreversible electroporation. IEEE Trans Biomed Eng. 2006 Jul;53(7):1409-1415.
8. Maor E, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. Technol Cancer Res Treat. 2007 Aug;6(4):307-312.
9. Charpentier KP, Wolf F, Noble L, Winn B, Resnick M, Dupuy DE. (2011). Irreversible electroporation of the liver and liver hilum in swine. HPB (Oxford). 2011 Mar; 13(3):168-173.
10. Wikipedia: The Free Encyclopaedia. Irreversible Electroporation.
11. Rubinsky B, Onik G, Mikus P (February 2007). "Irreversible electroporation: a new ablation modality-clinical implication". Technology in Cancer Research & Treatment. 6 (1):37-48.
12. Ringel-Scaia VM, Beitel-White N, Lorenzo MF, Brock RM, Huie KE, Coutermarsh-Ott S, et al. (June 2019). "High-frequency irreversible electroporation is an effective tumor ablation strategy that induces immunologic cell death and promotes systemic anti-tumor immunity". E. Bio-Medicine. 44: 112–125.
13. Gissel H, Lee RC, Gehl J (2011). "Electroporation and Cellular Physiology". In Kee ST, Gehl J, Lee EW (eds.). Clinical Aspects of Electroporation. New York, NY: Springer New York. pp. 9-17.
14. Zhang Y, Lyu C, Liu Y, Lv Y, Chang TT, Rubinsky B (June 2018). "Molecular and histological study on the effects of non-thermal irreversible electroporation on the liver". Biochemical and Biophysical Research Communications. 500 (3): 665–670.
15. Clinical trial number NCT02041936 for "Outcomes of Ablation of Unresectable Pancreatic Cancer Using the Nano Knife Irreversible Electroporation (IRE) System" at ClinicalTrials.gov.
16. Calvet CY, Mir LM (June 2016). "The promising alliance of anti-cancer electrochemotherapy with immunotherapy". Cancer and Metastasis Reviews. 35 (2): 165-177.
17. Pandit H, Hong YK, Li Y, Rostas J, Pulliam Z, Li SP, Martin RC (March 2019). "Evaluating the Regulatory Immunomodulation Effect of Irreversible Electroporation (IRE) in Pancreatic Adenocarcinoma". Annals of Surgical Oncology. 26 (3): 800–806.
18. Bulvik BE, Rozenblum N, Gourevich S, Ahmed M, Andriyanov AV, Galun E, Goldberg SN (August 2016). "Irreversible Electroporation versus Radiofrequency Ablation: A Comparison of Local and Systemic Effects in a Small-Animal Model". Radiology. 280 (2): 413–424.
19. Scheffer HJ, Stam AG, Geboers B, Vroomen LG, Ruarus A, de Bruijn B, et al. (2019-11-02). "Irreversible electroporation of locally advanced pancreatic cancer transiently alleviates immune suppression and creates a window for antitumor T cell activation". Oncoimmunology. 8 (11): 1652532.
20. Fuller GW (1898). Report on the investigations into the purification of the Ohio River water: at Louisville, Kentucky, made to the president and directors of the Louisville Water Company (Report). Louisville Ky.: Louisville Water Company. Van Nostrand Company 1898 Wikipedia the Free encyclopedia
21. Nollet JA (1754). Research on the specific causes of electrical phenomena. Paris: Guerin & Delatour.
22. Neumann E, Schaefer-Ridder M, Wang Y, Hofschneider PH (1982). "Gene transfer into mouse lyoma cells by electroporation in high electric fields". The EMBO Journal. 1(7): 841–845.
23. Mir LM, Belehradek M, Domenge C, Orlowski S, Poddevin B, Belehradek J, Schwaab G, Luboinski B, Paoletti C (1991). "[Electrochemotherapy, a new antitumor treatment: first clinical trial]". Comptes Rendus de l'Académie des Sciences, Série III. 313 (13): 613–618.
24. Okino M, Mohri H (December 1987). "Effects of a high-voltage electrical impulse and an anticancer drug on in vivo growing tumors". Japanese Journal of Cancer Research. 78 (12): 1319–1321.
25. Orlowski S, Belehradek J, Paoletti C, Mir LM (December 1988). "Transient electro permeabilization of cells in culture. Increase of the cytotoxicity of anticancer drugs". Biochemical Pharmacology. 37 (24): 4727-4733.
26. Daud AI, DeConti RC, Andrews S, Urbas P, Riker AI, Sondak VK, Munster PN, Sullivan DM, Ugen KE, Messina JL, Heller R (December 2008). "Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma". Journal of Clinical Oncology. 26 (36): 5896-5903.
27. Titomirov AV, Sukharev S, Kistanova E (January 1991). "In vivo electroporation and stable transformation of skin cells of newborn

mice by plasmid DNA". Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression. 1088 (1): 131-134.
28. Davalos RV, Mir IL, Rubinsky B (February 2005). "Tissue ablation with irreversible electroporation". Annals of Biomedical Engineering. 33(2):223-231.
29. Golberg A, Yarmush ML (March 2013). "Nonthermal irreversible electroporation: fundamentals, applications, and challenges". IEEE Transactions on Bio-Medical Engineering. 60 (3):707-714.
30. Tieleman DP, Leontiadou H, Mark AE, Marrink SJ (May 2003). "Simulation of pore formation in lipid bilayers by mechanical stress and electric fields". Journal of the American Chemical Society. 125 (21): 6382–6383.
31. Weaver JC (May 1994). "Molecular basis for cell membrane electroporation". Annals of the New York Academy of Sciences. 720(1):141-152.
32. Neumann E, Kakorin S, Toensing K (February 1999). "Fundamentals of electroporative delivery of drugs and genes". Bioelectrochemistry and Bioenergetics. 48(1):3-16.
33. Tarek M (June 2005). "Membrane electroporation: a molecular dynamics simulation". Biophysical Journal. 88 (6): 4045-4053.
34. Lee EW, Wong D, Prikhodko SV, Perez A, Tran C, Loh CT, Kee ST (January 2012). "Electron microscopic demonstration and evaluation of irreversible electroporation-induced nanopores on hepatocyte membranes". Journal of Vascular and Interventional Radiology. 23(1):107-113.
35. Chen C, Smye SW, Robinson MP, Evans JA (March 2006). "Membrane electroporation theories: a review". Medical & Biological Engineering & Computing. 44(1–2):5-14.
36. van Gemert MJ, Wagstaff PG, de Bruin DM, van Leeuwen TG, van der Wal AC, Heger M, van der Geld CW (February 2015). "Irreversible electroporation: just another form of thermal therapy?". The Prostate. 75(3):332–335.
37. Rubinsky L, Guenther E, Mikus P, Stehling M, Rubinsky B (October 2016). "Electrolytic Effects During Tissue Ablation by Electroporation". Technology in Cancer Research & Treatment. 15(5): NP95–NP103.
38. Klein N, Mercadal B, Stehling M, Ivorra A (June 2020). "In vitro study on the mechanisms of action of electrolytic electroporation (E2)". Bioelectrochemistry. 133: 107482.
39. Maor E, Rubinsky B (March 2010). "Endovascular nonthermal irreversible electroporation: a finite element analysis". Journal of Biomechanical Engineering. 132(3):031008.
40. Schoellnast H, Monette S, Ezell PC, Maybody M, Erinjeri JP, Stubblefield MD, Single G, Solomon SB (February 2013). "The delayed effects of irreversible electroporation ablation on nerves". European Radiology. 23(2):375-380.
41. Lee EW, Thai S, Kee ST. (September 2010). "Irreversible electroporation: a novel image-guided cancer therapy". *Gut and Liver*. 4 (Suppl. 1): S99–S104.
42. Neal RE, Davalos RV (December 2009). "The feasibility of irreversible electroporation for the treatment of breast cancer and other heterogeneous systems". Annals of Biomedical Engineering. 37(12):2615-2225.
43. Arena CB, Sano MB, Rossmeisl JH, Caldwell JL, Garcia PA, Rylander MN, Davalos RV (November 2011). "High-frequency irreversible electroporation (H-FIRE) for non-thermal ablation without muscle contraction". Bio-Medical Engineering Online. 10(1):102.
44. Qin Z, Jiang J, Long G, Lindgren B, Bischof JC (March 2013). "Irreversible electroporation: an in vivo study with dorsal skin fold chamber". Annals of Biomedical Engineering. 41(3):619-629.
45. Geboers B, Scheffer HJ, Graybill PM, Ruarus AH, Nieuwenhuizen S, Puijk RS, et al. (May 2020). "High-Voltage Electrical Pulses in Oncology: Irreversible Electroporation, Electrochemotherapy, Gene Electro transfer, Electrofusion, and Electro immunotherapy". Radiology. 295(2):254-272.
46. Aycock KN, Davalos RV (2019-12-01). "Irreversible Electroporation: Background, Theory, and Review of Recent Developments in Clinical Oncology". Bioelectricity. 1(4):214-234.
47. Ben-David E, Ahmed M, Faroja M, Moussa M, Wandel A, Sosna J, Appelbaum L, Nissenbaum I, Goldberg SN (December 2013). "Irreversible electroporation: treatment effect is susceptible to local environment and tissue properties". Radiology. 269(3):738-747.
48. "FDA Grants Prostate IDE Approval for AngioDynamics' NanoKnife System". Press Release. AngioDynamics. 13 June 2013.
49. "Angiodynamics, Inc. Enforcement Actions: Warning Letter" (PDF). Public Health Service. United States Food and Drug Administration. 2011-01-21.
50. Vroomen LG, Petre EN, Cornelis FH, Solomon SB, Srimathveeravalli G (September 2017). "Irreversible electroporation and thermal ablation of tumors in the liver, lung, kidney and bone: What are the differences?". Diagnostic and Interventional Imaging. 98(9):609-617.
51. Siddiqui IA, Kirks RC, Latouche EL, DeWitt MR, Swet JH, Baker EH, et al. (June 2017). "High-Frequency Irreversible Electroporation: Safety and Efficacy of Next-Generation Irreversible Electroporation Adjacent to Critical Hepatic Structures". Surgical Innovation. 24(3):276-283.
52. Nuccitelli R. (2017). "Tissue Ablation Using Nanosecond Electric Pulses". In Miklavčič O (ed.). Handbook of Electroporation. Cham: Springer International Publishing. pp. 1787-1797.
53. Kourounis G, Paul Tabet P, Moris D, Papalambros A, Felekouras E, Georgiades F, et al. (2017). "Irreversible electroporation (Nanoknife® treatment) in the field of hepatobiliary surgery: Current status and future perspectives" (PDF). Journal of B.U.On. 22(1):141-149.
54. Silk MT, Wimmer T, Lee KS, Srimathveeravalli G, Brown KT, Kingham PT, et al. (January 2014). "Percutaneous ablation of peribiliary tumors with irreversible electroporation". Journal of Vascular and Interventional Radiology. 25 (1): 112–118.
55. Scheffer HJ, Vroomen LG, Nielsen K, van Tilborg AA, Comans EF, van Kuijk C, et al. (October 2015). "Colorectal liver metastatic disease: efficacy of irreversible electroporation--a single-arm phase II clinical trial (COLDFIRE-2 trial)". BMC Cancer. 15(1):772.
56. Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, et al. (December 2016). "Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer". Annals of Surgical Oncology. 23(13):4352-4360.
57. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. (August 2011). "Pancreatic cancer". Lancet. 378(9791):607–620.
58. Månsson C, Brahmstaedt R, Nygren P, Nilsson A, Urdzik J, Karlson BM. (May 2019). "Percutaneous Irreversible Electroporation as First-line Treatment of Locally Advanced Pancreatic Cancer". Anticancer Research. 39(5):2509-2512.
59. Onik G, Mikus P, Rubinsky B. (August 2007). "Irreversible electroporation: implications for prostate ablation". Technology in Cancer Research & Treatment. 6(4):295-300.

60. Kasivisvanathan V, Emberton M, Ahmed HU. (August 2013). "Focal therapy for prostate cancer: rationale and treatment opportunities". Clinical Oncology. 25(8): 461–473.
61. Guenther E, Klein N, Zapf S, Weil S, Schlosser C, Rubinsky B, Stehling MK. (2019-04-15). Ahmad A (ed.). "Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments". PLOS ONE. 14(4): e0215093.
62. Stehling M. "Vitus Prostate Center - Privately owned Radiology Clinic"
63. Olweny EO, Cadeddu JA. (September 2012). "Novel methods for renal tissue ablation". Current Opinion in Urology. 22(5):379-384.
64. Wagstaff PG, de Bruin DM, Zondervan PJ, Savci Heijink CD, Engelbrecht MR, van Delden OM, et al. (March 2015). "The efficacy and safety of irreversible electroporation for the ablation of renal masses: a prospective, human, in-vivo study protocol". BMC Cancer. 15(1):165.
65. Wendler JJ, Pech M, Köllermann J, Friebe B, Siedentopf S, Blaschke S, et al. (March 2018). "Upper-Urinary-Tract Effects After Irreversible Electroporation (IRE) of Human Localised Renal-Cell Carcinoma (RCC) in the IRENE Pilot Phase 2a Ablate-and-Resect Study". Cardiovascular and Interventional Radiology. 41(3):466-476.
66. Ricke J, Jürgens JH, Deschamps F, Tselikas L, Uhde K, Kosiek O, De Baere T. (April 2015). "Irreversible electroporation (IRE) fails to demonstrate efficacy in a prospective multicenter phase II trial on lung malignancies: the ALICE trial". Cardiovascular and Interventional Radiology. 38(2):401-408.
67. Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, Roberts S, Evans P, Ball C, Haydon A. (May 2011). "Investigation of the safety of irreversible electroporation in humans". Journal of Vascular and Interventional Radiology. 2011 May; 22(5):611-621.
68. Usman M, Moore W, Talati R, Watkins K, Bilfinger TV. (June 2012) "Irreversible electroporation of lung neoplasm: a case series". Medical Science Monitor. 18(6): CS43-47.
69. Srimathveeravalli G, Wimmer T, Silk M, et al. (2013). "Treatment planning considerations for IRE in the lung: placement of needle electrodes is critical". J Vasc Interv Radiol. 24(4):S22.
70. Maor E, Ivorra A, Rubinsky B (2009-03-09). "Non thermal irreversible electroporation: novel technology for vascular smooth muscle cells ablation". PLOS ONE. 4(3):4757.
71. Xie F, Varghese F, Pakhomov AG, Semenov I, Xiao S, Philpott J, Zemlin C (2015-12-14). "Ablation of Myocardial Tissue with Nanosecond Pulsed Electric Fields". PLOS ONE. 10(12):e0144833.
72. Mandel Y, Laufer S, Belkin M, Rubinsky B, Pe'er J, Frenkel S (2013-01-01). "Irreversible electroporation of human primary uveal melanoma in enucleated eyes". PLOS ONE. 8(9):e71789.
73. Meijerink MR, Scheffer HJ, de Bree R, Sedee RJ (August 2015). "Percutaneous Irreversible Electroporation for Recurrent Thyroid Cancer--A Case Report". Journal of Vascular and Interventional Radiology. 26(8):1180-1182.
74. Deodhar A, Monette S, Single GW, Hamilton WC, Thornton RH, Sofocleous CT, Maybody M, Solomon SB (December 2011). "Percutaneous irreversible electroporation lung ablation: preliminary results in a porcine model". Cardiovascular and Interventional Radiology. 34(6):1278-1287.
75. Dupuy DE, Aswad B, Ng T. (April 2011). "Irreversible electroporation in a Swine lung model". Cardiovascular and Interventional Radiology. 34(2):391-395.
76. Garcia PA, Pancotto T, Rossmeisl JH, Henao-Guerrero N, Gustafson NR, Daniel GB, Robertson JL, Ellis TL, Davalos RV (February 2011). "Non-thermal irreversible electroporation (N-TIRE) and adjuvant fractionated radiotherapeutic multimodal therapy for intracranial malignant glioma in a canine patient". Technology in Cancer Research & Treatment. 10(1):73-83.
77. Garcia PA, Rossmeisl JH, Neal RE, Ellis TL, Olson JD, Henao-Guerrero N, Robertson J, Davalos RV (July 2010). "Intracranial nonthermal irreversible electroporation: in vivo analysis". The Journal of Membrane Biology. 236(1):127-136.
78. Lavee J, Onik G, Mikus P, Rubinsky B (2007). "A novel nonthermal energy source for surgical epicardial atrial ablation: irreversible electroporation". The Heart Surgery Forum. 10(2):E162-167.
79. Al-Sakere B, André F, Bernat C, Connault E, Opolon P, Davalos RV, Rubinsky B, Mir LM (November 2007). "Tumor ablation with irreversible electroporation". PLOS ONE. 2(11):e1135.
80. Calmels L, Al-Sakere B, Ruaud JP, Leroy-Willig A, Mir LM (December 2012). "In vivo MRI follow-up of murine tumors treated by electrochemotherapy and other electroporation-based treatments". Technology in Cancer Research & Treatment. 11(6):561-570.
81. Fini M, Tschon M, Ronchetti M, Cavani F, Bianchi G, Mercuri M, Alberghini M, Cadossi R (November 2010). "Ablation of bone cells by electroporation". The Journal of Bone and Joint Surgery. British Volume. 92(11):1614-1620.
82. Fini M, Tschon M, Alberghini M, Bianchi G, Mercuri M, Campanacci L, et al. (2011). "Cell electroporation in bone tissue.". In Lee E, Kee S, Gehl J (eds.). Clinical aspects of electroporation. New York, NY.: Springer. pp. 115–127.
83. Wong D, Lee EW, Kee ST (2011). "Translational research on irreversible electroporation: VX2 rabbit head and neck.". In Lee E, Kee S, Gehl J (eds.). Clinical Aspects of Electroporation. Berlin: Springer. pp. 231–236.
84. Maor E, Ivorra A, Rubinsky B (2009-01-01). "Non thermal irreversible electroporation: novel technology for vascular smooth muscle cells ablation". PLOS ONE. 4(3):e4757.
85. Au JT, Kingham TP, Jun K, Haddad D, Gholami S, Mojica K, Monette S, Ezell P, Fong Y. (2013). Irreversible electroporation ablation of the liver can be detected with ultrasound B-mode and elastography. Surgery. 2013 Jun; 153(6):787-793.
86. Lee EW, Chen C, Prieto VE, Dry SM, Loh CT, Kee ST. (2010). Advanced hepatic ablation technique for creating complete cell death: irreversible electroporation. Radiology. 2010 May; 255(2):426-433.
87. Dunki-Jacobs EM, Philips P, Martin RC 2nd. (2014). Evaluation of thermal injury to liver, pancreas and kidney during irreversible electroporation in an in vivo experimental model. Br J Surg. 2014 Aug; 101(9):1113-1121.
88. Sugimoto K, Moriyasu F, Kobayashi Y, Kasuya K, Nagakawa Y, Tsuchida A, Hara T, Iobe H, Oshiro H. (2015). Assessment of various types of US findings after irreversible electroporation in porcine liver: comparison with radiofrequency ablation. J Vasc Interv Radiol. 2015 Feb; 26(2):279-287.e3.
89. Appelbaum L, Ben-David E, Sosna J, Nissenbaum Y, Goldberg SN. (2012). US findings after irreversible electroporation ablation: radiologic-pathologic correlation. Radiology. 2012 Jan; 262(1):117-125.
90. Appelbaum L, Ben-David E, Faroja M, Nissenbaum Y, Sosna J, Goldberg SN. (2014). Irreversible electroporation ablation: creation of large-volume ablation zones in in vivo porcine liver with four-electrode arrays. Radiology. 2014 Feb; 270(2):416-424.
91. Faroja M, Ahmed M, Appelbaum L, Ben-David E, Moussa M, Sosna J, Nissenbaum I, Goldberg SN. (2013). Irreversible

electroporation ablation: is all the damage nonthermal? Radiology. 2013 Feb; 266(2):462-470.
92. Wagstaff PG, de Bruin DM, van den Bos W, Ingels A, van Gemert MJ, Zondervan PJ, Verdaasdonk RM, van Lienden KP, van Leeuwen TG, de la Rosette JJ, Laguna Pes MP. (2015). Irreversible electroporation of the porcine kidney: Temperature development and distribution. Urol Oncol. 2015 Apr; 33(4):168. e1-e7.
93. Agnass P, van Veldhuisen E, Vogel JA, Kok HP, de Keijzer MJ, Schooneveldt G, de Haan LR, Klaessens JH, Scheffer HJ, Meijerink MR, van Lienden KP, van Gulik TM, Heger M, Crezee J, Besselink MG. (2020). Thermodynamic profiling during irreversible electroporation in porcine liver and pancreas: a case study series. J Clin Transl Res. 2020 Mar 12; 5(3):109-132.
94. Dong S, Wang H, Zhao Y, Sun Y, Yao C. (2018). First Human Trial of High-Frequency Irreversible Electroporation Therapy for Prostate Cancer. Technol Cancer Res. Treat. 2018 July 25; 17: 1533033918789692.
95. Colletini F, Enders J, Stephan C, Fischer T, Baur A D J, Penzkofer T, Busch J, Hamm B, Gebauer B. (2019). Image-guided Irreversible Electroporation of Localized Prostate Cancer: Functional and Oncologic Outcomes. Vascular and Interventional Radiology 2019 June 4; 292(1):250-257.
96. Rojo RD, Perez JVD, Damasco JA, Yu G, Lin SC, Heralde FM 3rd, Novone NM, Santos EB, Lin SH, Melancon MP. (2021). Combinatorial effect of radium-223 and irreversible electroporation on prostate cancer bone metastasis in mice. Int J Hyperthermia. 2021; 38(1):650-662.
97. Lim, B., Kim, H.B., Jeong, S. *et al.* (2021). Novel platinum bipolar electrode for irreversible electroporation in prostate cancer: preclinical study in the beagle prostate. *Sci Rep* 11**,** 17194 (2021).
98. Blazevski A, Scheltema MJ, Amin A, Thompson JE, Lawrentschuk N, Stricker PD. (2020). Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment. BJU Int. 2020 Mar; 125(3):369-378.
99. Blazevski A, Scheltema M J, Yuen B, Masand N, Nguyen T V, Delprado W, Shnier R, Haynes A-M, Cusick T, Thompson J, Stricker P. (2020). Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort, European Urology Oncology. 2020; 3(3):283-290, ISSN 2588-9311.
100. Blazevski A, Amin A, Scheltema M J, Balakrishnan A, Haynes A M, Barreto D, Cusick T, Thompson J, Stricker P D. (2021). Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World J Urol. 2021 Apr; 39(4):1107-1114.
101. Blazevski A; Gondoputro W, Scheltema M J, Amin A, Geboers B, Barreto D, Haynes A-M, Shnier R, Delprado W, Agrawal S, Thompson J E, Stricker P. (2021). Salvage Robot-assisted Radical Prostatectomy Following Focal Ablation with Irreversible Electroporation: Feasibility, Oncological and Functional Outcomes. Posted Date: November 8th, 2021; Page 2-17.
102. Blazevski A Scheltema M, Yuen B, Cusick T, Haynes A-M, Stricker P. FR02-12 Lab to Lithotomy - A History of Irreversible Electroporation from Laboratory Technique to Prostate Cancer Treatment Journal of Urology 2019; Apr; 201 (Supplement 4).
103. Blazevski A, Scheltema M, Yuen B, Cusick T, Haynes A-M, Stricker P. (2019). MP74-16 Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging to Detect Residual Prostate Cancer Following Focal Therapy with Irreversible Electroporation, Journal of Urology 2019 April; 201(Supplement 4):e1079-e1079]
104. Morozov A, Taratkin M, Barrett E, Singla N, Bezrukov E, Chinenov D, Enikeev M, Rivas J G, Shpikina A, Enikeev D. (2020). A systematic review of irreversible electroporation in localised prostate cancer treatment. Andrologia First International Journal of Andrology. 2020 November; 52(10):e13789-e13789.
105. Scheltema M J, Chang J I, Böhm M, van den Bos W, Blazevski A, Gielchinsky I, Kalsbeek A M F, Leeuwen P J, Nguyen T V, de Reijke T M, Siriwardana A R, Thompson J e, de la Rosette J J, Stricker P D. (2018). Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World Journal of Urology. 2018 March 28; 36: 1383 – 1389.
106. Kızıl P G, Altan S A, Tarhan N Ç. (2021). Evaluation of clinical and mpMRI findings of irreversible electroporation therapy for the treatment of localized prostate cancer: Preliminary results. Turkish Journal of Urology. 2021 Jul 1; 47(4):299-304.

DOI: 10.31579/2690-1919/239