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NEW IMAGING TECHNIQUES (S RAIS-BAHRAMI AND K PORTER, SECTION EDITORS)

Irreversible Electroporation for the Ablation of Prostate Cancer

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Abstract

Purpose of Review Although still considered experimental, focal irreversible electroporation (IRE) as a primary treatment for prostate cancer (PCa) is considered one of the most promising ablative technologies for focal therapy. This review provides a description of the principle of IRE for the treatment of PCa, combined with an overview of the recent research.

Recent Findings It has been almost a decade since the first human studies of focal IRE for PCa were trying to demonstrate its feasibility and safety, and recently new data are emerging regarding the functional and oncological outcomes. It was shown that the expected ablation efficacy of IRE is dependent on increased safety margins of > 9 mm and an uninterrupted IRE procedure, but these findings need further investigation in larger cohorts and randomized control trials (RCT).

Summary Recent data from larger cohorts with a longer follow-up of up to 12 months prove that focal IRE as primary treatment for localized PCa is indeed safe, has effective short-term oncological control in selected patients, and it has good functional outcomes by retaining urinary function and causing only mild erectile dysfunction.

Keywords Prostate cancer · Focal therapy · Irreversible electroporation · IRE · Partial gland ablation · Review

Introduction

Prostate cancer screening, whether formal or informal, resulted in stage migration, with an increasing number of patients diagnosed at an earlier stage with smaller tumors and a greater tendency for unifocal or unilateral disease [1–3].

Contemporary management approach of these patients comprises of active surveillance or local radical treatment (surgery or radiation). It is evident, nevertheless, that radical treatment in very low-risk and low-risk patients results in overtreatment, with long-term complications such as incontinence and impotence, which greatly affects their quality of life [4]. Contrarily, active surveillance protocols do not have the complications of radical therapy, but the feeling of waiting for the cancer to worsen while not doing anything in the meantime, alongside with the morbidity of repeating biopsies, brings anxiety and psychological stress, which affects their quality of life [5, 6]. Focal therapy for prostate cancer has the potential to fill this management gap, by delivering almost similar to radical therapy cancer control while devoid of associated short and long-term complications. The fundamental rationale of focal therapy is to spare the organ, by aiming on the cancerous lesion, and thus sparing the healthy tissue and neighboring organs such as the neurovascular bundles, external sphincter, rectum, and urethra.

The recent technological advances of ultrasound and MRI in prostate imaging contributed to the development of the concept of focal therapy. These advances allowed us to better detect, visualize, and categorize the tumorous lesions of the prostate [7–10]. So the selective targeting of clinically significant lesions was feasible, predominantly the lesion accountable for potential disease progression, the "index lesion" [11]. Further technological advancement of all of the equipment involved will make the detection and targeting more accurate and precise, eliminating only the cancerous lesions, thus providing to the patient and the doctor the relief of having treated only the cancer while minimizing the side effects and complications.

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Even though, according to the recent EAU guidelines, focal therapy is still experimental and cannot be considered as a viable therapeutic alternative outside clinical trials for prostate cancer, it is becoming the new controversial topic about prostate cancer management, offering a large field for research and innovation.

A vast assortment of ablation energies are being investigated in the setting of focal therapy for prostate cancer. The main differentiation between the ablation modalities is whether ablation is based on thermal damage of tissue or non-thermal alterations leading to apoptosis and death at a cellular level. Each energy modality has its pros and cons, concerning ablation efficacy, cancer control as well as associated complications. Irreversible electroporation is one of the newest non-thermal ablation modalities involved in focal prostatic therapy.

Evidence Acquisition

We conducted a PubMed and Medline search until April 2019 to identify all publications related to irreversible electroporation for the ablation of prostate cancer. Original studies and reviews were included. Keywords used for the search were "irreversible electroporation," "IRE," "prostate cancer," "focal therapy," "ablation," "active surveillance," "partial ablation."

Historical Perspective and Mechanism of Action

Electroporation is a procedure in which brief, microsecond electric pulses, traveling between two or more electrodes, generate "nanopores" in the cell membrane. These nanopores allow for molecules to enter into the cell. According to the field amplitude, duration and number of electrical pulses this process can be temporary (reversible electroporation), or above a certain threshold permanent, causing cell destruction due to the incapability to preserve homeostasis due to the non-reversible loss of calcium ions and the constant disturbance of sodium/potassium gradient (irreversible electroporation) [12–14]. The breakdown and reseal ability of the cell membrane when introduced in an electric field were first demonstrated at a cellular level in the 1970s [15–20].

Over the last decades, reversible electroporation has been consistently used in the health field for transdermal drug delivery, for electrochemotherapy and for electro-gene therapy [21–23].

An unsuccessful application of reversible electroporation with subsequent cell death, thus irreversible electroporation, was considered as an undesirable side effect. Soon thereafter, it was realized that this complication could be used as a tissue ablation modality.

The fact that electrical currents cause cell death has been documented since 1754 from the studies of Nollet on the skin [24], while Fuller in 1898 described the bactericidal effect of electricity on water [25]. In recent years, pulsed electrical fields have also been researched significantly as a method of water decontamination [26, 27] and since 1961 in the food industry for sterilization and preprocessing of food [28]. Electrical fields leading to irreversible electroporation also became popular during the last decade as a way to ablate normal or cancerous mammalian cells in vitro [29]. This capability was applied successfully in vivo as confirmed during tumor ablation of the liver, pancreas, kidney, and lung [30–33], resulting in the production of IRE medical equipment to be used in minimally invasive surgery for tumor ablation [34].

Device and Procedure Description

The vast majority of the IRE procedures use the AngioDynamics Inc. HVP-01 Electroporation System (NanoKnife™ IRE System; Angiodynamics, Queensbury, NY, USA) which is approved in Europe (CE certificate), USA (FDA), and Australia, for the surgical ablation of soft tissue.

NanoKnife™ is the first commercially available apparatus of irreversible electroporation (IRE) for the ablation of tissue that is mainly cellular, and it comprises of two major components: a low-energy direct current (LEDC) generator and needle electrode probes (Fig. 1).

The procedure is performed in lithotomy position under general anesthesia with full muscle paralysis and prophylactic i.v. antibiotics. Full muscle paralysis is required to minimize patient movements due to whole body muscle spasms. The patient is catheterized, bladder is emptied, and 50 cc of sterile water is instilled into the bladder. The NanoKnife™ needle probes are transperineally inserted parallelly under biplanar TRUS guidance using a 5×5 mm mapping biopsy/brachytherapy template (Fig. 1). Using either MRI/TRUS fusion imaging or cognitively from mpMRI images, the probes are arranged in way that the target zone is encircled and the procedure is performed.

The electrical LEDC energy is distributed to the NanoKnife™ electrode probes that are strategically planted around the lesion and work in a two-pole operating mode, where one is the positive supply and the other is the negative return. Maximum 6 probes can be parallelly inserted depending on the size and shape of the target lesion in order to form numerous two-pole combinations, while the interprobe space must be between 10 and 20 mm. No grounding pad is needed. By retracting the protective cap of the probe, the effective tip of the probe can be adjusted between 0.5 and 2 cm, which means that for lesions greater than > 2 cm in depth, the probes

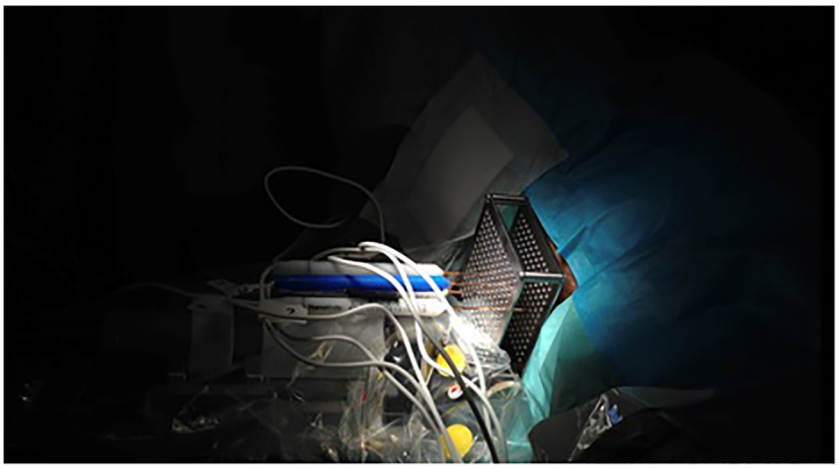

Fig. 1 Patient placed in the lithotomy position and placement of IRE probes in the lesion with the assistance of a brachytherapy stepping grid and TRUS

must be retracted and the energy reapplied. At least 5-mm space should be permitted from vital structures such as the rectum, urethra, urethral sphincter, bladder, and neurovascular bundle. Initial tumor safety margins were > 5 mm, but recent studies demonstrate that at least > 9 mm are needed. After the proper probe placement, the applicable settings for voltage, pulse number, and pulse length are entered in the generator user interface. Test pulses are initially delivered to demonstrate the electrical current dynamics. The energy delivery is monitored in real time with the ultrasound. The apparatus then charges for 30–40 s and produces a series of short electric pulses in a few seconds. Using the device software, corrections are made in order to keep the current within the optimal treatment range of 20–40 A. A final sequence of 70–90 pulses of 1500 V/cm per probe pair ablates the tissue with a pulse length of 70–90 μs. In some centers, patients are discharged home on the day of the procedure with the catheter, and the catheter is removed within 5 days, while in other centers, the catheter is removed in the morning of post-op day 1 and then discharged home.

Clinical Data

IRE Human Phase I/II Studies for Prostate Cancer

In the beginning of this decade, the first phase I–II trials in humans of focal IRE for the treatment of prostate cancer were completed, showing promising results of functional preservation and effective ablation, but with short follow-up of 1–6 months (Table 1). Onik et al. were the first to demonstrate the safety and feasibility of focal IRE, at 16 patients, with no complications perioperatively and the transperineal template–guided mapping biopsy (TTMB) at 3 weeks showing no tumor in the ablation zone [35].

Furthermore, Neal et al. were the first group to provide us with histology data of the effect of IRE in humans by performing IRE on 2 patients and then radical prostatectomy at 3 or 4 weeks post-IRE. Mild hematuria was the only post-op event, while the histology demonstrated no cancer at the ablation zone with tissue necrosis and inflammatory infiltration [36].

Moreover, Valerio et al. assessed the feasibility and safety of IRE on a larger group of 35 patients, with no serious complications and only mild hematuria, dysuria, and UTI as minor adverse events. All the patients who were continent before the procedure remained continent, while the mpMRI at 6 months showed residual disease at 6/34, and 2 of these patients were monitored with active surveillance, 3 had salvage HIFU or IRE, and 1 radical prostatectomy [37].

Additionally, in a multicenter study by Van den Bos et al. at Amsterdam AMC and Athens Medical School, 16 patients received IRE for 1–4 ISUP PCa 4 weeks before radical prostatectomy. Apart from proving the safety of IRE by having no major adverse events and good functional outcomes at 4 weeks post-IRE, this study demonstrated that radical prostatectomy after IRE is feasible, safe, and with no complications. The histological specimens of the radical prostatectomy at 4 weeks showed no viable cancer in the ablation zones, but the NVB was affected in 13/16 and the prostatic urethra in 9/16 patients, with unknown effects on the functional outcomes [38].

IRE as a Primary Treatment for Prostate Cancer

Ting et al., in Sydney, treated 32 patients for primary focal IRE, 25 of which were ISUP 1–3 and were included in the study. There were no changes in the functional outcomes at 6 months of the 18/25 who completed the EPIC questionnaires. Regarding the oncological results at 7 months after TTMB, there was no significant infield disease in the 21 patients, but there was 1 patient who had a newly found significant outfield disease, and there were 4/21 patients with significant disease at the adjacent zone. These 4 patients

Table 1 Clinical data from all major IRE studies

Studies	Authors	Patients #	ISUP GG	Clavien 1–2	Clavien 3	Residual tumor at follow-up	ED post-IRE	UI post-IRE
Phase I/II	Onik 2010	16	1–4	0/16	0/16	1/16 (outfield)	n/a	0/16
	Neal 2014	2	1–3	0/2	0/2	0/2 (after RP)	n/a	n/a
	Valerio 2014	34	1–4	18/34	0/34	6/34	1/20	0/24
	Van den bos 2016	16	1–4	15/16	1/16 (sepsis)	0/16 (after RP)	0/16	0/16
IRE as primary therapy	Ting 2016	25/23	1–3	5/25	1/25 (unrelated MI)	0/21 (infield) 5/21 (1 outfield but 4 adjacent)	0/18	0/18
	Murray 2016	25	1–3	14/25	2/25(UTI)	4/25 (all infield)	1/25	2/25
	Valerio 2016	16/20	1–2	10/16	0/16	7/16 (infield)	1/16	0/16
	Van den bos 2018	45/63	1–3	15/45	0/45	7/45 (infield) 4/45 (outfield)	8/26 (at 6mo) 3/13 (at 12mo)	0/45
Phase I/II H-FIRE IRE	Dong 2018	40	1–3	15/40	0/40	0/8 (after RP)	0/14	0/40
Salvage IRE after EBRT or Brachy	Scheltema 2017	18	2–5	7/18	0/18	2/10 (infield)	4/6	3/11
Salvage IRE after RP and EBRT	Gebauer 2017	3	n/a	3/3	1/3	n/a (MRI showed no viable tumor)	n/a	2/3

belonged to the first 12 patients in the series that had a treatment margin of 5 mm. Following these results, the treatment margin was widened to 10 mm, and all subsequent patients were free from significant infield or adjacent infield tumors on the follow-up TTMB biopsy. Three of these patients are on active surveillance, one is waiting for a re-IRE, and one had RARP [39].

Meanwhile, Murray et al. investigated the safety and clinical outcomes of 25 patients who underwent IRE as primary treatment, with a follow-up of 12 months. Apart from 14/25 who had minor adverse events, 2/25 patients had grade 3 complications, a UTI and an epididymitis. The routine follow-up biopsy at 6 months was positive in the ablation zone in 4/25, and 3 of these patients had radical prostatectomy. By 12 months, 1/25 had a new erectile dysfunction and 2/25 required a pad for urinary incontinence [40].

In the second study on focal IRE by Valerio et al., they recruited 20 patients with ISUP grade 1–2. In the 16 patients that were followed-up for 12 months, the urinary function improved slightly, while there was 1 patient that experienced new ED. The oncological outcomes with a TTMB biopsy at 6 months revealed residual disease in 7/16 patients, significant in 6/16, possibly because the margins of the study were much less than 9 mm [41••].

The largest cohort of IRE as a primary treatment for localized PCa was performed in Sydney by Van den Bos et al. A total of 63 patients underwent IRE, 45 of which had undergone follow up biopsy at 6–12 months at the time of publication. No major adverse events were noted, and the urinary function of all patients returned to baseline at 12 months, while there was a likelihood of impotence of 31% (8/26) at 6 months and 23% (3/13) at 12 months. The oncological control of the 45 patients that had a biopsy between 6 and 12 months showed significant infield lesions in 7/45 and significant outfield lesions in 4/45. It is important to note that the first 10 patients in the cohort were treated with a 5-mm margin and the rest with a 10-mm margin. After this margin increase, the infield occurrence dropped from 40 (4/10) to 8.6% (3/35) [42••].

In addition, Scheltema et al., part of the same group of researchers from Sydney, matched with propensity score 50 of those focal IRE patients with 50 bilateral nerve sparing robot-assisted radical prostatectomy (RARP) patients for 12 months. The functional results at 12 months revealed that IRE was significantly superior to RARP in preserving urinary continence by 14% and erectile function by 22%. At 12 months, no RARP patients had biochemical failure whereas 13/44 of the IRE patients had significant residual disease [43•].

It is evident that more data are needed to establish focal IRE as viable option for the primary treatment of PCa and that is why a large, prospective, multicenter RCT is being conducted by CROES [44].

New Developments of IRE for the Treatment of Prostate Cancer

High-Frequency IRE

In a phase I–II trial at Shanghai Hospital in China, Dong et al. were the first to utilize high-frequency IRE (HF-IRE) for focal therapy for PCa in 40 patients with a follow-up of 6 months. This is the only study in which they used their own developed composite steep pulse generator apparatus, and not NanoKnife™ used by all the other researchers. This device can produce bursts of HF bipolar pulses, which enables the procedure to be performed with a small amount of muscle relaxant. No major adverse events were recorded while sexual function was preserved in 14/14 patients and all patients retained their urinary function. Radical prostatectomy was performed in 8/40 patients 4 weeks post-HFIRE which showed no viable tissue in the ablated zone [45•].

Salvage IRE

Scheltema et al. demonstrated that salvage IRE with localized radio-recurrent PCa is a feasible and safe alternative in 18 patients with an average follow-up of 21 months. No major adverse effects and no rectal fistulas were seen. Regarding the functional outcomes, only one patient at 12 months required pads for urinary dribbling but 4/6 patients had ED in 6 months. As for oncological control, the follow-up biopsies at 6 months showed residual infield disease in 2/10 patients. Because of these promising results, "FIRE" trial, a prospective multicenter study, has been initiated to further investigate salvage focal IRE [46].

Most recently, Gebauer et al. investigated the effect of salvage IRE on 3 patients with local recurrence after radical prostatectomy and salvage radiation therapy. The mpMRI 1 day post-IRE showed no viable tumor in the ablation zone and there was a 55% decrease of the PSA levels at 3 months. No major adverse effects, urethrorectal fistulas, or rectal wall damage were seen, but all patients at 3 months experienced minor procedure–related complications; 2/3 had mild urinary incontinence requiring 1 or 2 pads, and 1/3 underwent internal urethrotomy due to an urethral stricture [47].

Safety and Advantages

For all new technologies that have an application in the medical field and especially in surgery, gradual steps must be taken to ensure safety. So after basic research and animal studies that demonstrate the feasibility and potential benefits of this new technology, promising data from limited human clinical testing, lets us proceed with more extended clinical trials. But from all the aforementioned trials, it is evident that IRE is a safe modality for the focal therapy for PCa with minimal morbidity, even when we compare it with other forms of focal therapy.

- Radical prostatectomy after IRE is safe and uneventful

While there is only limited clinical experience in a small number of patients, subsequent radical prostatectomy in patients 1 month after IRE ablation was no more demanding than any other radical prostatectomy [36, 48].

Present experience regarding the safety and efficacy of IRE in humans indicates no major complications during or after IRE [49]. This technology has been applied also in the liver [50, 51], pancreas [52, 53], kidney [13], lung [54], and prostate [37, 38]. Most adverse events were minor and correlated with the puncture itself rather than with the technology.

Recently, Scheltema et al. demonstrated that IRE is a feasible ablation modality for lesions in all the prostatic segments, without any significantly different effect on the QoL outcomes, although elderly patients and those with poor sexual function need to be advised regarding the risk of erectile dysfunction after IRE [55••].

- Sharp demarcation margins and uniform lesion ablation

Preclinical and clinical research observed no cold or heat sink phenomena (as in cryotherapy, HIFU, or RFA) as a result of the non-thermal nature of IRE. After the application of thermal ablation therapies, a transitional zone of partially affected tissue is seen in the periphery, but on the contrary post-IRE there is a sharp demarcation between ablated and non-ablated tissue. Because of the dipole principle of IRE, the ablated area is limited between the needles and thus more predictable, whereas in the thermal energies, it radiates outward and is not bounded. The fact that cancerous tissue is consistently destroyed within the electrical field and thus no skip lesions are observed makes IRE extremely effective [56].

The first studies experimented with a 5-mm safety margin around the targeted area, [41••] but recently Van den Bos et al. demonstrated that a safety margin of at least 10 mm is needed to significantly reduce the likelihood of having residual tumor from 40 to 8.6% [42••].

Concerningly, the dynamic changes during the procedure, because of varying tissue conductivity and heterogenicity, can lead to premature termination of the generator due to a high current and seem to be associated with in-field residual cancer. In addition, the formation of an "electric" sink phenomenon altering the anticipated ablation zone in a comparable way

with the heat/cold sink event is possible and requires further research [57].

- Fast ablation outcome and complete lesion resolution

The ablation zone in thermal ablative techniques is affected by the vascularity of the target tissue due to the heat/cold sink phenomenon, and thus the procedure time is prolonged by the repeated cycles that may be required. Additionally, the outcome of thermal ablation technologies takes several months to show a decrease in size and years to demonstrate complete resolution of the lesion, which makes follow-up and determination of treatment success or failure challenging even in the most experienced hands.

Contrarily, IRE is independent of thermal diffusion and the energy is delivered in very short pulses, producing rapid ablation, rendering IRE a fast procedure. Moreover the ablated area quickly resolves in scar/necrotic tissue in a couple of weeks with destruction of cancer cells without any residual cavity or distortion [58]. It is hypothesized that this is because the microvasculature, down to the arteriolar level, throughout the IRE lesion is preserved. Onik et al. postulated that IRE lesions are therefore able to heal throughout their volume, whereas thermal lesions are completely de-vascularized shortly after lesion creation and are slowly resolved from the edges of the lesions inward [59]. While the conservation of the microvasculature in the ablated area could be an issue, further research is required, especially in organs with tissue regeneration properties such as the liver.

- Effect on sensitive structures such as nerves, vessels, and urethra

Basic research and preclinical studies indicated that sensitive structures such as blood vessels, urethra, rectum, and nerves could be spared if they are in the IRE ablation zone. In addition, IRE seemed a very promising modality not only because of the sparing of sensitive tissues but also because it does not cause thermal damage and that it does not damage collagen and other interstitial constituents [60].

Recently, De Bruin et al. investigated the histopathological outcomes of 16 patients that underwent IRE treatment for PCa and a month later radical prostatectomy. The radical prostatectomy specimens showed that in the sharply demarcated ablation zone, there were no viable cells and there was only fibrotic and necrotic tissue. Contrarily, there was in-field deterioration to structures as the urethra, prostatic capsule, and neurovascular bundle, though the long-term effects remain unknown [56]. In these patients, exactly before the radical prostatectomy, there was a slight insignificant decrease in urinary function and quality of life [61].

- Better imaging during the procedure and follow-up

Thermal modalities like cryotherapy and HIFU, once activated render the ultrasound "blind" and useless to any new image information due to the high-echogenicity ice ball and the tissue out-gassing that occurs respectively. From the first studies, it was evident that the structural changes the targeted tissue underwent in IRE could be detected real-time via ultrasound, CT, or MRI [59]. Van den Bos et al. demonstrated that mpMRI and contrast-enhanced ultrasound are appropriate imaging modalities for assessing IRE effects [48] and most recently Giganti et al. concluded that with mpMRI, IRE ablation effects in men with PCa are visualized and these mpMRI-derived parameters (such as tumor, necrotic and fibrosis volumes) can be measured and are potentially useful for assessing efficacy in the short and medium term [62].

Conclusions

Irreversible electroporation is a new ablation modality with potential use in focal therapy for prostate cancer. Its main difference from other ablation modalities is that it is non-thermal in nature. This may explain its potential advantages as the rapid creation and resolution of the targeted necrotic lesion, the sharp demarcation between the ablated and non-ablated area as well as the potential to spare certain connective and neurological tissues such as blood vessels, ductal systems, urethra, and nerves.

Preliminary use of this technology has shown it to be both feasible and safe in treatment of prostate cancer patients. Only low-grade self-limiting complications were seen in initial patient series. One main advantage against the other modalities is that radical prostatectomy is feasible in case of treatment failure. There is good short-term oncological control, urinary continence is retained, and there is mild deterioration of erectile function. However, rigorous prospective studies with systematic assessment of the functional and the oncological outcomes are needed in order to move forward in the evaluation of IRE as a new technology for focal ablation in prostate cancer.

Compliance with Ethical Standards

Conflict of Interest Andreas Karagiannis and John Varkarakis each declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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