Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment

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Abstract

Introduction

Whilst whole gland radical treatment is highly effective for prostate cancer control, it confers significant impact on quality of life (QOL) and is unnecessary 'over-treatment' in many men with screening detected prostate cancer. Improvements in prostate biopsy and imaging have led to the increased interest in partial gland ablation to reduce treatment-related morbidity. Several energies for focal ablation have been trialled. Irreversible electroporation (IRE) is a novel technology which ablates tissue by delivering direct current between electrodes. This narrative review aims to document 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.

Methods

A literature search using MEDLINE, Embase, PubMed and Google Scholar was undertaken to identify historical perspectives and current clinical data relating to IRE for prostate cancer.

Results:

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 have been published in several papers, with preserved rates of (pad-free) continence in 91-100% of men and preserved erectile function in 79-100% of men. In-field recurrence rates range from 0% to 33%. The current

state of evidence for IRE in treatment of primary and salvage prostate cancer is considered IDEAL stage 2B.

Conclusions:

IRE is a new focal ablative technology for the treatment of localised prostate cancer in carefully selected men. Published cohorts reported encouraging short-term oncological and functional outcomes, however longer-term data is needed to validate this treatment before it can be recommended for widespread clinical use.

Introduction

Focal therapy is an emerging treatment option for men with localised prostate cancer. The interest in focal treatments is increasing due to recent improvements in disease localisation and risk stratification. Such improvements include novel imaging modalities (e.g. multiparametric magnetic resonance imaging [mpMRI] and prostate-specific membrane antigen – positron emission tomography [PSMA-PET]), and refinements in biopsy techniques (e.g. image-targeted biopsy and transperineal template biopsy). Focal ablation of the prostate has several potential aims, 1) To achieve equivalent oncological control as whole-gland radical treatments (radical prostatectomy, radiotherapy) while improving quality-of-life (QoL) and 2) to switch a patient requiring radical treatment into an active surveillance candidate. Both aims are achieved by ablating all regions containing significant cancer while preserving the unaffected prostate and adjacent structures (Figure 1). Multiple modalities and energy sources for focal ablation are available and are currently in clinical use (table 1) [1]. Irreversible electroporation (IRE) is a novel focal ablative modality under investigation. The importance of urologists understanding the scientific principles behind new technologies before they are utilised cannot be over-emphasised. This narrative review summarises the history of electroporation and how it has developed into a prostate cancer treatment. It provides an update of the available published data on IRE for prostate cancer and the future direction for this treatment modality.

Materials and Methods

A literature search was undertaken using MEDLINE, Embase, PubMed and Google Scholar. The following terms were entered into the search algorithm to identify peer-reviewed articles, 'prostate cancer', 'focal therapy', 'focal ablation', 'irreversible electroporation', 'reversible electroporation', 'electroporation', 'Nanoknife®', 'multiparametric MRI'. No time restriction was placed on the searches as the aim was to offer a historical perspective of the development of irreversible electroporation from scientific theory to potential prostate cancer treatment. The search was limited to articles in English. The authors reviewed the retrieved articles, and the references of the received articles were used when relevant.

History of Electroporation

The first recorded observation of the phenomenon of IRE was in 1754 by Nollet [2]. He applied electric sparks to human and animal skin and noticed the occurrence of red spots. Although unknown at the time, these spots were secondary to the damage of capillaries from electroporation. Interest subsequently increased into the effect of electricity on biological systems and soon Galvani showed that electricity applied to a dead frog's spinal cord led to muscle twitching [3]. It was also noticed that the damaging effects of lightning strikes were different to that of thermal energies, characterised by red 'Lichtenberg' figures on the skin of lightning-strike victims [4].

The first uses of pulsed electrical fields were in water purification. In the late 19th century it was observed that high-voltage electrical discharges had a bactericidal effect and could purify river water without increasing water temperature [5].

The bactericidal effects of IRE were further explored by Sale and Hamilton in the 1950s and 1960s. They showed that the bactericidal effect of electric fields was unrelated to the concurring thermal effect [6,7]. This was demonstrated by using ten very short (2- 20 μs) direct current electric pulses [7]. The electric field required to completely ablate the bacteria was as high as 16 kV/cm for *Escherichia coli* and 6 kV/cm for *Saccharomyces cerevisiae*.

Earlier in the 20th century experiments revealed the thickness of the cell membrane and its dielectric lipid bilayer arrangement [8]. This was an important step forward in the understanding of electroporation. Sale and Hamilton explained that the mechanism for the bacterial cell death from electric current was due to irreversible loss of membrane function as a semipermeable barrier [8,9].

Using spectroscopy, they observed the leakage of cell contents secondary to loss of cell membrane function.

Development of 'reversible' electroporation

Late in the 20th Century research focused on the field of 'reversible' electroporation. Electroporation can be reversible if the destabilization to the cell membrane is temporary and the cell is allowed to recover. In the 1980s this led to the introduction of reversible electroporation to induce cell fusion (electrofusion). This is now one of the main biochemical applications in the productions of hybridomas for antibody production [9].

Another application is the transfer of DNA into cells (electrotransfer). An early example of this technology was shown in a paper that demonstrated that a deficient gene could be transferred into the cell via plasmid DNA by the application of short electrical pulses to mouse lyoma cells [10]. Electrofusion and electrotransfer have since been commonly used in laboratories using benchtop electroporators.

Reversible electroporation has also been used in chemotherapy where electric pulses have been used to enhance the uptake of cytotoxic drugs into cancer cells (electrochemotherapy). Mir et al. showed that this could be used to facilitate the infiltration of bleomycin into malignant cells and performed the first clinical trial using this method [11]. This is an area of ongoing clinical research.

Development of 'Irreversible' Electroporation

IRE was initially considered the upper limit of reversible electroporation and was avoided as the aim was to create transient nanopores in the cell membrane while the cell survived. It has since been recognised that the mechanism of cell death following electroporation is due to excessive permeability and thus disrupting the osmotic balance of the cell beyond the capacity of cellular repair mechanisms (figure 2). In addition, it has been shown that in part, cell death following electroporation occurs as a result of chromosomal DNA fragmentation. This may be an indicator of late apoptosis [12].

In the early 21st century the foundation was laid for IRE as ablative modality of cancerous tissue [13]. Davalos et al. showed that IRE could be used to induce cell death while minimising harmful thermal

effects [13]. It was suggested that by maintaining important structural components, such as the extracellular matrix, healthy tissue regeneration could be facilitated. A number of subsequent animal studies showed that IRE could be applied in proximity to sensitive structures such as the liver hilum with preservation of bile ducts and hepatic vessels [14-16]. Histological assessment of rodent livers three hours post IRE ablation demonstrated that blood vessel architecture was preserved [17]. A similar histological effect was found in rodent carotid arteries four weeks post IRE ablation [14]. In this study, although the number of vascular wall smooth muscle cells decreased, the vascular connective tissue matrix was preserved [14]. This relative tissue-selectivity for the cell membrane, and the sparing of tissue scaffolds including vessels, is a unique feature that differs to thermal ablative modalities.

Principle behind using Irreversible Electroporation for Prostate Cancer

An ideal focal therapy modality for PCa would destroy cancerous cells while preserving or at least limiting the damage to the surrounding vital structures such as the neurovascular bundle, external sphincter, bladder neck, urethra and rectum. IRE aims to induce cell death via a non-thermal mechanism; therefore, it may differ in the preservation of surrounding vital structures as compared to other modalities that rely on non-selective thermal destruction. However, it is important to note, that while IRE may works primarily via a non-thermal mechanism it has been demonstrated to produce heat, as shown in porcine models [18].

The first trials of IRE were performed on Beagle dogs to assess the safety and feasibility of this technique. A total of 18 dogs underwent the IRE procedure of the prostate. Histopathological analysis showed that the neurovascular bundles appeared intact, bloods vessels-maintained patency and that there was no damage to the urethra or rectum [19,20]. Onik et al. showed that 2 weeks after IRE the ablated area was primarily replaced by collagenous tissue. Erectile function and urinary continence was preserved in all dogs. Post-IRE histopathological analyses have shown a sharp, well demarcated ablation zone after treatment [19-21], although the ablation zone was significantly larger than the electrode configuration thus the NVB was affected in most cases [21]. Figure 3 shows a region of post-treatment scar in the peripheral zone between normal transitional zone and seminal vesicle. This sharp demarcation between treated and not treated areas may be used for treatment planning.

IRE Procedure and Technique

The IRE procedure is performed under general anaesthesia and patients are given muscle relaxant as it is essential to avoid contractions during the procedure. The patient is positioned in lithotomy; an indwelling catheter is placed to empty the bladder and remains in situ for at least two days after the procedure (figure 4).

The IRE console contains two components, monopolar needle electrodes and a direct current generator controlled by computer-based treatment planning software (figure 5). Pre-operative targeted areas for ablation are based on mpMRI and template mapping prostate biopsies. 68-GA PSMA PET is increasingly being used pre-treatment and further aids treatment planning, especially with radio-recurrent disease. A transperineal template grid used for brachytherapy seed placement and transrectal ultrasound are used to position and guide the electrodes in the predefined targeted area. After electrode placement, IRE parameters including distances between electrodes and electrode exposure are entered into the planning software of the IRE system (figure 6) and the IRE treatment is then applied. Total procedure time is approximately one hour.

Clinical trials of IRE in Prostate Cancer

The first human studies evaluating the use of IRE in localised prostate cancer assessed safety and clinical feasibility. Neal et al. ablated two patients using IRE and then proceeded to radical prostatectomy [22]. Mild haematuria was the only post-operative adverse effect. Histopathological findings showed that within the ablation zone there were no viable prostate cancer cells, but regional tissue necrosis and inflammatory infiltration occurred. The treatment ablated a volume of prostate tissue without damaging neighbouring structures.

Another ablate-and-resect study was performed in which 16 men received IRE ablation of low- to high- risk prostate cancer 4 weeks before radical prostatectomy [23]. Histopathological analysis demonstrated no residual tumour or viable tissue within the ablation zone. This indicated that IRE can effectively ablate the tumour within the targeted area. The ablated tissue showed sharp demarcation of fibrotic and necrotic tissue from unaffected prostatic glandular tissue (figure 7). However, the neurovascular bundle was affected in 13/16 patients and the prostatic urethra in 9/16 patients.

An early phase I-II trial included 16 patients with low to high risk prostate cancer [24]. All patients had 4 electrodes placed and received 90 pulses of 70-100 µsec pulse length at 1500 V/cm. These

patients had repeat biopsy at 3 weeks which showed no evidence of remaining tumour or viable glandular tissue within the ablative zone. However, no follow-up study has been reported to ascertain whether these patients remained prostate cancer free.

Next, a phase I-II multi-centre trial of 34 patients underwent IRE using between 2 and 6 electrodes [25]. No serious side effects occurred, only mild haematuria (n = 5), dysuria (n = 6), urinary tract infection (n = 5) and failed trial of void (n = 2). Continence was preserved in all patients at 6 months follow-up. Potency was preserved in 19/20 (95%) patients that were potent prior to the treatment. Patients were monitored with multiparametric MRI (mpMRI). The mean ablation volume on imaging was 12 mL (IQR 5.6 – 14.5 mL). Residual disease was shown in six (18%) patients, four of which underwent salvage treatment (high-intensity focused ultrasound [HIFU] or radical prostatectomy) and two patients went onto active surveillance.

Murray et al reported a retrospective series of 25 patients with low to intermediate risk prostate cancer who underwent IRE ablation. This was a heterogenous cohort in terms of tumour location within the prostate and extent of partial ablation. The median voltage delivered was 2,340 V/cm (IQR 1,650 – 2,700) and 3 to 6 probes were used for tissue ablation. Follow up biopsy showed 4/25 (16%) had cancer in the zone of ablation at 6 months. Of those with 12-month follow-up, 2/17 (12%) required a pad for urinary incontinence and 1/13 (8%) with normal erectile function at baseline reported decreased potency requiring PDE5-Is [26].

The Nanoknife Electroporation Ablation Trial was a prospective cohort study of 20 men with anterior tumours treated with IRE [27]. It showed that 33.3% of men had in-field clinically significant disease at the 6-month follow up biopsy. This may be as a result of the small treatment margin of 5 mm based on the mpMRI lesion. It was shown by Le Nobin et al, that mpMRI underestimates tumour volume by up to 9 mm [28]. Furthermore, a study of anterior partial prostatectomies showed that tumour volumes in the anterior region of prostate were often underestimated due to technical difficulty of MRI interpretation in the transition and anterior fibro-muscular zones [29].

The importance of a larger treatment margin was exemplified in a prospective cohort study of 123 patients with predominantly intermediate risk PCa and a median follow-up of 36 months [30,31]. In this study no Clavien grade 3-4 adverse effects occurred. An important finding in this series is that after increasing the safety margin from 5-mm to 10-mm and surgeon experience improved that the likelihood of in-field recurrence decreased from 16% (7/45) to 2.7% (2/74) on 12-month

transperineal prostate biopsy. Out-field residual or recurrent significant disease was found in 12.1% (9/74) of patients. Failure free survival, defined as avoidance of whole-gland therapy or metastasis/death was 96.75% at 3 years follow-up. This study also showed that there was no significant change from baseline in physical, mental, bowel or urinary quality of life domains at 12-month follow-up. However, there was a small decrease in sexual quality of life (median score 65 at baseline v 50 at 12 months). Another recent prospective cohort study of 30 patients with median follow up of 20 months, showed similar oncological and function outcomes [32].

A pair-matched retrospective study utilised propensity-score matching to compare robot-assisted radical prostatectomy (RARP) versus IRE in terms of quality of life and early oncological control [33]. It showed that IRE had better functional outcomes: in men who were continent at baseline, pad-free continence at 12-months was 100% after IRE vs 86% after RARP; in men who were potent at baseline, erections adequate for intercourse at 12-months was 72% after IRE vs 50% after RARP However, 30% of the IRE group experienced biopsy-proven recurrence of significant cancer compared to 0% biochemical recurrence in the RARP group. This study included all IRE cases during the initial learning curve where system errors and a narrow 5mm margin increased the early failure rate.

A number of studies have investigated the utility of mpMRI in the follow-up of patients post focal treatment with IRE. Scheltema et al. showed that mpMRI was able to rule out high-volume residual PCa following focal therapy [34]. However, follow-up biopsies were still required as low-volume significant prostate cancer was still missed by mpMRI. More recently Giganti et al showed that mpMRI was able to visualise the IRE ablation zone and residual fibrosis in men with PCa [35].

A recent trial in China was the first to use high-frequency bipolar IRE in men with prostate cancer [36]. This aims to reduce muscle contractions that occur during monopolar IRE therapy. 40 men were treated between the age of 51 and 85 years of age. The number of electrodes varied from 2 to 6 depending on tumour characteristics. All patients received 250 high-frequency bipolar pulse bursts with the repeat frequency of 1 Hz. Each burst included 20 individual pulses of 5 microseconds. Using bipolar high-frequency IRE they determined the electric field lethality threshold to be 522 +/- 74 V/cm. Eight patients went on to have a radical prostatectomy 4 weeks after treatment. Histological analysis showed that the ablated area had diffuse necrotic glandular tissue without any viable tissue. The oncological outcome of the remaining 32 patients is yet to be determined. All patients were reported as continent 40/40 (100%) and sexual function was preserved in all patients that were

potent pre-treatment 14/14 (100%), although caution is warranted regarding these figures given that the methodology of QoL data collection was not reported, and no standardised questionnaires were used.

In addition to the primary treatment setting, there is increasing interest in utilising IRE in the salvage setting to treat men with radio-recurrent disease. Scheltema et al. studied the first 18 patients with localised, radiorecurrent PCa without evidence of metastatic or nodal disease and a minimum of 6 months follow up [37]. There were no high-grade adverse events. At 6 months there was a decline in sexual QoL (median 38 at baseline and 24 at 6 months) and urinary QoL (median 96 at baseline and 92 at 6 months). Ten patients had a follow up biopsy at 12 months and 8 (80%) were clear of any residual PCa. Longer-term data is available for other focal ablative modalities in the salvage setting [38]. This positive result suggests that focal ablation may be a feasible salvage option for localised radio-recurrent disease, especially in selected older men unfit for RP or unwilling to accept the high risk of complications, erectile dysfunction and incontinence. Given this, a prospective multicentre cohort study (FIRE trial, ACTRN12617000806369) has been initiated to further investigate the capacity of IRE to treat men with radio-recurrent prostate cancer.

Future perspectives and conclusions

Phase 1-2 studies have shown that IRE is a safe and feasible focal ablative modality with a low morbidity profile. Despite promising short- to medium-term oncological outcomes, no long-term data is currently available. There are a number of registries established to further assess the long term functional and oncological outcomes of IRE in prostate cancer. The Clinical Research Office of the Endourological Society (CROES) is collaborating with 10 centres in a worldwide registry. In addition, an Australasian IRE registry has been developed with a number of sites in Australia and New Zealand.

As yet there is no randomised controlled trial (RCT) assessing IRE in comparison to current standard of care in localised prostate cancer. Designing an RCT to assess a focal therapy modality would be challenging. Firstly, no consensus has been achieved in this area regarding a definition for oncological success. Also, given IRE is most suited to patients with intermediate risk prostate cancer, the design, feasibility study, funding and enrolment would be expected to take at least 5 years, then the results of a trial would require another 10-15 years of follow-up before firm conclusions could be made on oncological outcome, as seen recently in the ProTect study where even at 10-years follow-up, the metastasis and mortality rate was too low to assess survival outcomes [39]. One possible

solution would be to assess the capability of IRE to delay whole-gland therapy as the primary endpoint; a secondary endpoint would then be functional and oncologic outcomes in those requiring salvage radical treatment compared to those who underwent primary radical treatment. The only published RCT to date that assessed a focal ablative modality compared vascular targeted photodynamic therapy (VTP) to active surveillance in low-risk prostate cancer, where arguably any treatment is over-treatment [40]. In addition, the PART trial is a phase 3 multicentre RCT comparing VTP with radical whole-gland treatment (radical prostatectomy or radiotherapy), using a primary endpoint of freedom from significant cancer at 3-years. If a non-inferiority is shown with VTP compared to whole-gland treatment on freedom from significant PCa at three years, a potential trial design would be a head-to-head comparison of IRE versus VTP. However, if VTP is inferior to whole-gland treatment it could be considered to compare IRE versus radical prostatectomy since IRE may have a different in-field ablative effect.

A continuing challenge in focal therapy is selecting the correct patients and treatment planning. At present, approximately 10-15% of patients that are treated with IRE have a new lesion outside the ablation zone on follow-up biopsy [31] (figure 8). It will be crucial for the future of focal therapy to identify those patients that have multifocal disease early on so as to suggest whole gland treatment rather than focal therapy. Better imaging with 68Ga-PSMA PET fused with mpMRI may improve cancer localisation in the prostate and also allow for better treatment planning [41,42]. In addition, recent advances in genetic and epigenetic markers are showing promise in better understanding the behaviour of prostate cancer and may be able to predict which patients will fail focal treatment and would benefit from upfront whole-gland therapy.

While IRE is a promising focal ablative technique with good short-term oncological results and minimal morbidity, it should still be considered an investigational treatment performed only as part of prospective clinical registry studies or randomised trials until more long-term data is available [43,44].

Conflicts of interest

Dr. Blazevski reports grants from Garvan Institute of Medical Research, during the conduct of the study; and Proctor Fees (Getz healthcare); Dr. Amin reports grants from Garvan Institute of Medical Research, during the conduct of the study; Dr. Thompson reports grants from Garvan Institute of Medical Research, during the conduct of the study; Dr. Scheltema reports grants from Garvan Institute of Medical Research, during the conduct of the study; Dr. Lawrentschuk reports grants from Garvan Institute of Medical Research, during the conduct of the study; Dr. Stricker reports grants from Garvan Institute of Medical Research, during the conduct of the study; and is a consultant for Angiodynamics.

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Modality	Energy	Location/Methods	Advantages	Disadvantages	Repeatable
Irreversible Electroporation	Cell disruption through direct electric current	• Transperineal • Operating theatre	• Non-thermal mechanism • Can treat any segment of prostate • Confirmed ablation zone cell kill studies [23] • Short inpatient stay	• Requires a general anaesthetic • Requires muscle relaxant • Limited world-wide experience	Yes
High-Intensity Focused Ultrasound (HIFU)	Thermal injury through high-intensity ultrasound waves	• Transrectal • Operating theatre	• Medium-term data [48] • Minimally invasive • Short inpatient stay	• Difficult with anterior tumours • Requires a general anaesthetic • Difficult with large glands • Limited by gland volume • Contraindicated when significant intra-prostatic calcifications	Yes
Cryoablation	Freezing which leads to cell rupture by ice crystal formation, oedema and ischaemic apoptosis	• Transperineal • Operating theatre	• Ablative technology most extensively studied • Medium-term data [49] • Real-time monitoring • Short inpatient stay • Can treat larger volumes of tissue	• Thermal dispersion affecting surrounding structures • Technically challenging for lesions located in distal apex or near prostatic urethra and bladder neck	Yes
Laser Ablation	Photothermal injury thorough high-energy laser light	• In-bore transperineal or transrectal • Under conscious sedation	• Can perform without a general anaesthetic • MRI compatible • Accurate treatment planning and targeting • MR-based temperature monitoring gives real-time feedback • Short inpatient stay	• Patient comfort due to lying prone in MRI galley for extended period of time • Less optimal for larger lesions [50]	Yes
Brachytherapy (low-dose rate)	Radiotherapy	• Transperineal • Operating theatre	• Known technology • Apex lesions treatable • Can alter dosing	• Not repeatable • Unknown toxicity to untreated healthy prostate tissue	No

			• Short inpatient stay	• Rectal toxicity	
Photodynamic Therapy	Light-activated generation of reactive oxygen species leading to microvascular thrombosis	• Transperineal • Operating theatre • Requires IV photosensitiser	• Non-thermal mechanism • Ablate and resect studies available • Can treat any segment of prostate • Minimal thermal dispersion • Treatment zones can be carefully contoured • Short inpatient stay	• Involves injection of photosensitiser	Yes
TULSA	Thermal injury through high-intensity ultrasound waves	• Transurethral	• Minimally invasive • Short inpatient stay • MRI compatible	• Requires a general anaesthetic • Difficult with large glands • Limited by gland volume • Contraindicated when significant intra-prostatic calcifications	Yes

Table 1 – Summary of current focal therapy modalities.

Author	Study Design	Intent	Number of Patients treated	Mean Age (years)	Mean PSA (ng/mL)	AE's during procedure	Follow up	In-field recurrence	Functional Outcomes	Complications, number of patients (%)
Neal [22]	Phase I-II Single Centre	Primary	2	61	4.8	0	Radical Prostatectomy (3 to 4 weeks) after IRE	0/2	Not described	Not described
Onik [24]	Phase I-II Single Centre	Primary	16	40-78	3-7	0	3 weeks follow TTMB	0/16	Continence 100% Preserved potency 100%	Not described
Valerio [25]	Phase I-II Multicentre	Primary	34	65	6.1	0	mpMRI/PSA	6/24 = 16%	Continence 100% Preserved potency 95%	Grade I – 12 (35%) Grade II – 10 (29%) Grade II – 0
Ting [45]	Phase I-II Single Centre	Primary	32	67	6	0	6-month mpMRI and 6 to 12-month TTMB	0/21	Continence 100% Preserved potency 100%	Grade I – 5 (20%) Grade II – 0 Grade III – 1 (4%)
Van den Bos [23]	Phase I – II Single Centre	Primary	16	60	9	0	Radical Prostatectomy 4 weeks post IRE	0/16	Not reported	No serious events occurred
Murray [26]	Phase I-II Single Centre	Primary	25	63.2	4.3	0	mpMRI and targeted biopsies	4/25 (16%)	Continence 91% Preserved potency 92%	Grade I - 6 (22%) Grade II – 7 (29%) Grade III – 1 (7%)
Valerio [27]	Phase II Single Centre	Primary	19	60	7.5	0	TTMB 6 months post IRE	6/18 (33%)	Continence 100% Preserved potency 95%	Grade I -14 (74%) Grade II – 19 (100%) Grade III – 0
Van den Bos [30]	Phase II Single Centre	Primary	63	67	6	0	mpMRI at 6 months and TTMB at 12 months	7/45 (16%)	Continence 100%) Preserved potency 77%	Grade I - 15 (24%) Grade II – 7 (11%) Grade III – 0
Scheltema [37]	Phase I – II Single Centre	Salvage	18	71	3.5	0	mpMRI at 6 months and TTMB at 12 months	1/10 (10%)	Continence 73% Preserved potency 50%	Grade I – 5 (27%) Grade II – 2 (11%) Grade III – 0
Blazevski [31]	Phase II Single Centre	Primary	123	68	5.7	0	mpMRI at 6 months and TTMB at 12 months	2.7% (excluding initial 32 patients)	Continence 98.8% Preserved potency 93%	Grade I – 22% Grade II – 9% Grade III – 0

							(median f/u 36 mo)			
Collettini [32]	Phase II Single Centre	Primary	30	65.5	8.65	0	mpMRI and targeted biopsy at 6 months	17.9% (5/28)	- Pad-free continence at baseline 96.7% (29/30) and at 12 months 96.5% (28/29) - Erections sufficient for intercourse at baseline 83.3% (25/30) and at 12 months 79.3% (23/29).	Grade I – 20% Grade II – 10% Grade III – 3.3%

Table 2 - Results of studies applying IRE

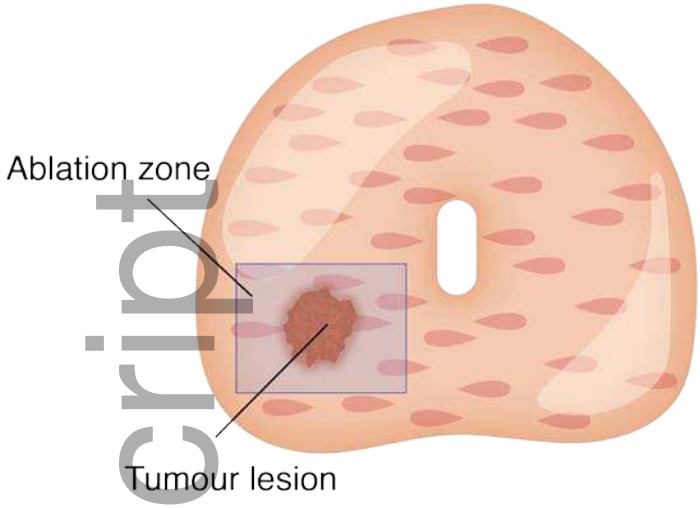

Figure 1 – Focal therapy aims to ablate all regions containing significant cancer while preserving the unaffected prostate.

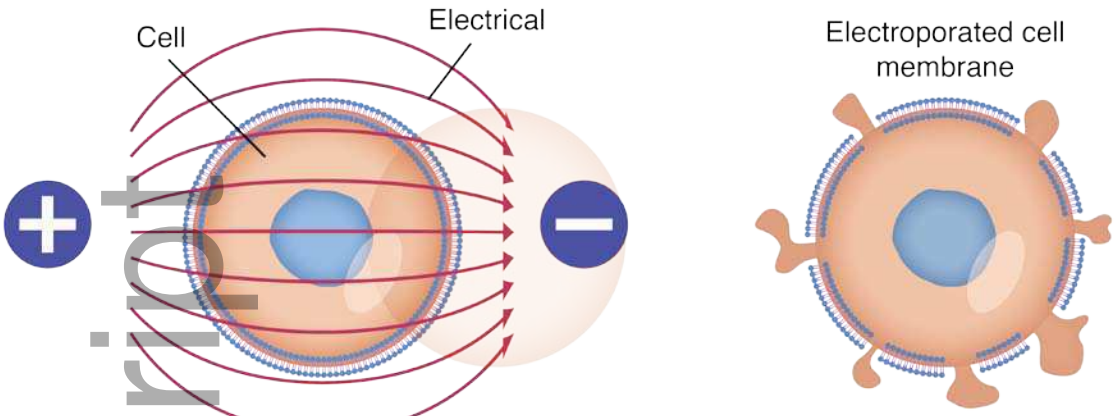

Figure 1 – IRE is based on the principle of electroporation

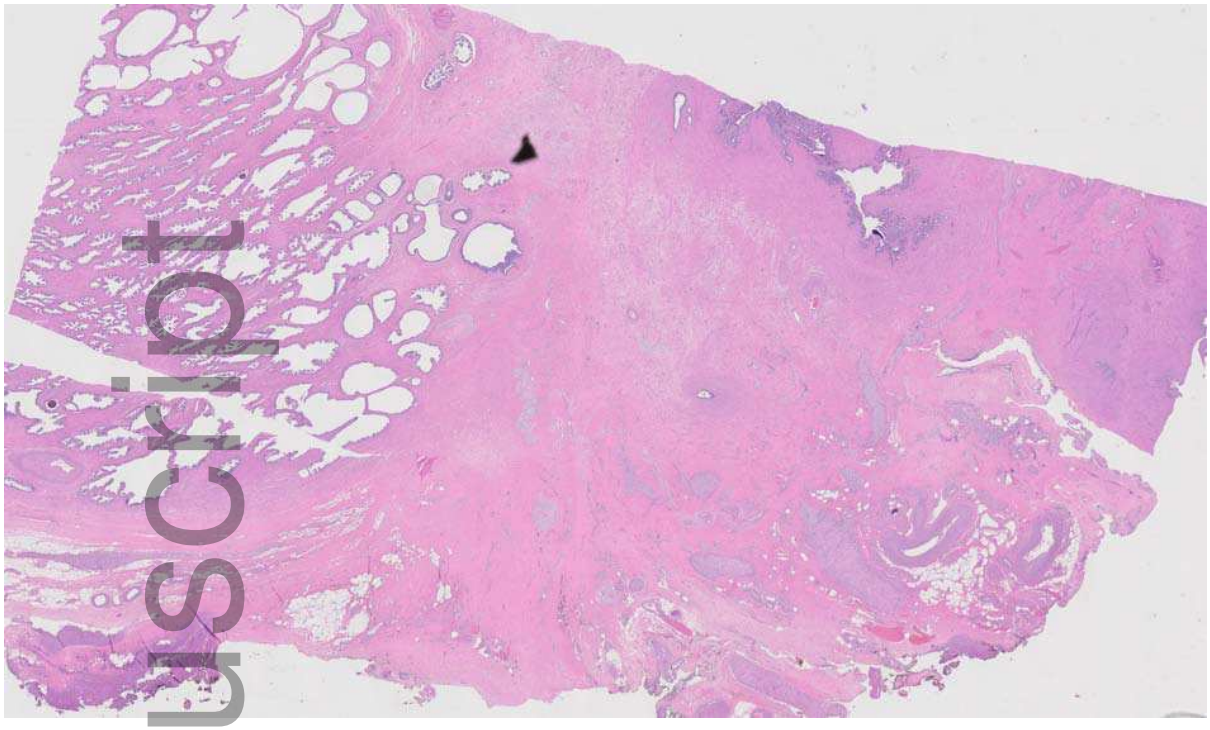

Figure 3 – Histopathology slide shows a region of post treatment scar in the peripheral zone between a normal transitional zone and seminal vesicle.

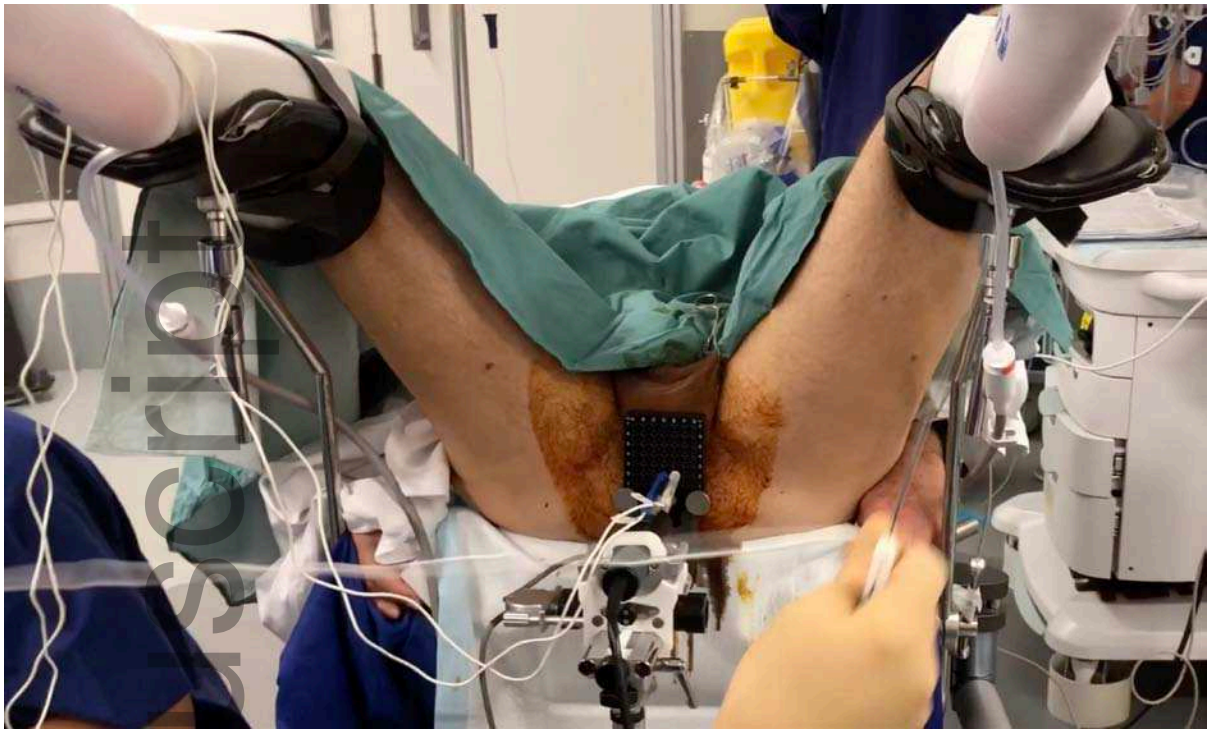

Figure 4 – Patient in lithotomy position with electrodes placed through the brachytherapy grid.

Figure 5 – Current version of the irreversible electroporation console (Nanoknife ™ version 3.0, Angiodynamics, Inc., New York, New York).

- *Dimensions (Width x Length x Height): 56 cm x 68 cm x 149 cm*
- *Weight: 66 kg*

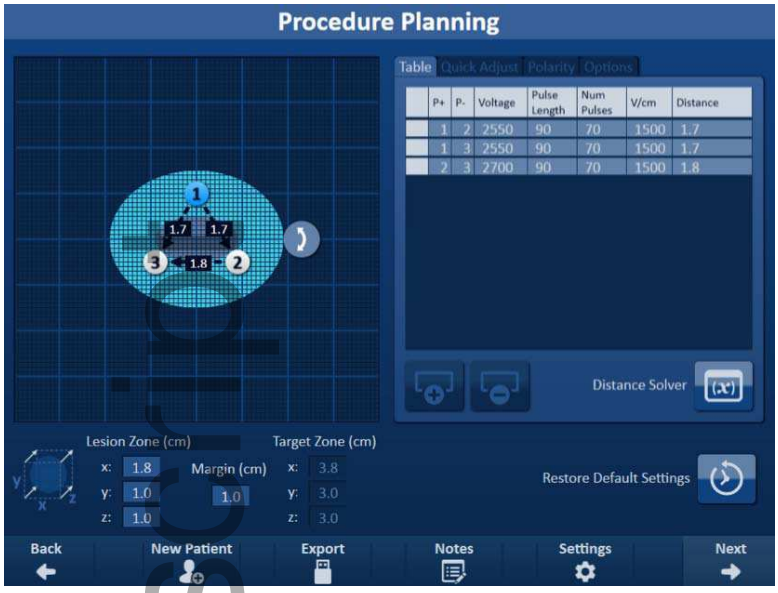

Figure 6 – Irreversible electroporation treatment planning screen (Nanoknife ™ version 3.0, Angiodynamics, Inc., New York, New York).

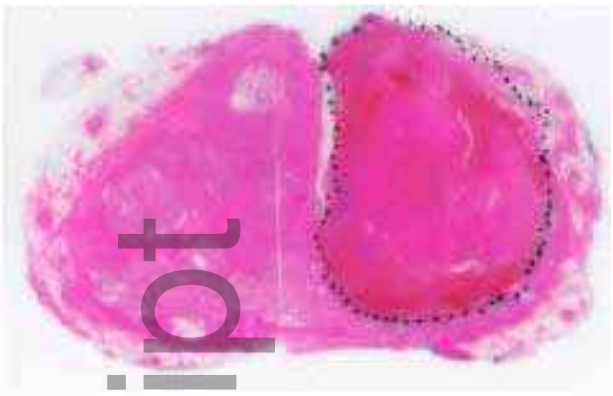

Figure 7 – Sharply demarcated ablation zone on whole mount pathology Reprinted with permission from Scheltema et al [55]

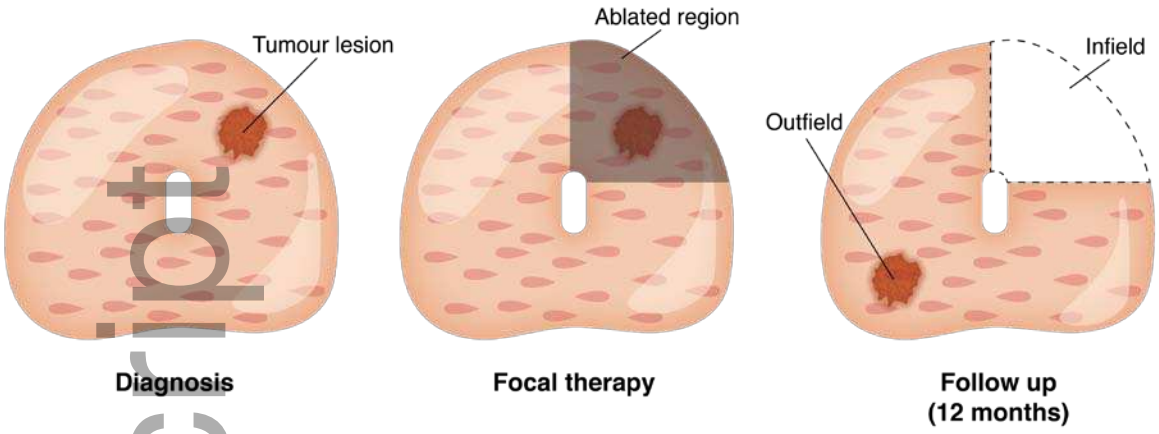

Figure 8 – A continuing challenge in focal therapy is predicting which patients will have outfield failure – that is which patients have treatment recurrence outside the ablation zone.