PUSHING THE LIMITS WITH NANOKNIFE®: A PROMISING NEW TECHNOLOGY IN LOCALISED PROSTATE CANCER MANAGEMENT

Caroline Charles,[1] *Jean de la Rosette,[2] *Mark Emberton[3]

1. Scilink Medical Writing, Saint-Pierre-d'Irube, France
2. Department of Urology, AMC University Hospital, Amsterdam, the Netherlands
3. Interventional Oncology, Division of Surgery and Interventional Science, University College Hospital, London, UK
**Correspondence to j.j.delarosette@amc.uva.nl and mark.emberton@uclh.nhs.uk*

Disclosure: M. Emberton has provided consultancy services to and received research funding from AngioDynamics Inc., SonaCare Inc., Sophiris Inc., Trod Medical, GSK, and Sanofi; and provided training for AngioDynamics Inc., and SonaCare Inc. J. de la Rosette is a consultant for AngioDynamics Inc.
Support: Funding for this article was provided by AngioDynamics.
Citation: *EMJ Urol* 2015;3[2]:90–102.

INTRODUCTION

In the last few decades, the ever-increasing improvements in cancer detection have allowed urologists to detect prostate cancer (PrC) at earlier stages: currently, in industrialised countries, most diagnosed prostate tumours are small and localised.[1] As a direct consequence, health-related quality of life (QoL) has become a prominent factor in treatment decision-making for localised PrC. Indeed, approaches such as radical prostatectomy (RP) and external beam therapy have been associated with significantly impaired urinary, bowel, and sexual functions,[2-4] and some authors might consider these options to be 'excess treatments'.[5] While there is continuing uncertainty regarding the superiority of one therapeutic modality over another, what has become certain is that maintaining QoL, especially in younger patients, is now playing a central role, thus generating interest in less radical options.

In recent years, focal therapy has emerged as a 'middle ground' option between active surveillance and radical modalities in patients with low-to-intermediate-risk PrC. Indeed, focal therapy has the potential to address the needs stated earlier and offer minimally invasive options to optimise risk stratification at diagnosis. These options include cryotherapy,[5,6] which is currently considered as an alternative option by the European Association of Urology (EAU) and American Urological Association (AUA) guidelines.[7-9] Other focal therapy options comprise experimental modalities such as high-intensity focused ultrasound (HIFU),[10-12] photodynamic therapy,[13,14] brachytherapy, irreversible electroporation (IRE), and focal laser ablation.[15,16] While the clinical data to date has confirmed the potential for these emerging techniques to provide higher benefit-to-risk ratio in localised PrC, most of these options are thermal options using energy to target cancerous cells, thus possibly generating tissue damage.

However, one of the upcoming techniques is non-thermal: IRE. IRE is a non-thermal modality that could very well have the potential to provide improved perioperative and long-term functional outcomes and reduced treatment-associated morbidity without compromising on the oncological results. This paper will provide an overview of the promising perspectives offered by IRE through a discussion with two key experts in the field, Prof Jean de la Rosette (Amsterdam, the Netherlands) and Prof Mark Emberton (London, United Kingdom); both are at the forefront of IRE clinical research, as they are the principal investigators for the Clinical Research Office of the Endourological Society (CROES) Registry and the Novel Endovascular Access Trial (NEAT), respectively.

Interview with Prof Jean de la Rosette

Prof Jean de la Rosette is a Professor and Chairman of the Department of Urology at AMC University Hospital in Amsterdam, the Netherlands.

Prof de la Rosette was chairman of the European Association of Urology (EAU) working party on benign prostatic hyperplasia guidelines from 1996 to 2004. He is a member of various urological societies: e.g. the Endourological Society, the American Urological Association (AUA), the European Association of Urology (EAU), and the Société Internationale d'Urologie (SIU).

Prof de la Rosette has authored over 300 peer-reviewed publications and many book chapters. He is also on the editorial board of the Journal of Endourology and European Urology.

Prof Jean de la Rosette is the Coordinating Investigator and Chairman of the CROES Registry on IRE for the ablation of PrC with use of the NanoKnife® device. CROES is an official organisation within the Endourological Society responsible for organising, structuring, and favouring a global network on endourological research.

The CROES registry is a multicentre, international, observational study aiming to evaluate the treatment of PrC in terms of recurrence, functional outcomes, and safety (Clinicaltrials.gov identifier: NCT02255890).

The primary objective of the registry is to assess the recurrence of PrC at 1 and 5 years, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline. Secondary study objectives will aim to establish which indications lead to treatment with IRE NanoKnife setting, and safety assessments measured by the number of complications and adverse events (AEs).

Inclusion criteria are as follows:
- *patient is diagnosed with histologically confirmed PrC*
- *patient is scheduled for IRE NanoKnife*
- *patient has signed informed consent form*

We interviewed Prof de la Rosette to discuss the increased interest in effective focal therapies for the treatment of low-risk PrC, the CROES Registry on IRE, and the NanoKnife system's potential (interview conducted on 4th March 2015).

Can you tell us more about the inception of the IRE CROES Registry? How did it come to be?

From a urological point of view, ablative treatment modalities are receiving increasing interest over resection or radiation therapy (RT) of the whole gland.

AngioDynamics holds a special interest in technology that can be applied in various oncological conditions and wants to position NanoKnife according to the highest standard possible.

To this effect, certain steps should be followed, namely Phase I/II studies to study the efficacy of the treatment, randomised clinical trials (RCTs) to study one versus another treatment option, and registry studies to determine the real-life position of such a therapy.

First, we concluded a Phase I/II study in a subgroup of 16 patients within a fully institutional review board (IRB)-approved setting (Clinicaltrials.gov identifier: NCT01790451).[17]

We offered patients who needed RP for a somewhat more extended (but still localised) disease the possibility to participate in a project where they would receive ablative treatment according to a fixed protocol, and then this would be followed by RP 4 weeks later.

The interesting part of this study was that in the 4 weeks follow-up for IRE treatment, we could evaluate the morbidity that the treatment could cause, and it was minimal. We had a special interest in voiding function disturbances and again these were minimal or non-existent. We also looked into patients' QoL related to the treatment, such as pain (minimal, only some discomfort

during the first days) and sexual functions (erections and ejaculations), which were not disturbed in the 16 patients.

Based on this strong foundation that QoL was not affected, we endeavoured to conduct efficacy assessments, meaning: *"If I treat a certain area to a protocol, is all the tumour which is within the area ablated: do we have skipped lesions?"* And again, we confirmed in all 16 patients that the fully treated area was completely ablated and that there was no vital tissue left.

Also of importance was that we wanted to know if we could properly monitor the effect of the treatment with an imaging modality 4 weeks, 6 weeks, 3 months, or even 1 year after the treatment. In the first few weeks, we were able to demonstrate that both magnetic resonance imaging (MRI) and multiparametric ultrasound could give us the information.

With the results of this Phase I/II study in mind, we felt that there was a strong argument to proceed to an RCT and also to continue with a registry: both were actually initiated more or less at the same time.

As the CROES was founded to support research in the field of endourology, in this registry all the research is co-ordinated by an independent society.

For patients, what would be the rationale to take part in the registry versus the RCT?

Some patients might feel that ablative treatment is attractive but they do not wish to participate in an RCT or they prefer to do it within a registry. The argument is that they are not interested in extended questionnaires to fill out, nor are they interested in coming to regular and fixed assessments.

The registry can also include patients who would like to have ablative therapy but would not be cleared to take part in an RCT.

An RCT is conducted in a very select patient population. In reality, a wide range of different patients are treated.

Let us say that within an RCT, erectile dysfunction is an outcome parameter: investigators have to exclude patients who have pre-existing potency problems. As the registry is a real-life data study, we are following up on multiple QoL parameters.

In addition, in a study protocol, elderly and more fragile patients may be excluded. However, patients may also ask if they can be candidates for such a treatment. Within a registry, we can properly document these subgroups and their additional benefits. We made this registry open on a global scale, for every centre that has access to IRE.

For such centres, what is the advantage for them to share their data?

Well there are multiple [advantages]: first of all, the data are shared with an independent society, which means a high level of quality control (QC) can be expected. Clinicians can compare the outcomes of their data set with data from the whole registry. We have learned from other technologies that have been introduced that this is important: for example, for brachytherapy with seed implant, the QC in the beginning was not optimal and there was a centre in the USA that performed hundreds of implants but these were not set optimally. If at an early stage a centre recognises that maybe the treatment is not optimal or that some complications arise, they can discuss the indications and maybe also receive our support to improve their outcomes.

The other advantage is that the centres get a certificate to prove that they are following the appropriate protocol. Such a certificate confirms that the institute is offering patients the highest quality of care, maybe not in a randomised study but within a registry and sharing, on a global basis, the data and outcomes.

I am very happy with the protocols and projects that we have embarked on to determine what the exact position of this technology is for the treatment of PrC. I am also glad that both endourological societies strongly support these projects in addition to AngioDynamics, even if these studies are independent.

Since the main unmet needs for resection are associated with impaired QoL and functional outcomes, do you feel that the registry will provide a population-based analysis that will help differentiate IRE in terms of functional outcomes, QoL, and the range of issues that patients are very keen to see addressed in the coming years?

With respect to many of the questions that are put forward, at this stage this would be speculation.

Of course, patients nowadays are more concerned about their QoL parameters than some years ago. Trying to preserve a good oncological outcome is still paramount, but maintaining QoL has become essential and is playing a central role. Ten years ago, patients were more concerned about the oncological outcomes ("Am I cured?"). At the moment, the questions are very specific: "I want to maintain my quality of life."

Patients have become increasingly aware that they have friends or relatives that have had treatment where the morbidity is playing a more prominent role now and they are not questioning whether they were cured, but rather if they were cured at a very high price.

In the end, patients need to have data that support this. I know that hundreds of patients have already been treated for PrC with NanoKnife, but if you look at the number of publications these are limited, which means the cases were not properly documented.

If that had been the case, they could have been in support of already having this treatment properly recognised and positioned within guidelines.

How many patients have been included in the registry so far, and how many do you expect to recruit?

We started in January 2015, so for now we have a handful of patients.

At present we have 20 international sites that are willing to recruit or to include data. If each centre recruits 30 cases we will have 600 patients in a year. But I am confident that we will have more centres throughout the world participating in this venture. So in 5 years we will have a minimum of 3,000 patients: that is a powerful data set.

Besides the Phase I/II study and the CROES registry, can you tell us more about the RCT on NanoKnife you mentioned earlier?

In the RCT *(Clinicaltrials.gov identifier: NCT01835977),* we want to study a subgroup of patients who have more limited disease in one lobe of the prostatic gland, and if we can, again safely and with minimal morbidity, treat that disease by targeting only the lesion, randomised against a more extended treatment.

This study has been initiated: IRB approval was recently granted at our department (Department of Urology, AMC University Hospital in Amsterdam, the Netherlands), and in Europe, seven centres are now preparing their IRB approval to get started as well.

Do you think NanoKnife has the potential to become part of salvage therapy strategies following RT failure?

At this point it would be pure speculation to say so. One-third of all patients who receive external beam RT show a failure after some time of follow-up: all possible additional treatments in this case harbour a risk. Ablative treatment, including IRE, in the case where a lesion is on the peripheral zone closer to the rectum, can cause significant harm with the development of a fistula.

Salvage therapy sounds attractive but we need to instruct our patients very carefully and also carefully document these data to know how far we can push technology and its applications. I would say we should first document the real possibilities and then go for the next steps instead of jumping on this group of RT failures.

Do you think NanoKnife could be more effective to healthcare payers as a less radical approach given its safety profile and associated costs?

Let us say in the ideal case scenario a patient comes to the hospital to receive IRE and leaves the same day or the next day, with no voiding complaints, no incontinence, and no erectile dysfunction. The only thing required is an MRI to confirm that the entire tumour has been eradicated and a close follow-up to check for recurrences. That is the drawback: the prostate is still there and the patient might develop a new prostatic cancer as it is related to the biological behaviour of the prostate.

However, you are right, QoL is important: the patient does not need to take oral medication to have improvement of sexual function, there is no need for physiotherapy for incontinence or for diapers to protect clothes against urine loss. Patients do not feel embarrassed or unhappy. A lot of additional costs are erased with this technology and this day-care case scenario.

If everything is put into balance, I think it would be in favour of IRE, but again this is pure speculation that needs to be confirmed.

Having said that, is it too soon to conduct health-economic studies of IRE?

Health economic studies warrant specific study design.

In the registry and the RCT cited above, the centres involved will include the economic data. But health economics is not an easy issue to assess: costs highly depend on the country as well as reimbursement parameters with respect to the alternatives.

Do you feel that some of the resistance to focal therapy will finally be overcome soon?

Any alternative will be embraced not only by the patient but also by the payers, if there is a significant benefit not only for patients but also in reducing costs. Once new treatment modalities are discussed in the guidelines, patients and practitioners believe in their validity. However, the treatment will still need to be tailored according to the clinical setting and patient characteristics.

Interview with Prof Mark Emberton

Prof Mark Emberton is a urologist and Professor of Interventional Oncology. He directs the Division of Surgery and Interventional Science at University College London (London, United Kingdom).

Within this centre of excellence, he is at the forefront of clinical research in urology and his principal interests lie in advancing research on the diagnosis (novel imaging techniques) and management (novel minimally invasive techniques) of prostate cancer.

He lectures widely and has authored over 300 articles in peer-reviewed journals.

Prof Emberton is the main investigator for the single-centre, prospective, development Stage IIa NanoKnife Electroporation Ablation Trial (NEAT, Clinicaltrials.gov identifier, NCT01726894), which is currently ongoing. The recruitment phase (20 men with localised PrC) was completed in 2014 and first results are expected in August 2015.

We interviewed Prof Emberton to discuss the increased interest in IRE for the treatment of low-risk PrC and the NanoKnife system's potential (interview conducted on 24th February 2015).

To you, what distinguishes IRE from other focal therapies?

The main difference between IRE and the other focal therapies is that it is non-thermal, and this attribute makes it unique amongst focal therapies: this is important, as heat is unpredictable in the body because there are mechanisms to redistribute heat in tissues.

I think cryotherapy is also difficult to predict because of the different vascularity among tissues and therefore the different amount of ice that is required. Also, it is difficult to control the outer limits of the ice bowl.

As IRE is non-thermal, the conductive properties of the tissue seem to be much more homogenous than the properties associated with the distribution of heat.

Moreover, it can also be used when the prostate is calcified (in which HIFU is contraindicated because the energy would be reflected and redistributed). These attributes of IRE technology certainly make it a distinct treatment modality.

So far, the clinical and safety data of focal IRE in PrC are encouraging. Could you update us on the status of NEAT?

We do not have any results yet and we will analyse the primary outcome once all the patients have completed the study. One of the most interesting things about the trial is the rate at which we recruited. Early PrC studies mostly, in fact exclusively, have failed to recruit in the past with about 10-15 studies closing early due to failure to recruit.

For the NEAT study, patients were fighting to be included because there were only 20 slots.

How do you explain this?

I think it is due to two reasons. First, this trial gives patients the opportunity to benefit from tissue-preserving therapy, as focal treatment for PrC is associated with much better functional outcomes. We think the morbidity aspect played a role in this fast recruitment. Patients very much respond to the idea of improved QoL.

Secondly, men liked the attributes of the technology: it is a quick, day-care procedure and it is a non-thermal technique.

You were part of a consensus meeting in June 2013 to discuss focal therapy.[18] Further to this meeting, do you envision focal therapy to become a standard first-line treatment in selected men with localised PrC (low-risk and low-risk shifting to high-risk) in the coming years?

It is becoming just that in our centre, for the treatment for men with focal moderate-to-high-risk disease.

Do you feel that some of the resistance to focal therapy seen in the field will finally be overcome, just as radical mastectomy was slowly replaced by breast-conserving surgery in early-stage breast cancer?

I think now there is a certain animosity and scepticism about the lack of long-term data, and possibly fear of new technologies that are evolving and are difficult to master.

Could this scepticism be due to the lack of large-scale trials difficult to implement in PrC?

Yes, but this did not stop some novel technologies before: most developed PrC modalities were developed without RCTs, such as RP, laparoscopic prostatectomy, and active surveillance. IRE is a fairly easy-to-do procedure: it would allow physicians to perform focal therapy in their own practice, without a long learning curve. But I agree, we do need to conduct randomised clinical trials for IRE in order to further establish this technique.

Do you think that IRE has the potential to become part of salvage therapy strategies following RT failure?

Very much so. I have used it on a couple of occasions, and with good results. This was conducted in difficult-to-treat patients, mainly after brachytherapy failure.

Could you please describe one case?

In one patient, brachytherapy failed and was followed by external beam radiotherapy, but the patient had a recurrence in the anterior part of the left side of his prostate.

I used IRE to treat him; as his prostate was quite small, cryoablation would have been difficult. There was also quite a bit of calcification in the prostate, so HIFU would have been difficult or impossible.

We conducted IRE with four needles around the lesion and obtained very good confluent necrosis of the lesion with a nice margin. He was treated without any observed toxicity. The patient is now stable at 1 year follow-up, without any sign of disease recurrence.

Could IRE be more cost-effective to healthcare payers as a less radical approach and associated clinical outcomes and safety profile?

It could be as it is a quick day-care treatment with less infrastructure required as compared with RP, radiotherapy, or proton treatment.

IRREVERSIBLE ELECTROPORATION: MECHANISM OF ACTION

IRE is a novel soft tissue ablation technique using non-thermal energy to create innumerable permanent nanopores in the cell membrane to disrupt cellular homeostasis (Figure 1). Disruption of cellular homeostasis triggers complete tissue death by means of apoptosis or 'apoptosis-mimetic' necrosis.[19-22] Electroporation works by providing a certain electrical field that has the ability to change the electrochemical potential across cell membranes, thus inducing instabilities in the polarised lipid bilayer and creating nanopores in the cell membrane. As a function of the field amplitude and duration, the permeabilisation can be reversible or irreversible.[23] With a pulse length of approximately 100 µs and an electric field of approximately 1 kV/cm (Figure 2),[23] the short and strong field produced by IRE generates apoptotic cell death, which comprises immune-mediated cell death and phagocytosis (macrophages aiding in clearing cell debris) leading

to tissue regeneration as a natural course of the cell cycle.[19,21,24]

Contrary to thermal ablation, which causes heat-induced protein denaturation, non-thermal necrosis generates an energy delivery producing transient tissue temperatures lower than 50°C with no Joule heating.[19,21] Thus, it has the ability to preserve critical structures within the IRE-ablated zone, affecting only the cell membrane and no other structure within the tissue, such as the urethra, the extracellular matrix, larger blood vessels (and blood flow), or nerves (Figure 3).[19,25-28]

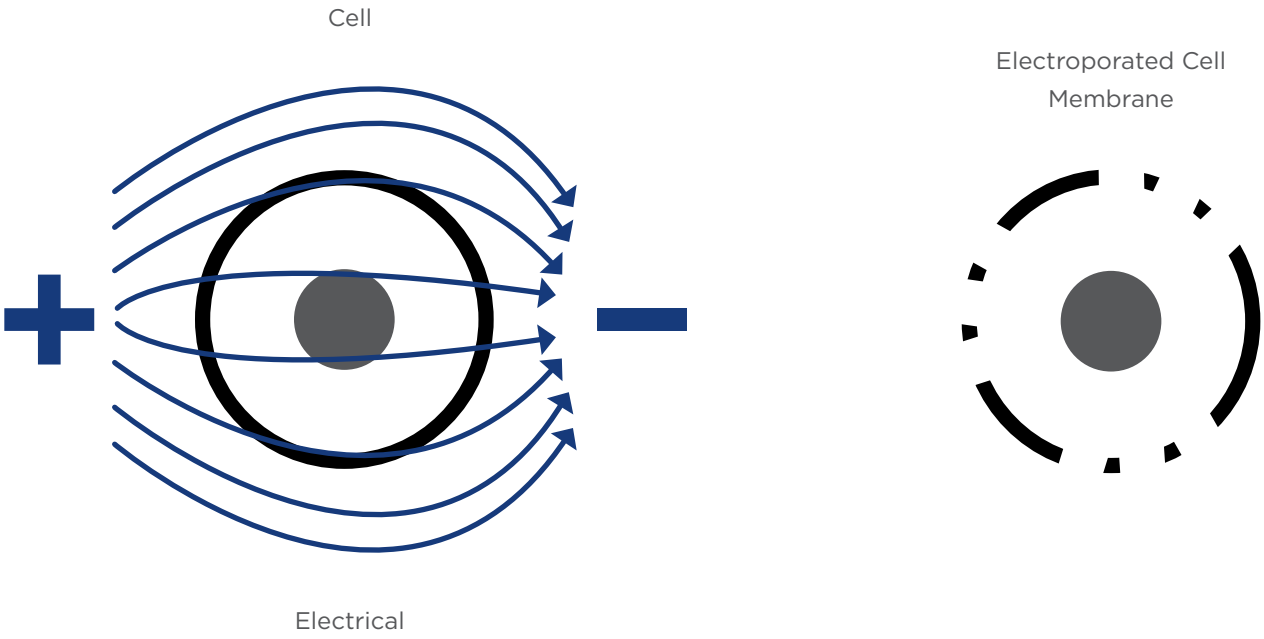

Figure 1: Irreversible electroporation: mechanism of action.
(AngioDynamics, data on file)

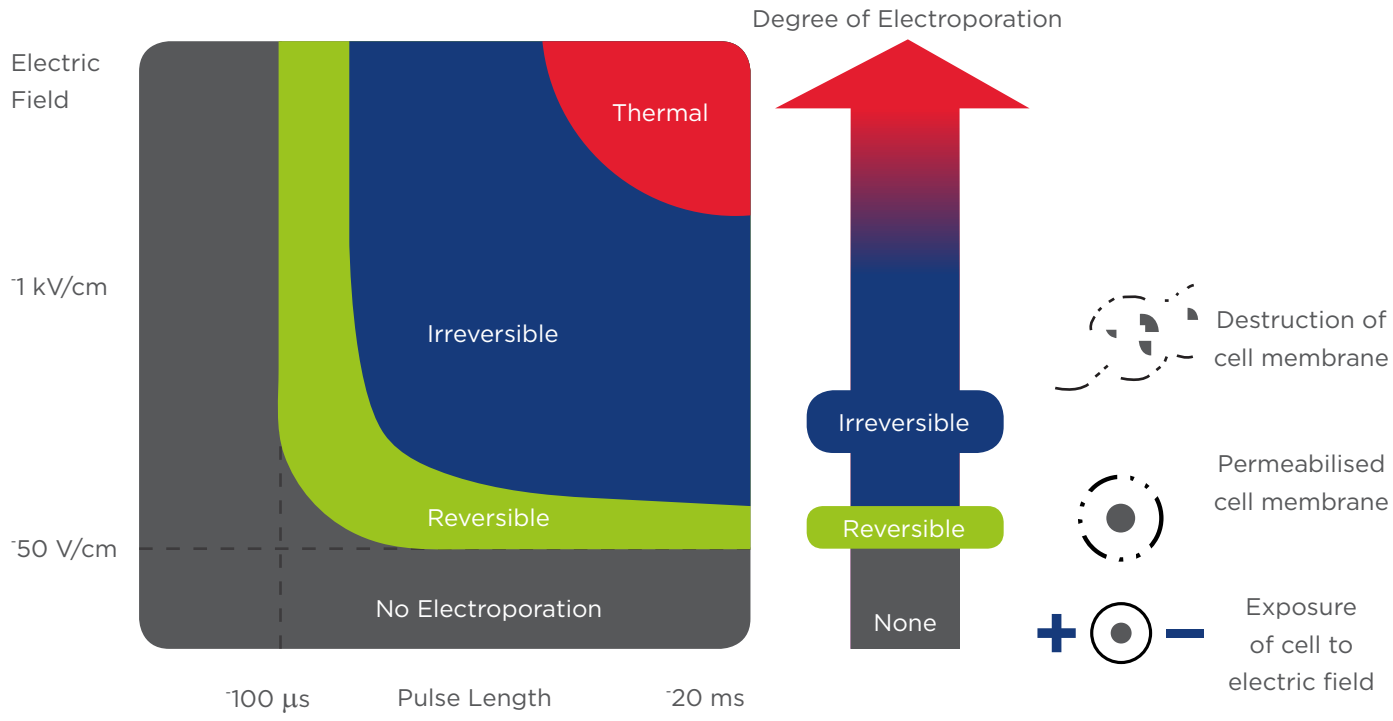

Figure 2: Electric field settings for reversible and irreversible electroporation.
Adapted from Bower et al.[40]

Moreover, while conventional thermal ablation techniques can be hindered by the 'heat sink effect' phenomenon, as perivascular tissues are not completely ablated and lead to incomplete ablation of the tumour, IRE can cause complete tissue death even when the ablation zone is close to a large vessel.[24] IRE produces an extremely sharp, well-demarcated, and predictable ablation area, and the transition between healthy and ablated tissue can be observed on a cellular level, thus contrasting with that observed with other ablative modalities.[20,25]

THE NANOKNIFE SYSTEM

The NanoKnife® system (AngioDynamics, Queensbury, New York, USA) is CE marked for cell membrane electroporation and consists of a NanoKnife generator (Figure 4) and up to six single-use disposable monopolar electrodes, comprising one activator radiofrequency identification (RFID) monopolar electrode (Figure 5), and up to five RFID monopolar electrodes (Figure 6). The electrodes are placed under computed tomography or ultrasound guidance. An electrocardiogram synchroniser (AccuSync® Synchronization Device; Figure 7) completes the system to limit the risk of ventricular tachycardia.[29]

PROCEDURE

The procedure is a 1-day, outpatient procedure: after waking up from general anaesthesia, the patient can return home the same evening or the next morning. A typical IRE procedure on a solid tumour uses about 90 100-microsecond pulses delivered by a certain number of needles (according to the pre-defined treatment strategy) that are positioned on the margin of the treated area, usually with ultrasound guidance.

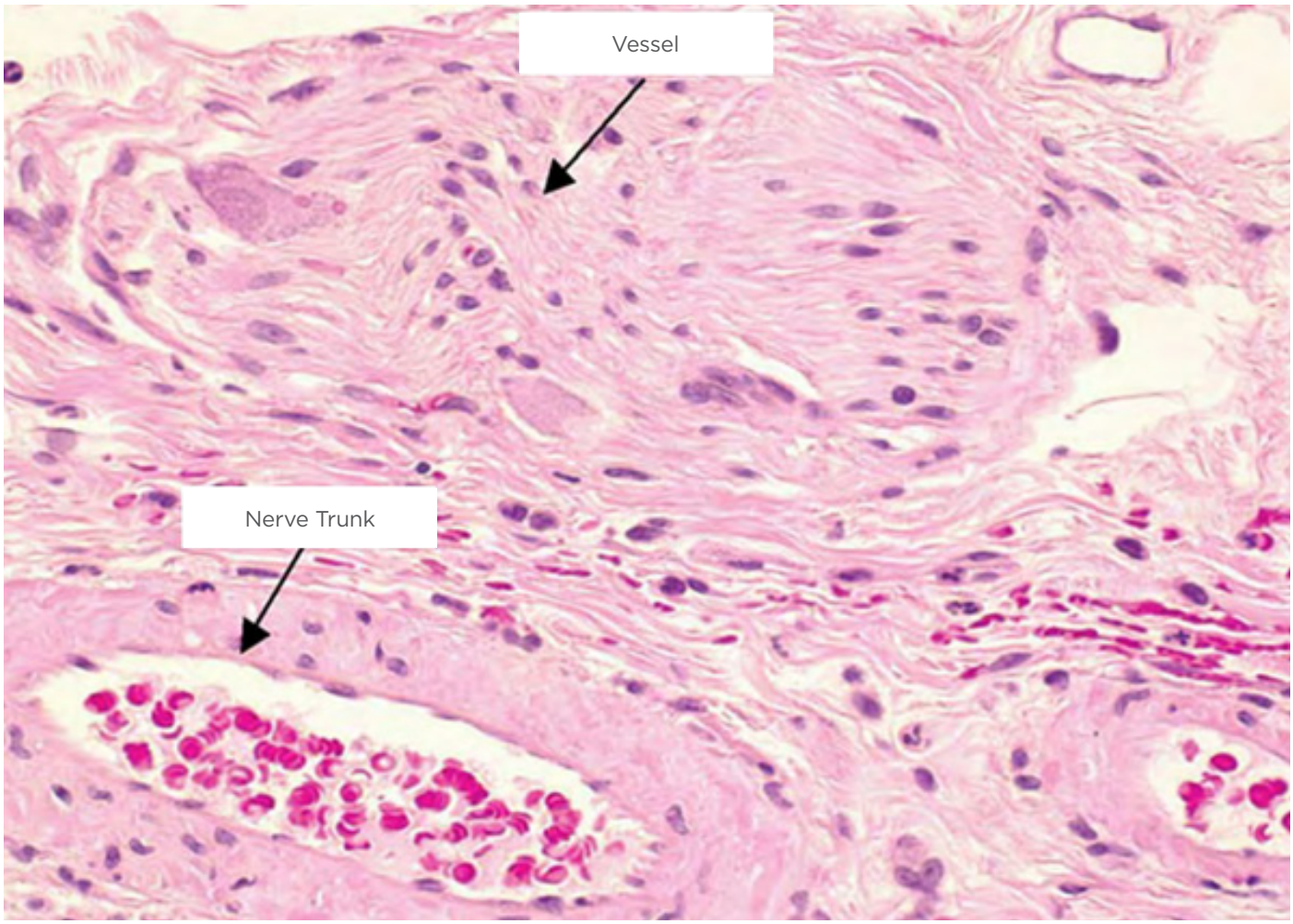

Figure 3: Irreversible electroporation (IRE) in the prostate: photomicrograph of a neurovascular bundle post-IRE.
Adapted from Onik et al.[20]

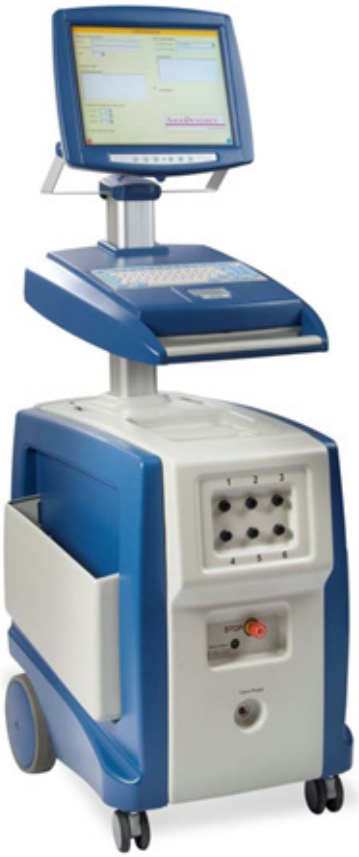

Figure 4: The NanoKnife® generator.
(AngioDynamics, data on file)

Figure 5: NanoKnife® activator RFID monopolar electrode.
RFID: radiofrequency identification.
(AngioDynamics, data on file)

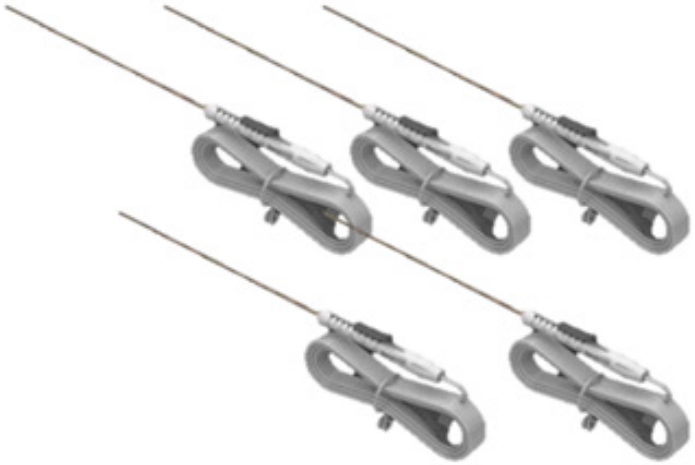

Figure 6: NanoKnife® RFID monopolar electrode (up to 5).
RFID: radiofrequency identification.
(AngioDynamics, data on file)

Figure 7: The AccuSync® synchronisation device.
(AngioDynamics, data on file)

Within three or four overlapping ablations, total IRE treatment time is under 5 minutes, which may correlate with reduced anaesthesia time, reduced post-ablation pain, decreased ablation-related complications, as well as decreased overall cost of ablation treatment, and it may provide an opportunity for treatment of multiple lesions or multiple treatments of a single lesion in one session.[19] MRI may be used pre and post-procedure to evaluate the evolution of the lesion.

Table 1: Available clinical data on IRE in localised PrC.

Study	Key findings
Pilot safety study[30]	**Objectives:** The primary objective of the study was to test the procedural and short-term safety of the device to ablate localised microfocal, low-grade PrC. A secondary objective was to evaluate the effectiveness of the treatment and its impact on quality of life of our patients. **Population:** 11 patients with PrC were enrolled after ethical committee approval and informed consent. **Eligibility criteria:** unilateral PrC on template-guided perineal biopsies (1.37 cores per cc), prostate specific antigen (PSA) <10 ng/ml, Gleason score <7, Stage cT1c/T2a. Mean pre-operative PSA was 6.43 ng/ml, mean prostate volume on transrectal ultrasound (TRUS) was 62.3 cc. Stage: cT1c=10 and cT2a=1. **Methods:** The procedure was performed under general anaesthesia using the brachytherapy grid to reach the same area where PrC was detected at biopsy. The mean number of needles used to treat the tumour area was 6.3 (range: 4-10). Mean treatment time was 7.8 min (range: 2-18 min). **Results:** No major complications occurred during the procedure. Hospital stay was 1 day for all patients. Prostate biopsy of the treated area was performed after 1 month using local anaesthesia. No major complications were observed after 14, 30, 90, and 180 days, and 19.2 months. A total of 1/11 patients (9%) had acute urinary retention and 3/11 patients (27%) had transient urge incontinence. The mean PSA after 30, 90, and 180 days, and 19.2 months went down to 3.5, 2.9, 3.3, and 3.12 ng/ml, respectively. The continence rate was 100%. The pathological report after 30 days was negative in 8/11 patients (73%). Coagulative necrosis, granulomatosis, fibrosis, and haemosiderosis were commonly reported. Persistent adenocarcinoma was present in 3/11 patients (27%) (1, 1, and 2 foci), respectively. One patient received RP, one was re-treated, and one is awaiting re-treatment. **Conclusion:** IRE is a safe procedure for focal therapy in localised low-risk PrC. It is relatively simple, minimally invasive, and effective. Further larger studies with longer follow-up are needed to confirm these preliminary results.
Pilot study[31]	**Objective:** To explore the first human use of IRE in this setting. **Population:** 16 patients (age range: 40-78) with localised PrC were treated with IRE. **Methods:** Patients were considered for cancer-targeted IRE ablation if (based on TRUS biopsies) their cancer was localised and the maintenance of potency and/or continence was a major concern of the patient. A total of 18 gauge IRE electrodes were placed under TRUS guidance percutaneously through the perineum. IRE probes were placed to cover the known area of cancer location based on the patients mapping biopsy. Four probes were placed in a roughly square array, 1-1.5 cm apart, with the known area of cancer in the centre of the array. At 3 weeks post-treatment additional transperineal ultrasound-guided biopsies were conducted in the previously known cancer loci and the immediate surrounding areas. **Main results:** Post-operative biopsies taken from the area of previously known cancer in 15 patients showed no evidence of cancer. There was one patient with a negligible PSA who refused a post-operative biopsy and one in whom a micro focus of Gleason score 6 cancer was found outside the treated area. This patient was successfully retreated with focal cryosurgery. In addition, there was no evidence for any viable glandular tissue in the biopsy specimens. Haematoxylin and eosin staining showed all epithelial elements gone. There were occasional areas with ghosts of glandular structures without viable cells present. Vascular elements were patent and intact nerve bundles with viable ganglion cells within them were noted, surrounded by necrotic tissue and fibrotic tissue. **Conclusion:** IRE is a new non-thermal ablation modality with significant advantages over heat or cold-based tumour destruction. Its ability to spare nerves and vessels apparently results in minimal effect on potency, making it particularly suited to the focal therapy of PrC.
Prospective study[32]	**Objective:** To evaluate the safety and clinical feasibility of focal IRE of the prostate. **Population:** A total of 34 patients undergoing focal IRE for localised PrC in two centres. **Methods:** Eligibility was assessed by multi-parametric MRI (mp-MRI) and targeted and/or template biopsy. IRE was delivered under TRUS guidance with two to six electrodes positioned transperineally within the cancer lesion. **Main Results:** Overall, 34 patients with a mean age of 65 years and a median PSA of 6.1 ng/ml were included. 9 (26%), 24 (71%), and 1 (3%) had low, intermediate, and high-risk disease, respectively. From a functional point of view, 100% (24/24) were continent and potency was preserved in 95% (19/20) of patients who were potent before treatment. The volume of ablation was a median 12 ml with a median PSA after 6 months of 3.4 ng/ml. Mp-MRI showed suspicious residual disease in 6 patients (25%), of whom 4 (17%) underwent another form of local treatment. **Safety:** After a median follow-up of 6 months (range: 1-24), 12 Grade 1 and 10 Grade 2 complications occurred. No patient had Grade ≥3 complication. **Conclusion:** Focal IRE has a low toxicity profile with encouraging genito-urinary functional outcomes. Further prospective development studies are needed to confirm the functional outcomes and to explore the oncological potential.

Table 2: Ongoing/upcoming clinical studies on IRE in localised PrC.

Ongoing/upcoming study	Study design, population, and outcomes
CROES Phase I study[17] (ClinicalTrials.gov Identifier: NCT01790451)	**Study design:** Multicentre prospective human pilot Phase I study. **Population:** 16 patients with PrC who are scheduled for RP will undergo an IRE procedure, approximately 30 days prior to the surgery. **Data collection:** Data of AEs, side-effects, functional outcomes, pain, and quality of life (QoL) will be collected and patients will be controlled at 1 and 2 weeks post-IRE, and 1 day pre-prostatectomy and post-prostatectomy. Prior to the IRE procedure and the RP, all patients will undergo an mp-MRI and contrast-enhanced ultrasound (CEUS) of the prostate. **Outcomes:** The efficacy of ablation will be determined by whole-mount histopathological examination, which will be correlated with the imaging of the ablation zone.
NEAT[33] (ClinicalTrials.gov Identifier: NCT01726894)	**Study design:** Single-centre prospective IIa study. **Population:** 20 men who have MRI-visible disease localised in the anterior part of the prostate will be recruited. Inclusion criteria include PSA ≤15 ng/ml, Gleason score ≤4 + 3, Stage T2N0M0, and absence of clinically significant disease outside the treatment area. **Data collection:** Treatment delivery will be changed in an adaptive, iterative manner so as to allow optimisation of the IRE protocol. After focal IRE, men will be followed during 12 months using validated patient-reported outcome measures (International Prostate Symptom Score [IPSS], International Index of Erectile Function [IIEF]-15, UCLA EPIC, EuroQoL 5D, Functional Assessment of Cancer Therapy-Prostate [FACT-P], Memorial Anxiety Scale for Prostate Cancer). Early disease control will be evaluated by multi-parametric and targeted transperineal biopsy of the treated area at 6 months. **Outcomes:** NEAT will assess the early functional and disease-control outcome of focal IRE using an adaptive design. **Estimated Primary Outcome Completion Date:** August 2015.
Phase II CROES Clinical Trial[34] (ClinicalTrials.gov Identifier: NCT01835977)	**Study design:** Phase II clinical trial. **Population:** Six European centres will randomise 200 patients into focal ablation versus extended focal ablation with tumour in one prostate lobe. The CROES will conduct a study titled *'Multicenter Randomized Two-Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localized Unilateral PrC.'* **Outcomes:** With this Phase II clinical trial, the investigators want to compare focal ablation versus extended focal ablation with IRE in patients with unilateral low-to-intermediate-risk PrC. Primary objectives are to determine if focal ablation has fewer side-effects than whole-gland ablations measured by IPSS, IIEF, time of catheter a demeure, Visual Analog Scale pain scores, and length of hospital stay. The secondary objective is to determine the oncological outcome of IRE focal ablation in comparison with extended focal ablation. This will be measured by standardised transrectal biopsies and mp-MRI findings in follow-up. Furthermore, the objective is to determine if there is a difference in the QoL between patients who are treated with focal ablation and those treated with extended focal ablation measured by FACT-P. **Estimated Primary Outcome Completion Date:** February 2018.
CROES Registry of Irreversible Electroporation for the Ablation of PrC With Use of NanoKnife Device[35] (ClinicalTrials.gov Identifier: NCT02255890)	**Study design:** Multicentre international registry (observational study). **Objectives:** The aim of this registry is to assess the recurrence of PrC at 1 and 5 years, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline. Secondary objectives are to establish which indications lead to treatment with IRE setting, and safety assessment measured by number of complications and AEs. **Target follow-up duration:** 5 years.

WHAT'S NEW ON FOCAL THERAPY FOR PROSTATE CANCER?

Highlights from the European Association of Urology Annual Meeting (Madrid, 20th-24th March 2015)

At EAU, Prof Emberton presented an interesting webcast, *'Evolving concept and technique in focal therapy, reality or myth?',* in which he reviewed the advantages of targeted biopsy for PrC detection and diagnosis versus a systematic approach, before discussing the need for tissue-preserving modalities in localised PrC.

Prof Emberton also examined the concept of treating the index lesion (which is thought to be responsible for disease progression) in multifocal localised PrC with focal ablation.[36] He welcomed the emergence of focal therapy as a legitimate new class of therapy, which now commends legitimacy and will most likely help refine the risk stratification rationales and treatment strategies.

In Vivo Data on a Novel Thermal Ablation Technique

A novel thermal ablation technique, convective water vapour therapy (steam), was explored in a prospective multicentre study: 14 patients underwent concomitant transperineal, ultrasound-guided vapour treatment followed by RP under the same anaesthetic.[37] Thermal ablation was clearly identified in all pathologic specimens. The peripheral and/or transition zones could be selectively targeted. Needle placement, vapour injections, and treated areas could be clearly visualised by real-time ultrasound monitoring. Extraprostatic tissue injury was not observed.

Follow-Up After Focal Therapy

The very interesting and crucial question of follow-up after focal therapy was addressed with the results of an international multidisciplinary (76 participants: 70% urologists, 28% radiologists, and 2% biomedical engineers) consensus questionnaire.[38] Indeed, since focal therapy predominantly preserves the prostate, the possibility of developing a new PrC remains, especially in elderly patients with risk factors. This Delphi consensus group concluded that in order to include focal therapy as a standard of care treatment, standardised follow-up is essential. The follow-up after focal therapy should be a minimum of 5 years and should include mp-MRI, prostate biopsies, and assessment of erectile function, QoL, urinary symptoms, and incontinence. All data should ideally be pooled in a common global database to provide important and consistent outcome data.

Moreover, van den Bos et al. presented the results of a prospective study conducted on 16 patients scheduled for RP and in which IRE procedures were performed approximately 4 weeks before surgery.[39] The aim of the study was to determine the most feasible imaging modality for accurate visualisation of the IRE ablation zone. Prior to and 4 weeks after the IRE procedure, imaging of the prostate was performed by ultrasound, CEUS, and mp-MRI. Grey-scale ultrasound and Tesla (T)2-weighed MRI were deemed insufficient to assess IRE ablation volume, while CEUS and dynamic contrast enhanced MRI were determined as the most feasible imaging modalities to visualise the IRE ablation zone, and closely matched the histopathology shape and volume of the ablation zones.

Acknowledgements

Medical writing assistance was provided by Dr Caroline Charles (Scilink Medical Writing).

REFERENCES

1. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. J Urol. 1994;152(5 Pt 2):1910-4.

2. Wilt TJ et al. Radical prostatectomy versus observation for localized prostate cancer. New Engl J Med. 2012;367(3): 203-13.

3. Smith DP et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. BMJ. 2009;339:b4817.

4. McCammon KA et al. Comparative quality-of-life analysis after radical prostatectomy or external beam radiation for localized prostate cancer. Urology. 1999;54(3):509-16.

5. Jácome-Pita F et al. Focal therapy in prostate cancer: the current situation. Ecancermedicalscience. 2014;8:435.

6. Truesdale MD et al. An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: recommendations for follow up. Cancer J. 2010;16(5):544-9.

7. Heidenreich A et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65(1):124-37.

8. Thompson I et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007;177(6):2106-31.

9. Babaian RJ et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol. 2008;180(5):1993-2004.

10. Ahmed HU et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011;185(4):1246-54.

11. Ahmed HU et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study.

Lancet Oncol. 2012;13(6):622-32.

12. Madersbacher S et al. Effect of high-intensity focused ultrasound on human prostate cancer in vivo. Cancer Res. 1995;55(15):3346-51.

13. Moore CM et al. Photodynamic therapy for prostate cancer--a review of current status and future promise. Nat Clin Prac Urol. 2009;6(1):18-30.

14. Arumainayagam N et al. Tookad soluble (padeliporfin) second generation vascular targeted photodynamic therapy (VTP) for prostate cancer: safety and feasibility. European Urology Supplements. 2010;9(2);294.

15. McNichols RJ et al. MR thermometry-based feedback control of laser interstitial thermal therapy at 980 nm. Lasers Surg Med. 2004;34(1):48-55.

16. Lindner U et al. Focal laser ablation for prostate cancer followed by radical prostatectomy: validation of focal therapy and imaging accuracy. Eur Urol. 2010;57(6):1111-4.

17. van den Bos W et al. The safety and efficacy of irreversible electroporation for the ablation of prostate cancer: a multicentre prospective human in vivo pilot study protocol. BMJ Open. 2014;4(10):e006382.

18. Donaldson IA et al. Focal therapy: patients, interventions, and outcomes-a report from a consensus meeting. Eur Urol. 2015;67(4):771-7.

19. Lee EW et al. Irreversible electroporation: a novel image-guided cancer therapy. Gut Liver. 2010;4 Suppl 1:S99-S104.

20. Onik G et al. Irreversible electroporation: implications for prostate ablation. Technol Cancer Res Treat. 2007;6(4):295-300.

21. Li W et al. The effects of irreversible electroporation (IRE) on nerves. PloS One. 2011;6(4):e18831.

22. Neumann E et al. Gene transfer into mouse lyoma cells by electroporation in high electric fields. EMBO J. 1982;1(7): 841-5.

23. Davalos RV et al. Tissue ablation with irreversible electroporation. Ann Biomed Eng. 2005;33(2):223-31.

24. Lee EW et al. Imaging guided percutaneous irreversible electroporation: ultrasound and immunohistological correlation. Technol Cancer Res Treat. 2007;6(4):287-94.

25. Rubinsky B et al. Irreversible electroporation: a new ablation modality--clinical implications. Technol Cancer Res Treat. 2007;6(1):37-48.

26. Martin RC 2nd et al. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. Ann Surg Oncol. 2013;20 Suppl 3:S443-9.

27. Maor E et al. The effect of irreversible electroporation on blood vessels. Technol Cancer Res Treat. 2007;6(4):307-12.

28. Bagla S, Papadouris D. Percutaneous irreversible electroporation of surgically unresectable pancreatic cancer: a case report. J Vasc Interv Radiol. 2012;23(1): 142-5.

29. Ball C et al. Irreversible electroporation: a new challenge in "out of operating theater" anesthesia. Anesth Analg. 2010;110(5):1305-9.

30. Brausi M et al. Irreversible electroporation (IRE), a novel technique for focal ablation of prostate cancer (PCa): results of a interim pilot safety study in low risk patients with PCa. Urology. 2011;78(3 Suppl):S304-5.

31. Onik G, Rubinsky B, "Irreversible electroporation: first patient experience focal therapy of prostate cancer," Rubinsky B (ed.), Series in Biomedical Engineering: Irreversible Electroporation (2010), Berlin: Springer Berlin Heidelberg, pp.235-47.

32. Valerio M et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. Prostate Cancer Prostatic Dis. 2014;17(4):343-7.

33. Valerio M et al. A prospective development study investigating focal irreversible electroporation in men with localised prostate cancer: Nanoknife Electroporation Ablation Trial (NEAT). Contemp Clin Trials. 2014;39(1):57-65.

34. van den Bos W et al. A randomized controlled trial on focal therapy for localized prostate carcinoma: hemiablation versus complete ablation with irreversible electroporation. J Endourol. 2013;27(3):262-4.

35. Clinical Research Office of the Endourological Society. Registry of irreversible electroporation for the ablation of prostate cancer with use of Nanoknife device. Clinical trial: NCT02255890. https://clinicaltrials.gov/ct2/show/NCT02255890.

36. Ahmed HU et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate cancer: a Prospective Development Study. Eur Urol. 2015; doi:10.1016/j.eururo.2015.01.030. [Epub ahead of print].

37. Dixon C et al. Development of convective water vapor therapy (steam) for focal therapy of Prostate cancer. In vivo treatment and immediate radical prostatectomy. Eur Urol. 2015;14(2):e827-e827a.

38. Muller BG et al. Follow-up modalities in focal therapy for prostate cancer: Results from a Delphi consensus project. Eur Urol. 2015;14(2):e829-e829b.

39. van den Bos W et al. Imaging of the ablation zone after focal irreversible electroporation treatment in prostate cancer. Eur Urol. 2015;14(2);e828-e828a.

40. Bower M et al. Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. J Surg Oncol. 2011;104(1):22-8.