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INITIAL ASSESSMENT OF SAFETY AND CLINICAL FEASIBILITY OF IRREVERSIBLE ELECTROPORATION IN THE FOCAL TREATMENT OF PROSTATE CANCER

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Abstract

Background—To evaluate the safety and clinical feasibility of focal Irreversible Electroporation (IRE) of the prostate.

Methods—We assessed the toxicity profile and functional outcomes of consecutive patients undergoing focal IRE for localised prostate cancer in two centres. Eligibility was assessed by multi-parametric MRI (mpMRI) and targeted and/or template biopsy. IRE was delivered under transrectal ultrasound guidance with two to six electrodes positioned transperineally within the cancer lesion. Complications were recorded and scored accordingly to the NCI Common Terminology Criteria for Adverse Events; the functional outcome was physician reported in all patients with at least 6 months follow-up. A contrast-enhanced MRI one week after the procedure was carried out to assess treatment effect with a further mpMRI at 6 months to rule out evidence of residual visible cancer.

Results—Overall, 34 patients with a mean age of 65 years (SD= ±6) and a median PSA of 6.1 ng/ml (IQR= 4.3 - 7.7) were included. Nine (26%), 24 (71%) and one (3%) men had low, intermediate and high risk disease, respectively (D'Amico criteria). After a median follow-up of 6

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months (range 1-24), 12 grade 1 and 10 grade 2 complications occurred. No patient had grade >/= 3 complication. From a functional point of view, 100% (24/24) patients were continent and potency was preserved in 95% (19/20) men potent before treatment. The volume of ablation was a median 12ml (IQR= 5.6 - 14.5ml) with the median PSA after 6 months of 3.4ng/ml (IQR= 1.9 - 4.8ng/ml). MpMRI showed suspicious residual disease in six patients, of whom four (17%) underwent another form of local treatment.

Conclusions—Focal Irreversible Electroporation 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.

Keywords

focal therapy; irreversible electroporation; prostate cancer; toxicity

Introduction

The therapeutic ratio – benefit to harms - of standard therapies used in the treatment of localised prostate cancer is low [1]. As a result, much clinical and research effort has centred on reducing the side-effects of current radical therapies. Focal therapy has emerged as one such strategy that might reduce harms whilst retaining benefit of cancer control.

Focal therapy, in its various forms, has been evaluated in early prospective proof of concept studies and is currently fully recruited to a randomised controlled trial in Europe [2-4]. Whilst these studies used High Intensity Focused Ultrasound (HIFU) and Vascular Targeted Therapy, respectively, other studies/case series have evaluated cryotherapy and thermal laser [5-8]. The results of all these reports have been summarised in a recent systematic review [9] showing that incontinence is 0-5%, impotence is 0-46% and disease control using biopsies is 77-96.3%. Early toxicity from these various ablative modalities can be high with recto-urethral fistula reported in up to 2.4% patients.

Irreversible Electroporation (IRE) is a non-thermal energy source that is being used in the USA and in Europe by interventional radiologists in liver, kidney and pancreas in a primary, salvage and palliative role [10-13]. Although it is approved and being used in both jurisdictions in the treatment of prostate cancer, only few case reports of its use in this role exist in the urological literature [14,15].

This report combines the work of two groups working independently who adopted the IRE technology early and applied it very selectively in a real practice clinical setting with careful institutional audit of results.

Materials and Methods

Design/Population

This is a two-centre (Princess Grace Hospital in London/UK, and St.Vincent's Prostate Cancer Centre, Sydney/Australia) retrospective analysis of men with localised prostate

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cancer treated with IRE. It represents the two learning curves within these two institutions (August 2011 to August 2013). Internal Review Board exemption was granted.

As part of the local approach for accurately characterising treatment-naïve patients interested in tissue-preserving approaches, all men underwent multi-parametric MRI (1.5 or 3T mpMRI with a pelvic coil; T2-weighted/dynamic-contrast enhanced/diffusion-weighted sequences; the OsiriX® Imaging Software was used for post-acquisition processing and reporting) and histological verification of suspicious areas by targeted and/or transperineal template mapping biopsy. All patients in this cohort had one MRI visible lesion concordant with histological findings showing clinically significant prostate cancer in this area. Any Gleason pattern >/=4 and/or cancer core length >/=4mm was considered clinically significant cancer. Informed consent was obtained from all patients after thoroughly discussing the potential risks along with the possible advantages of this new technology.

Procedure

IRE was delivered using the Nanoknife™ System (AngioDynamics®, Queensbury, NY, USA). The Nanoknife System is composed of a generator, which deploys low-energy direct current (LEDC) that leads to cell death by the formation of nanopores within the cell membrane rather than heating effect [16,17]. According to the treatment strategy and to the characteristics of the area to target, a certain number of needles are positioned to delineate the treatment area. Maximum electrode exposure length per needle is 2cm, and the distance between two needles should not exceed 2cm again; therefore, the number of needles was proportional to the treatment area. Once, the electrodes have been inserted, the distances between each two electrodes are measured on the transrectal ultrasound axial view. The device was set to deliver 90 pulses with a pulse length at 70μsec. The treatment to deliver was then automatically calculated by the system on the basis of the number of needles employed, the distances between them and the active electrode length used in order to obtain an optimal electrical field between 20-40 Ampere, which seems to causes complete ablation within the target area with no thermal damage [16]. Before delivering all the 90 pulses, a ‘test pulse’ at 10 pulses was delivered in order to verify the actual electrical field in the tissue. Indeed, current above the upper threshold of 40 Ampere may cause out-field treatment and heating damage, whereas current below the lower limit of 20 Ampere may lead to under-treatment. Therefore, if the current was in this range, the remaining 80 pulses were delivered, whereas in the opposite case the treatment planning was modified. Of note, the system calculates the current separately between every two needles, so it is possible to modify selectively the treatment only in the area needed without affecting the remaining parameters.

Electrodes were positioned at the margin of the lesion under transrectal ultrasound guidance using a brachytherapy stepper and grid set up (Figure 1). As this was part of the learning curve of both institutions, it was not possible to standardise the intervention. Men treated in the early part of the experience had small volume lesions, and were treated cautiously with 2 electrodes into the target area. As experience accumulated, in an iterative manner, targets of greater volume were targeted with 4-6 needles. Since the maximum electrode exposure length is 2cm, if a lesion was long than this in the ‘Z’ plane of the prostate, a pull-back and

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second treatment was used. The target volume was defined by mpMRI and histopathology with a safety margin of 3-5 mm.

Intravenous cefuroxime and gentamicin antibiotics were administered at induction; patients were under general anaesthesia with deep muscle paralysis using pancuronium bromide. Continuous peri-operative electrocardiographic monitoring with ECG was maintained. Urinary catheters were managed differently in the two centres. The Princess Grace Hospital cohort had either a urethral or a supra-pubic catheter placed at the time of the procedure, and a first attempt to remove the catheter was performed between three and five days after treatment. At St. Vincent's Prostate Cancer Centre, a urethral catheter was inserted for the procedure, and removed at the end of the procedure unless the target lesion abutted the urethra.

Follow-up

Early contrast-enhanced MRI was obtained after one week to evaluate local effect of the treatment, and to rule-out rectal damage which might indicate a recto-urethral fistula. On this scan, the ablation area was calculated by planimetry. Patients were then followed up by clinical visits with serum PSA levels every three months. Also, a late mpMRI was performed six months after the procedure, and then once a year. All MRIs were reported by one experienced radiologist per centre using the Likert scale to define the likelihood of residual disease (1= extremely unlikely; 2= unlikely; 3= equivocal; 4= likely; 5= extremely likely). Residual disease was evaluated by comparing post-IRE MR-images with pre-operative scans in which the treated lesion was visible. Residual cancer was suspected in case of an early enhancing focus on dynamic contrast sequence and residual restricted diffusion in the treatment area. In this study, values 3 to 5 were considered suspicious for residual cancer. During the perioperative period and the follow-up, complications were reported per type, and retrospectively scored according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Genito-urinary outcome is only reported for patients who were potent and/or continent before treatment, and with at least six months follow-up. Potency and urinary continence were physician-evaluated on the basis of patient reported ability to have erections sufficient for penetrative sexual intercourse and no pad use, respectively. The use of pre-operative and post-operative PDE-5 inhibitors was not systematically recorded.

Statistics

Continuous variables are given using the mean ± standard deviation (SD), or using the median and the overall/ interquartile range (IQR) according to their distribution; categorical variables are given using frequencies and percentages. Each patient was censored up to the time of last follow-up. All analyses were performed using SPSS® version 20.0 (Armonk, NY: IBM corporation).

Results

Overall, 34 patients were treated using primary focal IRE across the two centres, Princess Grace Hospital (n=20) and St. Vincent Prostate Cancer Centre (n=14). Basic patients'

characteristics and histological findings are summarized in table 1. Mean age was 65 ± 6 years; median PSA was 6.1 ng/ml (IQR= 4.3 - 7.7). A few men (n=2; 6%) had only transperineal targeted biopsy, whereas the majority (n=32; 94%) had template prostate mapping with additional targeted biopsy, although the biopsy density was variable, as shown in table 1. According to the D'Amico risk stratification nine (26%), 24 (71%) and one (3%) patients were stratified as low, intermediate and high risk, respectively.

Table 2 summarises the perioperative outcomes. In each patient, a median of four probes were employed, the median operative time from insertion of needles to completion was 27 minutes (range 11-55). Thirty-two patients (94%) were discharged the same evening of the day of the procedure and two stayed overnight. In nine (26%), no catheter was inserted during the procedure, whereas in the remaining either a supra-pubic (n= 9; 26%) or an urethral catheter (n= 16; 48%) was inserted. Median catheterisation length was 3 days (range= 0 - 9).

Toxicity

Genito-urinary toxicity is displayed in table 3; overall adverse events stratified by the NCI-CTCAE grade are displayed in table 4. All complications were grade 1 or 2, and no severe adverse event occurred. No patients had a recto-urethral fistula, and none had a urethral stricture. Non genitourinary adverse events occurred in four men. One patient had self-resolving per-operative tachycardia requiring 24-hour inpatient surveillance with no additional intervention; one patient stayed over-night for 'social reasons'; and two patients needed prolonged wound dressing at the site of the suprapubic catheter following catheter removal.

Successful catheter withdrawal at first attempt was achieved in 32 patients (94%). Some patients had either dysuria (n=6; 18%), or debris and/or hematuria (n=5; 15%) at one of the follow-up visits. Five patients (15%) developed uncomplicated urinary tract infection that were all managed with oral antibiotics.

Functional Outcome

Median follow-up was six months (range= 1–24) with 24 patients (71%) having a follow-up of at least 6 months (table 5). Potency was preserved in 95% (19/20) potent men before treatment, whereas all men continent before treatment were still continent (no pad usage) after treatment (24/24). No rectal dysfunction was recorded; however, this was probably not specifically and systematically investigated at follow-up.

Early disease control

On early MRI, the ablation area was estimated to be a median of 12ml (IQR= 5.6 - 14.5ml) (figure 2). Median PSA at 6 months was 3.2ng/ml (IQR= 1.9 - 4.8). In the follow up period, mpMRI showed suspicious residual disease in six patients. Two of these patients remain on surveillance since the PSA dropped significantly from pre-operative values. Four patients (17%) underwent a secondary treatment. Three patients had a secondary focal ablation in the same area, one using IRE and two using HIFU. Only one patient had histological verification of failure with transperineal targeted biopsy detecting residual Gleason 3 + 4.

He chose to undergo radical prostatectomy, which showed residual disease stage T2c Gleason 3 + 4. Unfortunately, the procedure was performed in another institution, and no zonal analysis was reported; therefore, it was not possible to determine the local effect of IRE in the treated area. Greater follow-up is required to determine the success of this further therapy. No patient died, had metastasis, or switched to systemic treatment.

Discussion

This study shows that focal IRE seems to be well tolerated in a heterogeneous group of patients across two centres. The genito-urinary outcomes, in terms both of erectile function and urinary continence, appear particularly encouraging. Longer follow-up in a protocol driven study is needed to derive any conclusion with respect to the cancer-control outcomes.

Limitations

Before discussing our findings, it is important to acknowledge the limitations of this study. First, the functional outcomes are reported on the basis of physician-reported measures, so may be overestimated. We are currently recruiting to a prospective ethics committee approved registered trial in the UK with embedded patient questionnaires to overcome this shortcoming [18]. Second, both the short follow-up and the absence of systematic histological verification of complete ablation in the treatment area do not allow us to draw any conclusion with respect to the efficacy of IRE in prostate cancer. In fact, as PSA kinetics alone are not specific enough to predict recurrence after focal treatment, we also used postoperative mpMRI to determine local failure. Although this tool seems promising in detecting recurrent disease after tissue-preserving treatment, it has not been validated yet in IRE [19-21]. Third, heterogeneity clearly exists in terms of patients' characteristics, selection of patients and standard operating procedures. All patients underwent mpMRI for eligibility, but the histological verification modality ranged from a few targeted biopsies of suspicious areas to full prostate mapping with additional samples derived from MRI-targets according to physicians' choice and preoperative mpMRI results. While this might have hindered the selection of patients, in both centres the diagnostic accuracy of the mpMRI protocol has been previously verified and negative predictive value for ruling out significant disease was at 90-95% [22,23]. Fourth, the retrospective nature of the study along with the small sample size represent additional limitations.

Clinical Implications

A recent systematic review of ablation modalities used for focal treatment of prostate cancer has shown that various modalities have been already used in selected patients with variable results [9]. However, IRE might have potential advantages over these. First, the non-thermal nature of the tissue damage seems to lead to very tight cell-kill zones in animal experiments and this might have advantages in prostate cancer focal therapy by allowing greater control over ablation of the target area [24]. Further, the local ablation should not be hindered by the so called 'heat sink' effect that can limit the efficacy of thermal ablation.

Another potential characteristic of IRE is the possibility of tissue-selectivity. Animal studies have shown that when an appropriate electrical field is employed, complete destruction of

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the target area can be achieved without damaging the collagenous structures - such as nerves, vessels and the urethra. In randomized controlled studies in which IRE was delivered to 30 rat sciatic nerves, whilst there was a decrease in nerve conductivity immediately after the procedure, after seven weeks, electrophysiological, functional and histological findings showed that the nerves had fully recovered [25]. Similar findings were demonstrated in focal IRE of canine prostates, in which the urethra and the neurovascular bundles were not affected histologically [24,26].

Finally, the procedure time is considerably shorter compared to other focal treatments. This is due to the fact that once the needles are positioned, the exposure time for a complete ablation is less than five minutes per lesion.

The interesting finding in this study remains the low toxicity, with no severe complication after treatment, and no recto-urethral fistulae. If we compare these results with the toxicity and the functional outcomes of current technologies used in focal therapy in prostate cancer, IRE is certainly encouraging [9]. This low toxicity is probably related to the inner characteristics of the energy discussed above.

From a disease control point of view, it is difficult to draw any definitive conclusions. This series should be regarded as the first step in the investigation of IRE in clinical studies. Recently, guidelines have been issued to guide researchers on how to assess new technologies in surgery [27-29]. This framework includes an initial phase of liberal, but safe clinical assessment by experts in the field [27]. Experience gained through this phase has allowed standardisation of the technique to take place through an iterative process of modifications to the technique. As a result, recruitment to a prospective development study evaluating disease control outcomes with post-treatment biopsies as well as prospective patient reported outcomes on genitourinary and rectal function has just begun [18]. Focal IRE may enhance the perioperative outcome and the functional preservation in patients undergoing prostate cancer focal treatment. However, rigorous prospective studies with systematic assessment of the functional and of the oncological outcomes are needed in order to move forward in the evaluation of this new technology.

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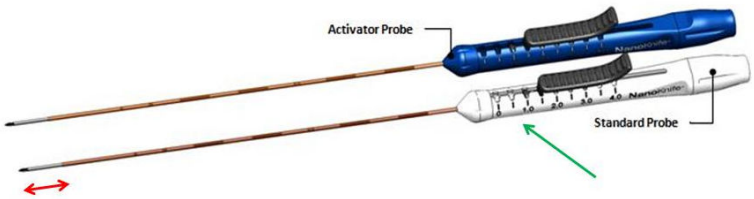

Figure 1. This figure shows a representation of the electrodes used for Irreversible Electroporation with the Nanoknife® system (Image Courtesy of AngioDynamics).

For each treatment, one activator probe (blue probe) is always needed and up to five standard probes (white probe) are employed, according to the size of the lesion. For both probes, a thumb slide situated at the handle of the electrode (green arrow) controls an adjustable insultation sheath which exposes the active length (red arrow) when retracted. In this representation, an active length exposure at 1.5cm is set.

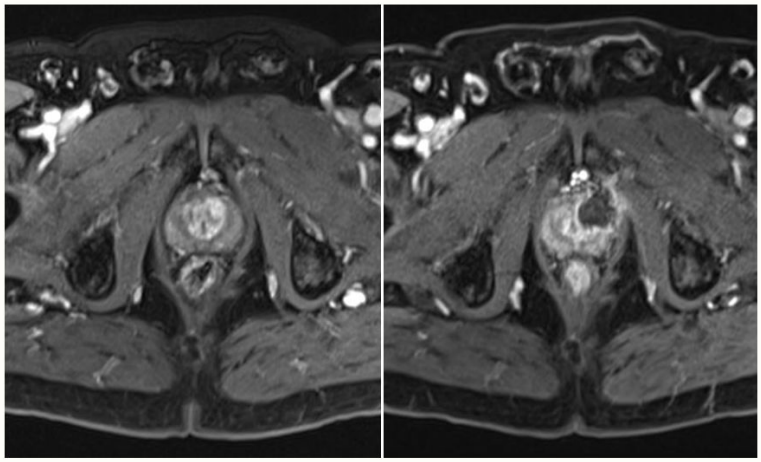

Figure 2. The left image shows a preoperative contrast-enhanced MR sequence highlighting a suspicious lesion in the left anterior area of the prostate. The right image shows successful ablation of this lesion with limited damage to surrounding structures after focal irreversible electroporation.

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Table 1

Clinical and histological characteristics of patients undergoing focal Irreversible Electroporation.

Variable		Value
Age in years (mean ± SD)		65 ± 6
PSA in ng/ ml (median; IQR)		6.1; 4.3 – 7.7
Prostate Volume in ml (mean ± SD)		42.4 ± 14.6
Number of Cores Taken (median; IQR)		25; 19 – 29
Number of Positive Cores (median; IQR)		3; 2 – 5
Biopsy Density - no of cores/ prostate ml (median; IQR)		0.6 (0.43 - 0.78)
Maximum Cancer Length in mm (mean ± SD)		6 ± 3
% Maximum Cancer Length (mean ± SD)		50 ± 30%
Gleason Score		
	3 + 3	9 (26%)
	3 + 4	19 (56%)
	4 + 3	5 (15%)
	4 + 4	1 (3%)
Risk Classification (D'Amico)		
	Low	9 (26%)
	Intermediate	24 (71%)
	High	1 (3%)

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Table 2

Perioperative outcome after focal Irreversible Electroporation

Variable		Value
Number of probes used (overall range)		4 (2 – 6)
Procedure time in min. (overall range)		27 (11 – 55)
Catheterisation at the time of surgery		
	None	9 (26%)
	Suprapubic	9 (26%)
	Urethral	16 (48%)
Hospital Stay in days (overall range)		1 (1 – 2)
Catheterisation Time (overall range)		3 (0 – 9)
Successful voiding after first catheter withdrawal		32/ 34 (94%)

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Table 3

Genito-urinary and rectal toxicity after focal Irreversible Electroporation.

Toxicity Event	Number of Patients (%)
Urethral Stricture	0
Urinary Retention	2 (6%)
Debris and/ or hematuria	6 (18%)
Dysuria	5 (15%)
Urinary tract infection	5 (15%)
Recto-Urethral Fistulae	0

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Table 4

Overall toxicity classified according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

CTCAE Grade	Definition	Number of Patients (%)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	12 (35%)
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living	10 (29%)
3	Severe or medical significant, but not immediately lifethreatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living	0
4	Life-threatening consequences; urgent intervention indicated.	0
5	Death related to Adverse Event	0

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Table 5

Functional and oncological outcomes after focal Irreversible Electroporation.

Variable	Value
Follow-up in months (median; overall range)	6 ; 1 – 24
No of patients with at least 6 months follow-up	24 (71%)
Potency Preservation	19/ 20 (95%)
Continence Preservation	24/ 24 (100%)
Volume ablated on MRI in ml (median; IQR)	12; 5.6 - 14.5
PSA at 6 months (median; IQR)	3.4; 1.9 – 4.8
Secondary Treatment	4/ 24 (17%)
Metastasis or Death	0