

Nanoknife Electroporation Ablation Trial (NEAT): a prospective development study investigating focal irreversible electroporation for localised prostate cancer

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ABSTRACT

Purpose

Irreversible electroporation (IRE) has attractive attributes for focal ablation, namely non-thermal effect, precise demarcation of treatment, and tissue-selectivity. We report on a prospective development study investigating focal IRE.

Materials and Methods

20 men with the following characteristics were recruited: anterior MR-visible index lesion concordant with transperineal targeted and template prostate mapping biopsy, absence of clinically significant disease elsewhere (UCL definition 2), and PSA \leq 15 ng/ml. Our primary objective was to determine the side-effect profile at 12 months. Secondary objectives included domain-specific toxicity profile using patient-reported outcomes, and early disease control using MR-targeted biopsy.

Results

Nineteen patients with median age at 60 years (IQR 53-66) and median PSA at 7.75 ng/ml (5.5-10.03) were treated. Sixteen patients were available for estimating first outcome as one was lost to follow up, and two had another form of treatment by study end. All men (16/16) had pad-free/leak-free continence at 12 months. The proportion of men with erections sufficient for penetration decreased from 12/16 (75%) to 11/16 (69%). No serious adverse events were recorded. There was a statistically significant improvement in urinary symptoms (UCLA-EPIC change, $p=0.039$; IPSS change, $p=0.001$). Erectile function remained stable (IIEF-15 change, $p=0.572$). The median PSA significantly dropped to 1.71 ng/ml ($p=0.001$). One man refused control biopsy. No residual disease was found in 11 patients (61.1%). One man (5.6%) harboured clinically insignificant disease; the remaining six (33.3%) harboured clinically significant disease.

Conclusion

Focal IRE has low genito-urinary toxicity. Additional studies are needed to optimise patient selection and treatment parameters.

MANUSCRIPT

1. Introduction

Focal therapy has been proposed as an alternative strategy to maintain the oncological benefit of ~~current~~ radical treatments while decreasing treatment-related side-effects⁻¹. This strategy aims to treat the ~~so-called~~ index lesion. It seems a legitimate option in light of new evidence showing that despite prostate cancer is generally multifocal ~~in most cases~~, secondary low-grade lesions have a slow and often indolent behaviour^{-2, 3}. The proposition being that in the majority the natural history of the disease seems to be driven by one aggressive clone located within the index lesion^{-3, 4}.

~~Various~~A number of sources of energy have been used to ablate prostate cancer in a focal manner. Across all series, pad-free continence, potency ~~preservation~~, and absence of residual disease were achieved in 95-100%, 54-100% and 83-100% men, respectively⁻⁵. The majority of focal therapy series report the results of thermal sources of energy, whose lethal effect is a consequence of extreme temperatures ~~within the target area~~: cryotherapy needles decrease the temperature below -40 °C; high intensity focused ultrasound (HIFU) devices raise the temperature above +60°C⁻⁶. Novel sources of energy might overcome the shortcoming of thermal technologies, which do not have well controlled and sharp demarcations between treated and untreated areas. ~~Further, they are subject to the “heat-sink effect” from vessels.~~

Irreversible electroporation (IRE) seems to provide selective ablation with sharply demarcated margins within the target area⁻⁷. Using pulsed low energy direct current, IRE leads to cell apoptosis by the formation of nano-pores within the membrane cell⁻⁸. Further, the ablation seems to be tissue-selective with collagenous structures recovering ~~shortly~~ after treatment, although this has been recently challenged by a stage I study^{-9, 10}.

IRE has so far been adopted by a few expert centres, ~~although rigorous assessment in prospective studies using validated outcome measures is lacking~~¹⁰⁻¹³. To our knowledge, this is the first ethics-committee approved prospectively registered study evaluating focal IRE with intention to treat.

2. Materials and Methods

2.1 Study design ~~and patients~~

We have previously reported ~~in detail~~ the design of the Nanoknife Electroporation Ablation Trial (NEAT)¹⁴. Briefly, this is a stage IIa prospective development study adherent to the Idea, Development, Evaluation, Assessment and Long-term (IDEAL) recommendations for evaluating novel surgical procedures ([NCT01726894](#))¹⁵. ~~The NEAT trial was approved by the Dulwich Research Ethics Committee and by the University College London Hospitals Joint Research Office (clinicaltrials.gov NCT01726894).~~ The trial was regularly audited by an independent data monitoring committee (IDMC). Enrolment began in October 2013 and ceased in June 2014 with follow-up till September 2015. Men with ~~histologically proven visible anterior prostate cancer anterior to the urethra and concordant with multiparametric MRI results~~ were invited to participate. We decided to only treat anterior disease as the predictability of the IRE created ablative effect was hitherto unknown and staying anterior permitted plenty of prostate tissue posteriorly ~~in case the ablation effect was unpredictable~~ in order to minimise the risk of rectal damage. A complete list of inclusion and exclusion criteria is given in table 1.

2.2 Study interventions

2.2.1 Cancer ~~risk and~~ localisation ~~assessment~~

Only men who underwent multiparametric MRI (mpMRI) and template prostate mapping biopsy (TPM) were considered for this trial. MpMRI ~~was performed prior to biopsy, and~~ followed a ~~local~~ standardised protocol including T2-, diffusion-weighted and contrast-enhanced sequences¹⁶. MpMRI was reported by an experienced radiologist with 10 years in prostate imaging using the 27 sectors standardised scheme to draw the exact location of all lesions detected with a Likert score ≥ 3 . ~~For each visible lesion, the exact Likert score was assigned, and the volume was calculated.~~

Cancer localisation was verified by either TPM with 5mm sampling density, or by TPM with limited sampling ~~in all modified Barzell zones~~ plus targeted biopsy to mpMRI visible lesions. To be eligible the anterior MR-visible lesion had to be concordant with the biopsy results. Presence of secondary lesions ~~elsewhere~~ was permitted, provided that these were considered clinically insignificant, according to the UCL definition 2 ~~for interpreting transperineal biopsy~~ (maximum cancer core length ≤ 3 mm and Gleason score 3+3)¹⁷.

2.2.2 IRE ~~and therapy escalation~~

Before the procedure, the MR-images were uploaded on the UCL SmartTarget® non-rigid image-fusion software to facilitate planning. Focal-IRE was performed under general anaesthesia with the patient ~~positioned~~ in the lithotomy position. ~~A~~ Prophylactic antibiotics were administered at induction; deep muscle paralysis was achieved during the delivery of energy. After having positioned a urethral or a suprapubic catheter, 19G electro-needles were positioned transperineally under transrectal ultrasound (TRUS) guidance through a brachytherapy grid. We used a bi-planar TRUS probe (Hitachi Preirus, Hitachi Aloka Medical America, Inc. Wallingford USA) mounted on a CIVCO EX³™ modular stepper fixed on the patient table. The needles were positioned at the margin of the target lesion, respecting at least a 5mm distance from the urethra. We used the Nanoknife® system to deliver IRE (AngioDynamics, New York, USA). The stepper was connected to an external platform to achieve TRUS image registration with the MR ~~images~~. Based on an add-on algorithm to the UCL SmartTarget, the software determined the location ~~(‘x’ and ‘y’ coordinates)~~ of the electro-needles on the brachytherapy grid. The operator was free to modify these coordinates, based on his own judgment; ~~but~~ discrepancies were recorded. The active length of each

electro-needle can vary between 0.5-2cm; this was determined by the operator based on the tumour cranio-caudal extension (~~z-plane~~). After inserting the needles, the distance between them was calculated on the axial TRUS view, and uploaded in the device software (figure 1).

The IRE protocol used included 90 pulses with a pulse length at 70 μ s; based on needle distance from each other, the device developed a specific treatment planning, ~~altering the electrical field~~. After achieving deep muscle paralysis, the first 10 pulses were delivered and the actual electrical field was measured. If this was within the target of 20-40 A, the remaining 80 pulses were delivered; otherwise the treatment planning was modified accordingly before continuing tissue ablation. At the end of the energy delivery, needles were pulled out, and the catheter was left in place. Focal-IRE was carried out as a day-case procedure with discharge the same evening, or the following morning if the case was treated in the evening.

As per IDEAL guidelines in this early stage of assessment, we included ~~within the study~~ a therapy escalation. Since we could not alter the treatment planning to deliver more energy – as ~~>40~~ A may lead to thermal effects while ~~<20~~ A may lead to under-treatment – we decided to include a therapeutic escalation based on target volume in the first nine patients. In the first group of three patients, the upper threshold for treatment was a tumour volume representing 15% of the ~~overall~~ prostate volume. This was increased at 40% and 50% for the second and third group of three patients, respectively. Early toxicity data from each group of 3 underwent mandatory IDMC review prior to ~~any~~ further treatments.

2.2.3 Follow up

Early contrast MRI and catheter withdrawal were organised 3-10 days after ablation. Clinical review with PSA measurements was organised at 6 weeks, 3, 6, 9 and 12 months. Patients responded to validated questionnaires at each time point, and adverse events were recorded and scored using the Common Terminology Criteria for Adverse Events version 4. ~~A detailed summary of trial flow and visits is given in~~ (table 2). The questionnaires included the International Prostate Symptom Score (IPSS), IPSS Quality of Life (IPSS-QoL), 15-Item International Index of Erectile Function (IIEF-15), UCLA Expanded Prostate Cancer Index

Composite (UCLA-EPIC) ~~urinary and bowel domain~~, European Quality of Life 5-dimensions (EQ-5D QoL), Functional Assessment of Cancer Therapy for Prostate (FACT-P), and Memorial Anxiety Scale for Prostate Cancer (MAX-PC). At 6 months, mpMRI was carried out and reported ~~as previously described~~ with the likelihood of presence of residual disease, both in the treated and untreated zones. All men underwent transperineal targeted biopsy of the treated area with at least one biopsy per one millilitre of residual tissue. Additional targeted biopsies were performed in case of Likert ≥ 3 elsewhere. As in the selection process, the UCL definition 2 was employed to define ~~what constitutes~~ residual clinically significant disease after focal IRE ablation.

2.3 Objectives

The primary objective was to determine the side-effect profile of focal-IRE. Secondary objectives included to determine domain-specific toxicity profile, the early disease control and the rate of trifecta (erections sufficient for intercourse, leak-free continence and absence of clinically significant disease).

2.4 Statistical analysis

In light of the primary outcome, the sample size was calculated ~~for precision~~ around common genito-urinary side-effects after prostate cancer treatment. With an expected 5% rate of incontinence, and 10% of erectile dysfunction, we estimated that 20 patients would represent an optimal sample size to determine precise estimates around these key outcomes¹⁴.

Continuous variables are given as median and interquartile range; categorical variables as frequencies and percentages. Variation in between visits of continuous variables is displayed using box-and-whisker plots. To determine whether there was significant differences between baseline and 12 months visits of continuous variables, two-tailed Wilcoxon signed rank test was used. Statistical significance was set at ≤ 0.05 ; data were analysed using using SPSS® version 20.0 (Armonk, NY: IBM corporation).

3. Results

3.1 Study population & perioperative outcomes

20 patients were recruited ~~over nine months~~. 19 patients were treated while one patient was excluded because of recrudescence on an anal fistula which made him not suitable for IRE ablation. ~~According to the NCCN classification, 7 (36.8%) and 12 (63.2%) patients were considered at low and intermediate risk, respectively.~~ According to UCL risk stratification, 2 (10.5%), 4 (21.1%) and 13 (68.3%) men were considered at low, intermediate and high risk, respectively (Table 3). Median procedure time (surgeon starts and finishes the procedure) was 64 minutes (range 55-80) for an overall median anaesthetic time of 95 minutes (range 80-110) (Table 4).

3.2 Primary outcome

Of 19 patients, 16 completed all trial visits and the 12 month follow-up. Of the remaining three, one preferred to continue his follow-up from 12 months onwards in another hospital; two men with residual disease had focal HIFU and radical prostatectomy, at 10 and 11 months, respectively. As the primary outcomes we are calculated as the variation between baseline and 12 months visit, these three patients were censored from this analysis, but were still considered for the estimation of adverse events, histological outcomes and variation of patient-reported outcome measures all over the study.

In terms of men with pad-free and pad-free/leak-free continence, the proportion remained stable between baseline and 12 months follow-up at 16/16 (100%; 95% CI 81-100%). In terms of absolute erectile function, the proportion of men with erections sufficient for penetration decreased from 12/16 (75%) to 11/16 (69%). In terms of relative erectile function, of 12 patients with erections sufficient for penetration, 10 (83% 95% CI 55-95%) remained so. The use of PDE-5 inhibitors remained stable at 2/16 men (13%).

There were no serious adverse events. Overall, 14 grade I and 19 grade II adverse events occurred, respectively. Of these, 10 urinary adverse events were considered “possibly” to “likely” related to the

operation: 5 (26.3%) persistent debris, haematuria or dysuria; 4 (21%) urinary tract infection; 1 (5.2%) urethral stricture (requiring dilation under local anaesthetic).

3.3 Secondary outcomes

Changes over time of validated questionnaire results are displayed in supplementary figures 1-9. There was a statistically significant improvement in urinary symptoms, as measured by the UCLA-EPIC urinary domain ($p=0.039$), IPSS ($p=0.001$) and IPSS-QoL ($p=0.028$). Erectile and bowel functions remained stable, as measured by the IIEF-15 ($p=0.572$) and UCLA-EPIC bowel domain ($p=0.128$), respectively. Health-related quality-of-life remained stable, as measured by EQ-5D VAS ($p=0.154$), the FACT-P ($p=0.169$) and the MAX-PC ($p=0.463$).

In terms of cancer control, the median PSA significantly dropped from 7.75 to 1.71ng/ml, corresponding to 78% decrease ($p=0.001$; IQR 1.33-4.67; supplementary figure 10). The 6 months mpMRI showed no new lesion not detected at the outset of the study. One man refused biopsy, with his 6 months MR scan showing equivocal findings (Likert 3). No residual cancer was found in 11 (61.1%) (figure 2). Infield rResidual disease was found in 7 (38.9%): 1 (5.6%) harboured clinically insignificant disease (1 core from total 9 positive with 3mm of Gleason 3+3) and the remaining 6 (33.3%) harboured clinically significant disease (figure 3). Of these, one was clinically significant by means of cancer core length 7mm (Gleason 3+3=6), but the others harboured Gleason 3+4=7 with a median MCCL 4mm (IQR 2.5-5-5). Of these 6, one underwent radical prostatectomy which showed pT2cN0 Gleason 3+4=7 with significant post-treatment effect, and residual tumour volume measuring 0.8ml. One underwent focal-HIFU while two were on the list for focal-HIFU and focal cryotherapy, respectively, by study end. The remaining patients with residual disease chose to undergo active surveillance. No man died or developed distant disease.

Overall, among the 12 patients with good functional status at baseline which completed the study, six (50%; 95% CI 25-75%) achieved trifecta status.

4. Discussion

Focal-IRE delivered to the index lesion conferred a low rate of genito-urinary toxicity with preservation of continence in all men and preservation of potency in around 80%. The treatment seemed to have minimal impact on health status and no serious adverse events occurred. The ablation results were less satisfactory with one-third harbouring clinically significant disease following treatment.

Our study has some limitations. First, the sample size was small and some estimates have wide confidence intervals. Whilst the sample size was adherent to the IDEAL recommendations for assessment of novel technologies within stage IIa studies, only 16/20 (80%) patients had data available at 12 months for measurement of the primary outcome. Indeed, one man was not treated, one preferred to be followed elsewhere, and two had further local treatment. Second, we selected only men with visible anterior disease. Therefore, the results of this study might not be applicable to all men with local disease undergoing focal-IRE. Finally, this study should be regarded as an evaluation of a novel technology – IRE – rather than an evaluation of focal therapy ~~as a strategy~~. This is in light of the short follow-up, the small sample size and the novelty of the procedure.

Our early prospective development study confirms the low toxicity of focal-IRE. There were no serious adverse events and genito-urinary functional preservation was high. This might reflect the intrinsic characteristics of IRE leading to ablation with little damage to surrounding structures or might be related to the anterior location of the ablated area, well away from both neurovascular bundles and the external urinary sphincter. Further, focal-IRE seems to lead to a significant improve in voiding and storage urinary symptoms. This is also likely to be related to the anterior location of the tumours leading to benign prostatic hyperplastic tissue undergoing treatment effect as well.

The disease control based on post-IRE biopsies was somewhat lower than reported with thermal ablation methods. There might be few explanations for this. First, in a post-hoc analysis we compared patients' and

tumour characteristics in order to explore predictors of failures (~~supplementary~~ table 51). Tumour volume and aggressiveness did not seem different in the two groups; the only statistically significant predictor was the laterality of the tumour, whether it was unilateral or bilateral ($p=0.049$). In other words, if the tumour crossed the midline anteriorly, it was more likely to be incompletely treated. Whether this was because of the transurethral catheter presence provoking variation of the electric field, or due to the location of the needles which were positioned at least 5mm from the urethra, remains to be determined. Second, the margin of the treatment areas were tight. Indeed, we positioned the needles just at the margins of the lesion ~~to treat~~. Recent evidence, ~~after the trial treatments~~, shows that the oncological margin to achieve complete ablation should be up to 9mm in larger lesions, a threshold that we did not respect ~~in this study~~¹⁸. Third, we currently lack reliable measures of intraoperative monitoring during ablation. The delivery of energy is actually visible on TRUS; however, validated quantitative or qualitative measures to interpret these images are not available, at present. Finally, the treatment protocol employed ~~in this study~~ has been derived from liver ablation, and might be inappropriate for prostatic tissue ablation. Another group using the same treatment protocol as ours reported similar positive biopsy rate after focal IRE⁻¹². Other groups achieved better histological outcomes. In one study, complete ablation was achieved within the targeted area using a modified protocol employing 90 pulses with a pulse length at $90\mu s$ ⁻¹⁰; in another study, residual cancer was detected in 16% men, although the authors did not report on the pulse length employed⁻¹³.

5. Conclusion

Focal IRE confers low risk of genito-urinary toxicity. The rate of residual disease in the treatment area might be the result of narrow margins, or incomplete ablation using the protocol delivered ~~within this trial~~. Further studies are needed to determine optimal selection criteria and ~~optimal~~ treatment delivery.

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Conflict of Interest

Angiodynamics Inc. (New York, USA) has supported this trial by providing the device and the probes cost-free for all the patients within the study. M. Valerio has received funding for conference attendance from Geoscan Medical and from AngioDynamics. M. Emberton and H.U. Ahmed receive funding from Sonacare, GSK and Advanced Medical Diagnostics for clinical trials. M. Emberton is a paid consultant to Steba Biotech, AngioDynamics and SonaCare Medical (previously called USHIFU). H. U. Ahmed is a paid consultant to Sonacare Medical (through membership of Data Monitoring and Safety Board for a clinical trial using the Sonablate™500 HIFU device in the USA). Both have previously received consultancy payments from Oncura/GE Healthcare and Steba Biotech. L. Dickinson has received trial funding support from SonaCare Medical and previously consultancy fees from SonaCare Medical and Oncura. None of these sources had any input whatsoever into this article.

Legends

Table 1

NEAT inclusion and exclusion criteria.

Table 2

Trial flow.

Table 3

Patients' characteristics.

Table 4

Treatment parameters.

[Table 5](#)

[Post-hoc analysis looking at predictors of residual disease at control targeted biopsy.](#)

Figure 1

Diagram showing axial and sagittal views of four electro-needles positioned to ablate a lesion in the left anterior area of the prostate. Reused with permission for printed and electronic versions from "Valerio M, Dickinson L, Ali A et al. A prospective development study investigating focal irreversible electroporation in men with localised prostate cancer: Nanoknife Electroporation Ablation Trial (NEAT). *Contemp Clin Trials*, 39: 57, 2014".

Figure 2

Case study with no residual tumour in the treated area.

Figure 3

Case study with residual tumour at the apical margin of the treated area.

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