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Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort

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Abstract

Background: Focal irreversible electroporation (IRE) can be used to treat men with localised prostate cancer (PCa) with reduced impact on quality of life (QoL).
Objective: To assess oncological and functional outcomes.
Design, setting, and participants: To report on a prospective database of patients undergoing primary IRE between February 2013 and August 2018. A minimum of 12-mo follow-up was available for 123 patients. Median follow-up was 36 mo (interquartile range [IQR] 24–52 mo). A total of 112 (91%) patients had National Comprehensive Cancer Network intermediate risk and 11 (9%) had low risk. A total of 12 (9.8%) had International Society of Urological Pathology (ISUP) grade 1, 88 (71.5%) had ISUP 2, and 23 (18.7%) had ISUP 3.
Intervention: Focal IRE ablation of PCa lesions.
Outcome measurements and statistical analysis: Follow-up involved serial prostate-specific antigen (PSA), multiparametric magnetic resonance imaging (mpMRI), and transperineal template mapping biopsy (TTMB) at 12 mo. Failure-free survival (FFS) was defined as progression to whole-gland or systemic treatment or metastasis/death. Functional outcomes were assessed.
Results and limitations: Median age was 68 yr (IQR 62–73 yr). Median preoperative PSA was 5.7 ng/ml (IQR 3.8–8.0 ng/ml). On post-treatment TTMB, in-field recurrence was present in 2.7–9.8% of patients. FFS at 3 yr was 96.75%, metastasis-free survival 99%, and overall survival 100%. A total of 18 patients required salvage treatment (12 had repeat IRE; six had whole-gland treatment). The negative predictive value of mpMRI was 94% and sensitivity 40% for detecting in-field residual disease 6 mo after treatment. Among patients who returned questionnaires, 80/81 (98.8%) remained pad free and 40/53 (76%) had no change in erectile function.

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Conclusions: Focal IRE in select patients with localised clinically significant PCa has satisfactory short-term oncological outcomes with a minimal impact on patient QoL.

Patient summary: In this study, 123 patients underwent focal therapy using irreversible electroporation. Follow-up biopsy was clear of residual disease in 90.2–97.3% of patients. Of patients, 96.75% avoided whole gland treatment at 3 yr.

1. Introduction

Prostate cancer (PCa) is among the leading causes of cancer-related death in men [1]. Radical treatment for localised PCa provides excellent oncological control but confers a major impact on quality of life (QoL) [2,3]. This has led to the development of focal ablation (FA) for PCa, which aims to achieve equivalent oncological control whilst improving QoL preservation. This is achieved by ablating areas containing significant cancer while preserving the unaffected prostate and adjacent structures. Multiple modalities for FA are in clinical use; however, published evidence is limited [4]. The only randomised trial assessing a FA modality was comparing photodynamic therapy with surveillance in low-risk PCa [5].

The long natural history of the disease makes it challenging to assess the efficacy of FA in terms of PCa-specific survival. Whilst a number of studies have reported oncological outcomes, the majority have solely relied on prostate-specific antigen (PSA) testing and magnetic resonance imaging (MRI) with only selective targeted biopsies [6,7]. This may overestimate the efficacy of FA as there is limited evidence regarding the diagnostic accuracy of multiparametric MRI (mpMRI) after focal treatment [8,9]. However, Dickinson et al. [10] showed a high negative predictive value of mpMRI to detect in-field residual PCa after high-intensity focused ultrasound (HIFU).

Irreversible electroporation (IRE) is an FA technology that ablates prostate tissue by delivering a high-voltage electric current between electrodes [11]. The objective of this study was to assess efficacy and QoL in the largest cohort of men treated with IRE in the primary setting using a rigours transperineal template mapping biopsy (TTMB) at 12 mo after treatment. Secondary objectives were (1) to evaluate the diagnostic accuracy of mpMRI in the detection of residual PCa and (2) to examine failures in order to learn potential future predictors of failure.

2. Patients and methods

Following institutional review board approval (HREC approval SVH 13/018 and 16/110), data were retrieved from a single-centre (St Vincent's Prostate Cancer Centre, Sydney, Australia) prospective database of patients treated with primary focal IRE between February 2013 and August 2018. Patients with minimum 12-mo follow-up who met the consensus guidelines for primary FA were included in the analysis. Written informed consent was obtained from all patients.

2.1. Patient selection and cancer localisation

All patients underwent mpMRI (3 Tesla; T2-weighted, dynamic contrast enhancement, diffusion-weighted imaging sequences) using the Prostate Imaging Reporting and Data System (PI-RADS) v2. All mpMRI findings were reported by an experienced uroradiologist. Patients were considered only for FA if they had a unilateral or midline anterior/posterior index lesion on mpMRI. Next, coregistration with histology from biopsy was required. Eighty-five men underwent TTMB ± mpMRI targeted biopsy, 24 men underwent mpMRI targeted–only biopsies because they had undergone template biopsies within <12 mo, and 14 men had transrectal ultrasound (TRUS) biopsy. Further details on biopsy technique are provided in the Supplementary material. All preoperative biopsies were centrally reviewed by a single uropathologist. Only patients with Gleason score ≤7 (International Society of Urological Pathology [ISUP] ≤3) and low- (high volume ≥4 mm) to intermediate-risk PCa (D'Amico) were considered for focal IRE treatment. Only patients with PSA <15 ng/ml were included in the study (Supplementary Table 1).

2.2. Irreversible electroporation procedure

The IRE procedure was performed in our institution by a single urologist. A comprehensive description of the procedure is provided in the Supplementary material [12]. Safety margins of 5 or 10 mm from the targeted area were used to adjust for MRI volume underestimation. Treatment margin of 10 mm was applied to all cases after it was shown that mpMRI underestimated the tumour boundary by up to 9 mm [13]. The number of electrodes placed was dependent on the size and location of the lesion. A 5 mm distance was applied from vital structures if tumour location and safety margin permitted.

2.3. Follow-up

Serial PSA levels were measured every 3 mo for at least 2 yr. Follow-up mpMRI was performed at 6 mo. As part of our institutional protocol, follow-up TTMB with additional targeted biopsies of the ablation zone and margins was performed at 12 mo (further details provided in the Supplementary material).

2.4. Statistical methods and outcome measures

2.4.1. Oncological outcomes

Oncological outcomes were analysed for treated patients meeting the consensus criteria and with a minimum of 12-mo follow-up. The PSA nadir was compared with baseline PSA. On mpMRI assessment, the in-field region of interest was defined using a binary variable (suspicious or nonsuspicious). The out-of-field region was assessed using PI-RADS v2. Follow-up biopsies were reported as follows: (1) negative, (2) in-field recurrence if PCa found within the intention-to-treat region, or (3) out-of-field recurrence if PCa was outside the intention-to-treat region. Biopsies were described as adjacent if they were in the region immediately adjoining to the ablation zone.

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Significant PCa on follow-up biopsy was defined as Gleason score ≥3 + 4. A significant positive biopsy found within the targeted area was deemed in-field treatment failure and any found outside the target zone was designated as out-of-field failure. The analysis was performed for the entire cohort, and then for patients after the treatment margin was increased and technical skills improved.

Failure-free survival (FFS) was defined as progression to whole-gland or systemic treatment or metastasis/death. FFS was reported at 3 yr after initial treatment and was stratified for both the ISUP subgroup and the National Comprehensive Cancer Network (NCCN) risk category.

Metastasis-free survival and overall survival were calculated at 1, 3, and 5 yr after IRE.

2.4.2. Diagnostic accuracy of mpMRI

To assess the accuracy of mpMRI for the detection of residual PCa after IRE treatment, a 2 × 2 contingency table was used to calculate sensitivity, specificity, positive predictive value, and negative predictive value (NPV). Follow-up template biopsies were used as a histopathological reference following the methods described by Scheltema et al. [14]. Analysis was performed for the whole gland, in-field and out-of-field regions, with 95% confidence intervals.

2.4.3. Safety assessment

Adverse events were recorded using the Clavien-Dindo classification.

2.4.4. QoL and functional outcomes

The QoL and functional data were prospectively collected from patients who provided consent using the Expanded Prostate Cancer Index Composite (EPIC), including urinary, sexual, and bowel domains and the American Urological Association symptom score. The 12-item Short-Form (SF-12) health survey physical component summary and mental component summary scores were used to assess overall health status. Questionnaires were completed at baseline, 6 wk, and 3, 6, 12, and 24 mo postoperatively. Continence was defined as patients reporting no use of pads to control urine leakage. Patients were leak free if they reported leakage of urine either rarely or never. Potency was defined as erections firm enough for intercourse more than half of the time.

2.5. Statistical methods

Pearson's chi-square test was performed to assess association between the frequency for in-field and that for out-of-field significant PCa on repeat prostate biopsy. The linear mixed-effect model was used to assess the QoL differences over time. In this model, each QoL variable was modelled as a linear function of time (intercept and slope) for each individual, and the collection of slopes from all individuals was then used as an estimate of average change. Statistical significance was based on the *t* test for the estimate. A *p* value of <0.05 is considered statistically significant. All analyses were conducted with the R-statistical environment.

3. Results

3.1. Patient characteristics

Patient characteristics ($n = 123$) and selection flowchart are summarised in Table 1 and Fig. 1, respectively (treated between February 2013 and September 2018). The median (interquartile range [IQR]) follow-up is 36 (24–52) mo and preoperative PSA 5.7 ng/ml (IQR 3.8–8 ng/ml). A total of 112 (91%) patients had intermediate-risk disease and 11 had low-risk disease. A total of 12 (9.7%) patients had ISUP grade 1, 88 (71.5%) had ISUP grade 2, and 23 (18.7%) had ISUP grade 3.

Table 1 – Baseline clinicopathological characteristics

Median (IQR) age (yr)	68 (62–73)
Median (IQR) serum PSA (ng/ml)	5.725 (3.8–8.0)
Median (IQR) prostate volume on MRI (ml)	40 (30–60)
Median (IQR) PSA density (ng/ml)	0.14 (0.10–0.187)
Number of lesions on mpMRI	
0	2
1	104
2	17
PI-RADS score	
1–2	6
3	20
4	68
5	35
Median (IQR) lesion volume on mpMRI (cm^3)	0.485 (0.255–1.0975)
Biopsy results	
TRUS template biopsies (±targeted cores)	*n* = 14
Median (IQR) number of cores taken	13 (10–16)
Median (IQR) number of positive cores	2 (2–4)
Transperineal template biopsies (±targeted cores)	*n* = 85
Median (IQR) number of cores taken	26 (22–34)
Median (IQR) number of positive cores	4 (2–6)
Targeted-only transperineal biopsies (previous template within <12 mo)	*N* = 24
Median (IQR) number of cores taken	6 (4–7)
Median (IQR) number of positive cores	3 (2–4)
Disease distribution on biopsy	
Significant unilateral disease	86
Significant single midline lesion (anterior/posterior)	14
Significant unilateral disease + contralateral insignificant disease	23
Gleason score	
Gleason 3 + 3 (ISUP grade 1)	12
Gleason 3 + 4 (ISUP grade 2)	88
Gleason 4 + 3 (ISUP grade 3)	23
D'Amico risk classification	
Low	11
Intermediate	112
Median (IQR) proportion of grade 4 tumour in biopsy (%)	10 (5–30)

IQR = interquartile range; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; TRUS = transrectal ultrasound.

3.2. Oncological outcomes

3.2.1. Histopathology

One-hundred and two patients (83%) had undergone follow-up biopsy at the time of analysis. The remaining patients were either waiting for follow-up biopsy or refused due to reassuring mpMRI/PSA.

In-field recurrence was present in 10/102 (9.8%) at 12 mo. Out-of-field recurrence occurred in 13/102 (12.7%). Overall, 79/102 (77.5%) of men were free from significant PCa at 12 mo after IRE.

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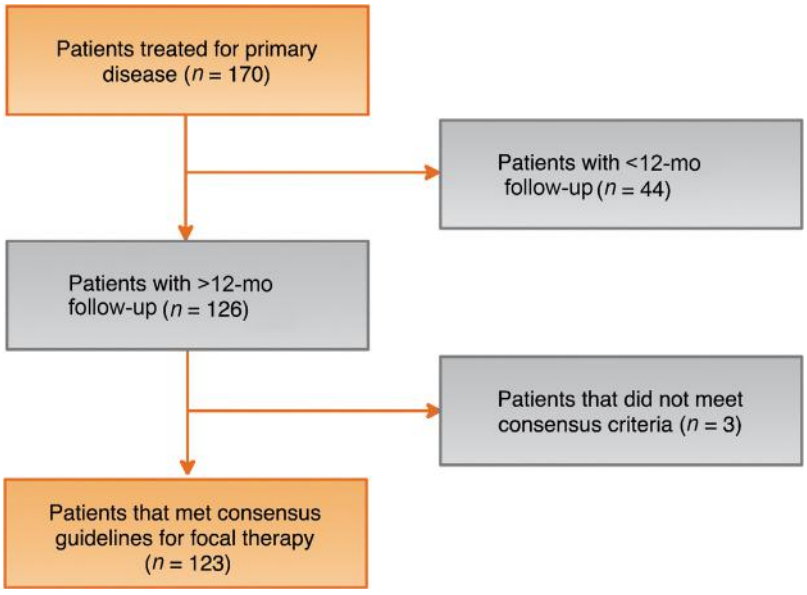

Fig. 1 – Patient selection flowchart.

After correcting for the initial 32 patients (increased treatment margin and improved technical skills), the in-field recurrence rate decreased to 2/74 (2.7%); out-of-field recurrence rate remained similar at 9/74 (12.1%) (Table 2). Overall, 63/74 (85.1%) were free of significant PCa at 12 mo after treatment. Allowing for up to two IRE treatments, six of 123 (4.8%) required salvage whole-gland treatment at a median follow-up of 36 mo.

Multivariate analysis showed that multiple lesions on preoperative mpMRI were a predictor of residual disease ($p < 0.0001$). Patients who had TRUS biopsy preoperatively had a 42% failure rate compared with 20% in patients who had a transperineal biopsy, although this was not statistically significant. No other preoperative characteristic predicted residual significant PCa on follow-up biopsy (Supplementary Table 2).

Overall FFS at 3 yr was 96.75%. Fig. 2 shows Kaplan-Meier curve stratified for both ISUP subgroups and NCCN risk groups. Metastasis-free survival was 98.5% (68/69) at 3 yr and overall survival was 100% (69/69) at 3 yr.

3.2.2. *Imaging and prostate-specific antigen*

Compared with baseline PSA (median 5.725 ng/ml; IQR 3.81–7.96 ng/ml), the median PSA at 12 mo decreased by 56.5% to 2.5 ng/ml (IQR 1.43–5.675 ng/ml).

3.2.3. *Salvage treatment for patients who failed primary IRE*

Eighteen patients required salvage treatment after IRE for recurrence/residual PCa. Twelve had repeat IRE procedure for out-of-field recurrence. Of these patients, eight of 12 (75%) were clear of PCa on repeat biopsy. Two patients developed further localised recurrent disease and were referred for external beam radiation therapy (both are currently disease free). One patient had low-dose-rate brachytherapy for a significant out-of-field recurrence. Three patients underwent salvage robot-assisted radical

Table 2 – Oncological follow-up for all patients and for those excluding the initial cohort of patients after the treatment margin was increased to 10 mm and technical skills were improved (initial cohort of 32 patients was excluded from analysis)

	All patients	Excluding initial cohort
PSA nadir (IQR)	3.48 (1.43–5.67)	3.37 (1.04–5.7)
mpMRI at 6 mo ($n = 112$)		
Clear	90/112 (80%)	70/80 (87.5%)
In-field lesion	3/112 (2.6%)	1/80 (1.25%)
Adjacent to field (marginal)	6/112 (5.4%)	3/80 (3.75%)
Out-of-field lesion	11/112 (9.8%)	6/80 (7.5%)
In- and out-of-field lesion	6/112 (5.4%)	0
Biopsy results ($n = 102$)		
Median (IQR) number of cores taken	25 (22–31)	
Median (IQR) number of positive cores	1 (0–3)	
Significant in-field disease, *n* (%)	10/102 (9.8)	2/74 (2.7)
Significant out-of-field disease, *n* (%)	13/102 (12.7)	9/74 (12.1)
Whole gland free of clinically significant cancer at 12 mo, *n* (%)	79/102 (77.5)	63/74 (85.1)

IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.

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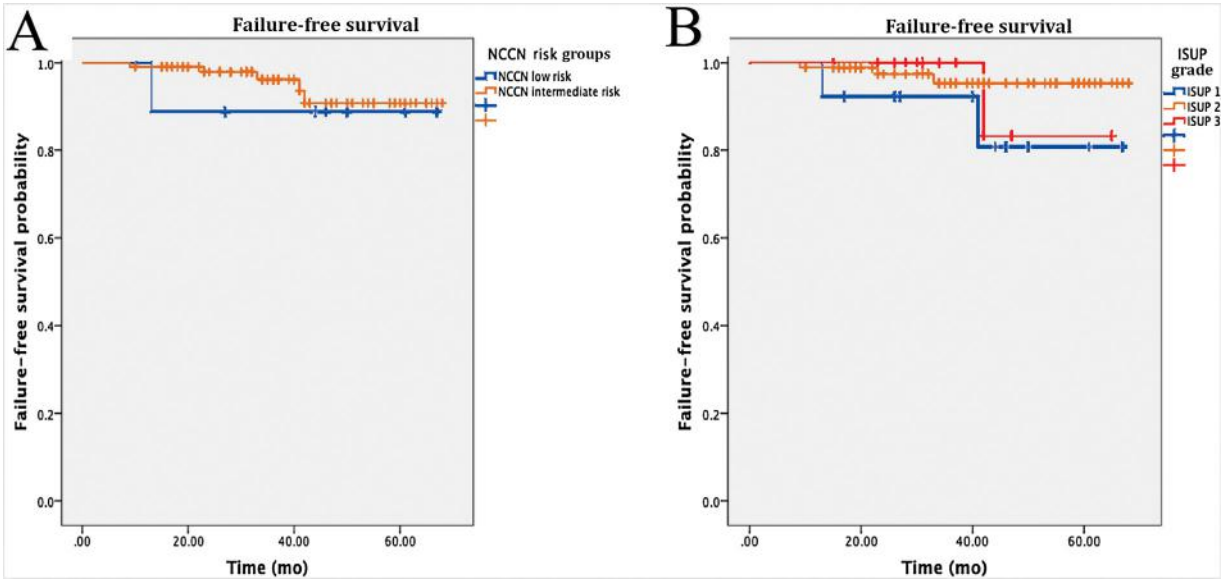

Fig. 2 – (A) Kaplan-Meier curve showing failure-free survival defined as progression to whole-gland or systemic treatment, or metastasis/death in patient undergoing irreversible electroporation for clinically significant localised prostate cancer, stratified by National Comprehensive Cancer Network (NCCN) category. (B) Kaplan-Meier curve showing failure-free survival defined as progression to whole-gland or systemic treatment, or metastasis/death in patient undergoing irreversible electroporation for clinically significant localised prostate cancer, stratified by ISUP grade. ISUP = International Society of Urological Pathology.

prostatectomy (RARP; median follow-up 32 mo). All PSA levels are <0.01 ng/ml. Continence was maintained after salvage RARP, whilst sexual function was maintained following penile rehabilitation and use of PDE5 inhibitors. Fig. 3 shows regions of post-treatment scar. The remaining patients are currently under active surveillance.

3.3. *Diagnostic accuracy of follow-up mpMRI*

The diagnostic accuracy of follow-up mpMRI to detect residual PCa is summarised in Table 3. Of note, the NPV of mpMRI to detect in-field residual PCa was high at 94%. However, the sensitivity was low at 40%. This may be explained by the low prevalence of residual disease. The NPV of post-treatment mpMRI to detect residual disease in the whole gland was 85%.

3.4. *QoL and functional outcomes*

Twenty-seven patients (22%) described postoperative symptoms of dysuria, urgency, haematuria, and perineal pain (Clavien-Dindo 1). Eleven patients (9%) experienced grade-2 complications, including urinary tract infection, severe urgency/frequency, or incontinence. No perioperative complications were recorded. There were no cases of Clavien-Dindo grade 3 or higher (Supplementary Table 3).

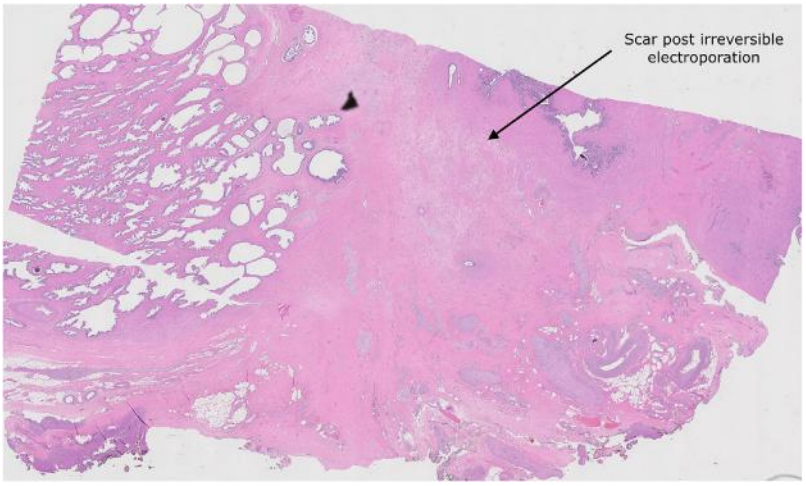

Fig. 3 – Scar after irreversible electroporation treatment - region of post-treatment scar in the peripheral zone between the transitional zone on the left and seminal vesicle on the right.

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Table 3 – Diagnostic accuracy of multiparametric MRI for residual PCa (fraction, 95% confidence interval)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
In-field	40 (4/10, 12–73)	98 (90/92, 92–99)	67 (4/6)	94 (90/96)
Out of field	54 (7/13, 25–80)	92 (82/89, 84–97)	50 (7/14)	93 (82/88)
Whole gland	52 (11/23, 35–75)	88 (70/79, 79–94)	55 (11/20)	85 (70/82)

GS = Gleason score; MRI = magnetic resonance imaging; NPV = negative predictive value; PCa = prostate cancer; PPV = positive predictive value.
Definition of residual prostate cancer: GS $\geq$ 3 + 4.

Eighty-four (68%) primary IRE patients consented to undergo QoL evaluation and completed the baseline questionnaire (Fig. 4). This showed that there was a decline in urinary function 6 wk after IRE, but that this recovered to baseline after 3 mo and thereafter (p = 0.0944). Of patients who completed questionnaires, 81 were pad free and 75 leak free before treatment. Of these, 80/81 (98.8%) remained pad free and 70/75 (93.3%) remained leak free at 12 mo after treatment. Seven patients (8.6%) required at least one pad at 6 wk after treatment, but this resolved by 12 mo.

There was a mild but significant decrease in sexual function, with a median EPIC score of 65 at baseline versus 50 at 12 mo (p = 0.00001). Of 53 patients who were potent before treatment, 40 (76%) had no change in potency at 12 mo, nine (17%) had erections firm enough for some sexual activity, and four (7%) did not have erections firm enough for any sexual activity.

No significant differences were observed between baseline and 12 mo in physical (p = 0.7522), mental (p = 0.7337), bowel (p = 0.636), and urinary QoL domains (p = 0.0944).

4. Discussion

This is the largest reported cohort of patients treated with IRE. We demonstrated that IRE achieved excellent oncological control, especially after the treatment margin was

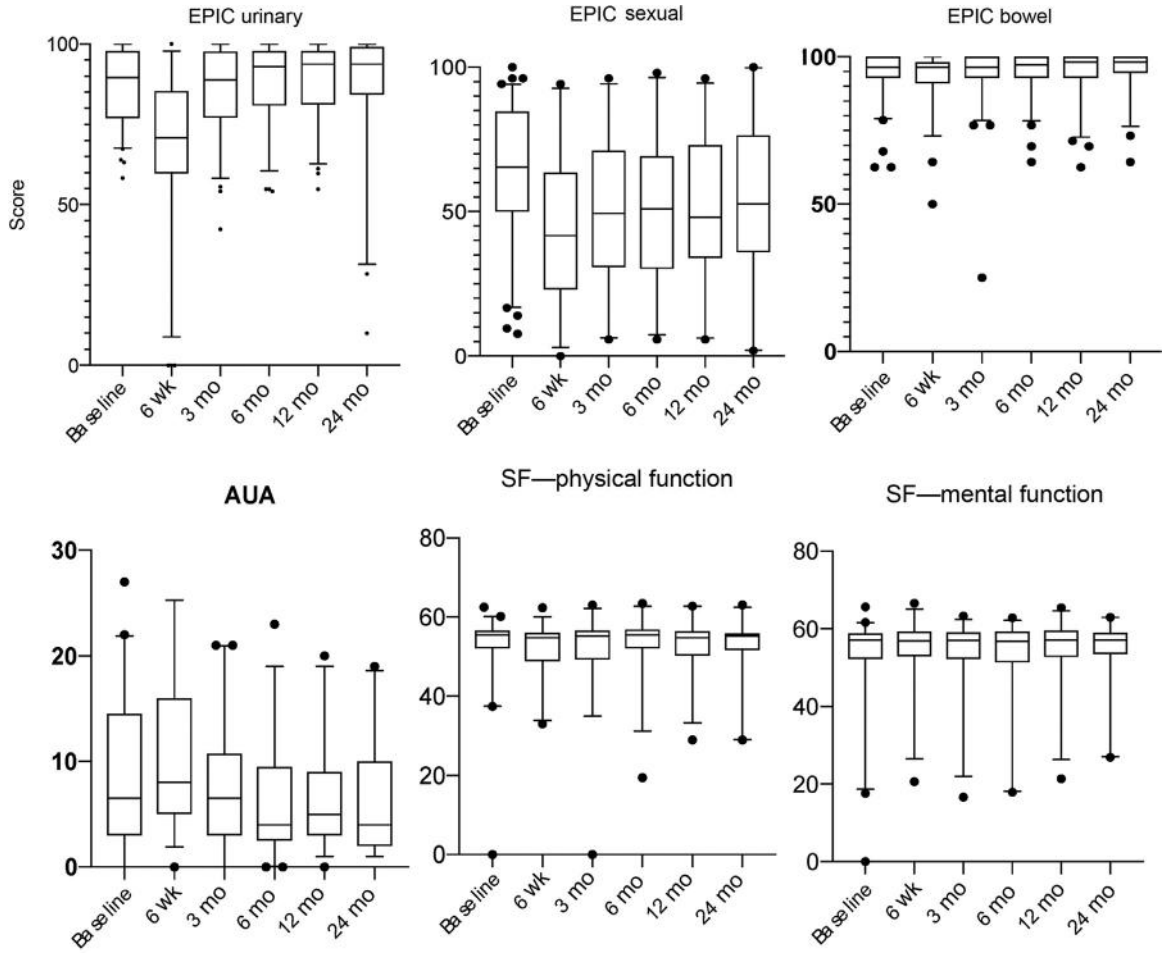

Fig. 4 – Quality of life after primary irreversible electroporation, measured using the expanded Prostate Cancer Index Composite (EPIC) questionnaire including urinary, sexual, and bowel domains. Health status measured using 12-item Short Form (SF-12) physical component summary scores. AUA = American Urological Association.

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increased to 10 mm and surgeon experience improved (97.3% free of significant cancer in field). A major strength of this study is that unlike most recent FA studies, we routinely performed a follow-up TTMB at 12 mo, providing a robust reference test against which to assess oncological control.

This result is consistent with a radical prostatectomy validation cohort study [15]. Whilst other earlier studies showed higher in-field recurrence rates, they were smaller and had narrower ablation field margins [16,17]. The results also show that IRE can be used safely and effectively in any prostate segment.

A redo IRE treatment was shown to be safe and effective. It is critical to note that in many other FA series, the definition of a successful outcome allows for one retreatment [7]. Allowing one retreatment, 87% (89/102) of all patients and 95.8% (69/72) after excluding the initial group of patients were free from any significant PCa on follow-up biopsy. Patients who progressed to whole-gland treatment tolerated it well.

The QoL analysis demonstrated excellent preservation of urinary continence (98.8% of patients remained pad-free continent), and 76% of men had no change in erectile function at 12 mo. It is important to highlight that this cohort comprised patients of an older age group (median age 68 yr) and had consequently lower baseline erectile function (EPIC sexual summary score 65).

Whilst our data showed that mpMRI had a high NPV for detecting in-field (94%) and whole-gland (85%) residual disease, the sensitivity was very low at 40% and 52%, respectfully. The difference between NPV and sensitivity may be explained by the low prevalence of residual disease in this series. A similar result was shown by Scheltema et al. [14].

Recent significant FA studies have relied on FFS as the primary outcome. Guillaumier et al. [7] showed FFS of 88% at 5 yr for focal HIFU and Shah et al. [18] showed FFS of 90.5% at 3 yr for focal cryotherapy. However the true prevalence of residual PCa cannot be quantified, given only approximately one-third of patients received a biopsy after FA and most biopsies were MR-targeted only. The need for a routine template biopsy is exemplified by another study, which reported that 26.5% of patients had residual PCa in the treated area despite most demonstrating an appropriate PSA decrease and negative mpMRI after HIFU [6]. A number of Delphi consensus statements recommend routine biopsy as part of the follow-up in patients undergoing FA [7,19].

Limitations of this study include short-term follow-up (median 36 mo) and heterogeneity in the patient cohort. In addition, whilst the outcome measures were predefined and collected prospectively, it was not part of a prospective trial and the database was analysed retrospectively.

The assessment of treatments of localised PCa is challenging [20]. Furthermore, PCa patients will consider forgoing a survival benefit for improved functional outcomes [21]. FA aims to avoid or at least delay the morbidity associated with whole-gland therapy. The group of patients most likely to benefit from FA are those with intermediate-risk PCa.

5. Conclusions

Our study provides encouraging short-term oncological results for IRE based on TTMB. Additionally, functional outcomes are also promising. The ideal patient should have localised intermediate-risk PCa with a unifocal lesion on mpMRI, which has concordance with biopsy. The next step is to develop a multicentre, randomised controlled trial. With the expansion and distribution of uro-oncological departments offering IRE, such a trial is a near-term possibility.

Author contributions: Alexandar Blazevski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Blazevski, Scheltema, Stricker.
Acquisition of data: Blazevski, Masand, Yuen.
Analysis and interpretation of data: Blazevski, Scheltema, Yuen, Shnier, Delprado.
Drafting of the manuscript: Blazevski.
Critical revision of the manuscript for important intellectual content: Scheltema, Thompson, Stricker.
Statistical analysis: Nguyen.
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Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2019.04.008.

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