World Journal of Urology (2021) 39:1107–1114
https://doi.org/10.1007/s00345-020-03275-z

ORIGINAL ARTICLE

Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE)

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Received: 24 November 2019 / Accepted: 25 May 2020 / Published online: 2 June 2020

Abstract

Introduction and objective To assess the safety, oncological and quality-of-life (QoL) outcomes of focal ablation of apical prostate cancer (PCa) lesions with irreversible electroporation (IRE).

Methods Patients were included in the study if they had a PCa lesion within 3 mm of the apical capsule treated with IRE. The IRE procedure was performed in our institution by a single urologist. The QoL and functional data was collected prospectively from patients who provided consent using the Expanded Prostate Cancer Index Composite (EPIC). Oncological follow up included 3-month PSA levels, mpMRI at 6 months and transperineal biopsy at 1-year post treatment.

Results A total of 50 patients had apical PCa lesions treated between February 2013 and September 2018. Median follow-up was 44 months. There were no Clavien–Dindo grade 3 events or higher. No perioperative complications were recorded. No significant difference was observed in the EPIC urinary or bowel QoL domain between baseline and 12-month post-treatment. One patient (2%) required one pad per day for urinary incontinence 12-month post-treatment. There was a small but significant decline in EPIC sexual QoL (65 at baseline and 59 at 12-month post-IRE). Of patient's potent pre-treatment, 94% remained potent after treatment. The median PSA nadir decreased by 71% (6.25–1.7 ng/mL). Only one patient (2.5%) had in-field residual disease on repeat biopsy.

Conclusion Focal ablation using IRE for PCa in the distal apex appears safe and feasible with acceptable early QoL and oncologic outcomes.

Keywords Irreversible electroporation · Apex · Apical · Prostate · Prostate cancer · Focal therapy

Introduction

Focal ablation (FA) for prostate cancer (PCa) has been proposed as a less morbid treatment modality for carefully selected men with localised disease [1, 2]. It remains experimental due to a lack of long-term oncological outcome data, but medium-term results appear promising [3, 4]. Recent advances in tumour localisation using mpMRI and better understanding of the underlying pathology has led to increased interest in prostate-sparing treatments for selected patients [5]. A number of different energy sources are available for focal ablation [high-intensity focused ultrasound (HIFU), cryotherapy, irreversible electroporation, laser, vascular-targeted photodynamic therapy, focal brachytherapy]; each with different characteristics [2].

A recent approach, termed the *a la carte* model, suggests that different segments of the prostate are better suited to particular ablative modalities [6]. Posterior tumours can be

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-020-03275-z) contains supplementary material, which is available to authorized users.

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ablated by all FA modalities, while for anterior lesions, all energies except transrectal HIFU appear suitable. However, for apical tumours, only focal brachytherapy and photodynamic therapy are suggested to be appropriate [6]. This is due an increased risk of urethral sphincter damage with thermal-based modalities. A recent European Section of Urotechnology (ESUT) position statement suggested that further evidence is required comparing different ablative modalities with respect to apical treatments (Fig. 1) [7].

Irreversible electroporation (IRE) ablates prostate tissue by delivering high-voltage electric current between transperineally inserted electrodes [8]. Recent literature has demonstrated that IRE confers good short-term oncologic outcomes and a minimal impact on quality-of-life (QoL) [9, 10]. This may be due to three important properties of IRE that overcome certain limitations of other FA modalities: (1) reliable ablation within the intended field; (2) a sharp and reproducible border at the edge of the intended ablation field; (3) no 'halo' rim or radius of damage to tissues within the 3–5 mm immediately adjacent to the ablation field. However, limited data is available regarding the treatment of apical PCa lesions with IRE.

The objectives of this study were to assess the safety, QoL and oncological control in men with localised apical PCa treated with focal IRE ablation.

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 September 2018. Only patients with apical PCa with a minimum of 12-month follow-up who completed QoL questionnaires were included in the analysis. Written informed consent was obtained from all patients.

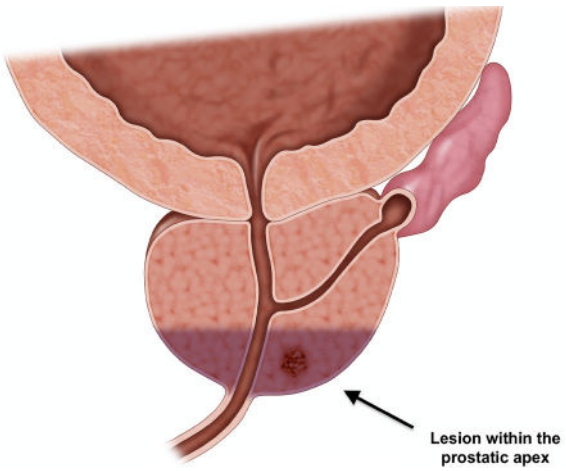

Fig. 1 Illustration of apical lesion within 3 mm of apical capsule that requires ablation of the distal apex. ©The Authors

Patient selection and cancer localisation

All patients underwent multiparametric (mp) magnetic resonance imaging (MRI) (3-T) reported according to the Prostate Imaging Reporting and Data System (PI-RADS) v2. All mpMRI findings were reported by an experienced uro-radiologist. Patients were only considered for FA if they had a unilateral or midline anterior/posterior index lesion on mpMRI. Lesions were classified as apical if they were in the distal third of the prostate. Patients were only included in this study if the MRI-lesion extended to within < 3 mm of the apical capsule/border and thus required the IRE ablation to incorporate the distal 3 mm of the prostate. Co-registration with histology from biopsy was required (Fig. 2). All men underwent a template biopsy (either trans-rectal [TR] or transperineal [TPB]) with additional targeted cores of all suspicious lesions on MRI that were not adequately sampled by the template (Table 1) [Supplementary Material]. Median of 25 cores were taken (interquartile range 22–31). All preoperative biopsies were centrally reviewed by a single uro-pathologist.

Irreversible electroporation (IRE) procedure

The IRE procedure was performed in our institution by a single urologist using an IRE device and 18-gauge electrodes (Nanoknife®; Angiodynamics, Queensbury, NY, USA). All patients were positioned in lithotomy position under general anaesthesia and deep-muscle paralysis. A transrectal ultrasound was used to visualise the prostate and a brachytherapy grid was used to place the electrodes. An indwelling catheter was placed to empty the bladder. Four to six electrodes were placed through the perineum via the template grid to surround the PCa lesion. The lesion was defined based on prostate biopsy and mpMRI images. A 10 mm intra-prostatic margin was applied to prostate stroma surrounding the targeted area to allow for MRI volume underestimation [11]; for lesions extending close to the prostate capsule (including the apex), the ablation zone was adjusted to give a 2–3 mm margin beyond the capsule, thus ensuring complete ablation of the apex with minimal damage to the superior rhabdosphincter. The active tip varied between 15- and 20-mm exposure. The distances between the electrodes were measured using TRUS and entered into the Nanoknife system. Patients were only included in this study if the ablation zone

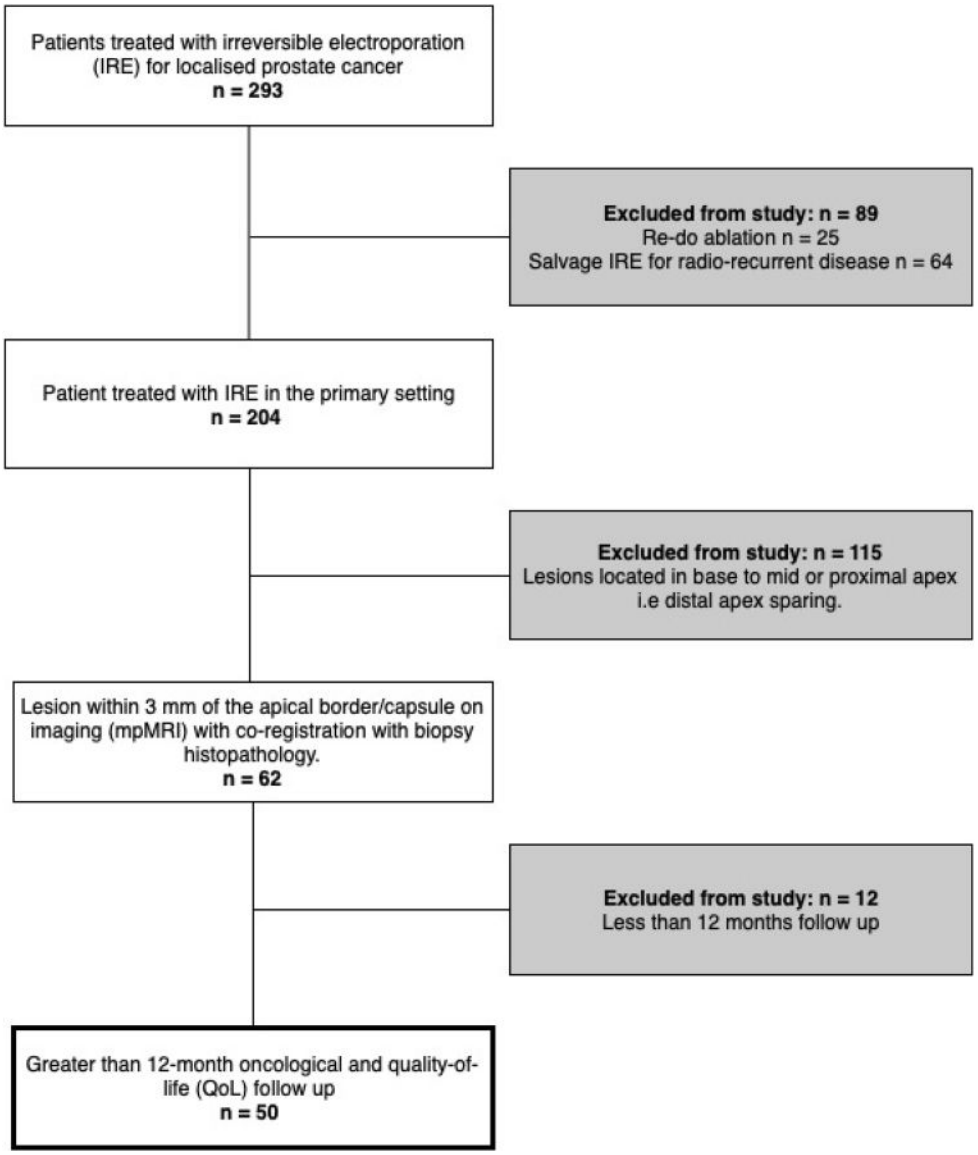

Fig. 2 Patient selection flow-chart

included the distal 3 mm of the apex. For these lesions the electrodes were placed to ensure complete ablation of the distal apex (Fig. 3). An initial ten pulses were delivered to ensure sufficient current was delivered between the electrodes (20–40 A). If sufficient then the remaining 80 pulses were given. The indwelling catheter remained in situ until a trial of void at 2–5-day post-treatment. All patients underwent a T2-weighted MRI prostate within 3–7 days following the IRE treatment to ensure adequate ablation of the targeted area (Fig. 4).

Safety assessment

Adverse events were recorded using the Clavien–Dindo classification.

Quality-of-life (QoL) and functional outcomes

QoL and functional data was prospectively collected from patients who provided consent using the Expanded Prostate Cancer Index Composite (EPIC), including urinary, sexual and bowel domains. Questionnaires were completed at baseline, 6 weeks and 3, 6, 12 and 24 months. Patients were only included in the study if they had completed at least 12 months of the questionnaires.

Oncological follow-up

As part of our institutional protocol, serial PSA levels were measured every 3 months for the first 2 years. Follow-up mpMRI (3-T) was performed at 6 months and TPB with additional biopsies of the ablation zone and margins

Table 1 Baseline clinicopathological characteristics

Median (IQR) age (years)	68 (63–71)
Median (IQR) serum PSA (ng/mL)	6.25 (4.35–8.9)
Median (IQR) prostate volume on MRI (mL)	39 (30–60)
Median (IQR) PSA density (ng/ml)	0.157 (0.11–0.23)
Number of lesions on mpMRI	
1	48
2	2
PI-RADS score	
1–2	2
3	10
4	24
5	14
Biopsy results	
Median (IQR) number of cores	25 (22–31)
Median (IQR) cores positive	4 (3–5)
Gleason score	
3 + 3 (ISUP grade 1)	5
3 + 4 (ISUP grade 2)	37
4 + 3 (ISUP grade 3)	6
4 + 4 (ISUP grade 4)	2
D'Amico risk classification	
Low	5
Intermediate	43
High	2
Median (IQR) proportion of grade 4 tumour in biopsy (%)	10 (5–30)

performed 6–12 months. Follow up biopsies were reported as follows: (1) negative, (2) in-field recurrence—defined as any PCa found within the intention-to-treat zone, or (3) out-of field—defined as any PCa found outside the intention-to-treat zone. Significant PCa on follow-up was defined as Gleason score $\geq 3+4$. Failure-free survival was defined as progression to whole-gland or systemic treatment or metastasis/death. FFS was reported at 3 years after initial treatment.

Statistical methods

Statistical analysis was performed using SPSS software (v24). Wilcoxon's signed rank test and Wilcoxon's rank sum test (both two-tailed) were used to assess statistically significant differences in paired continuous variables (all questionnaire outcomes at baseline and 12 months). A Chi-square test for differences between posterior and anterior ablation was performed for urinary incontinence, urinary leakage and potency post treatment. P values < 0.05 were taken to indicate statistical significance.

Results

Patient characteristics

A total of 50 patients, treated between February 2013 and September 2018, were included in the study. Patient characteristics are summarised in Table 1. The median follow-up was 44 (interquartile range [IQR] 30–60) months and the median pre-operative PSA was 6.25 (IQR 4.35–8.9) ng/mL. A total of 43 (86%) patients had intermediate-risk, five (10%) had low-risk and two (4%) had high-risk disease. A total of five (10%) had ISUP grade 1, 37 (74%) had ISUP grade 2, six (12%) had ISUP grade 3 and two (4%) had ISUP grade 4 disease.

Quality-of-life and functional outcomes

Ten patients (20%) described postoperative symptoms including dysuria, urgency, haematuria and perineal pain (Clavien–Dindo 1). Nine patients (18%) experienced complications including urinary tract infections, severe urgency/

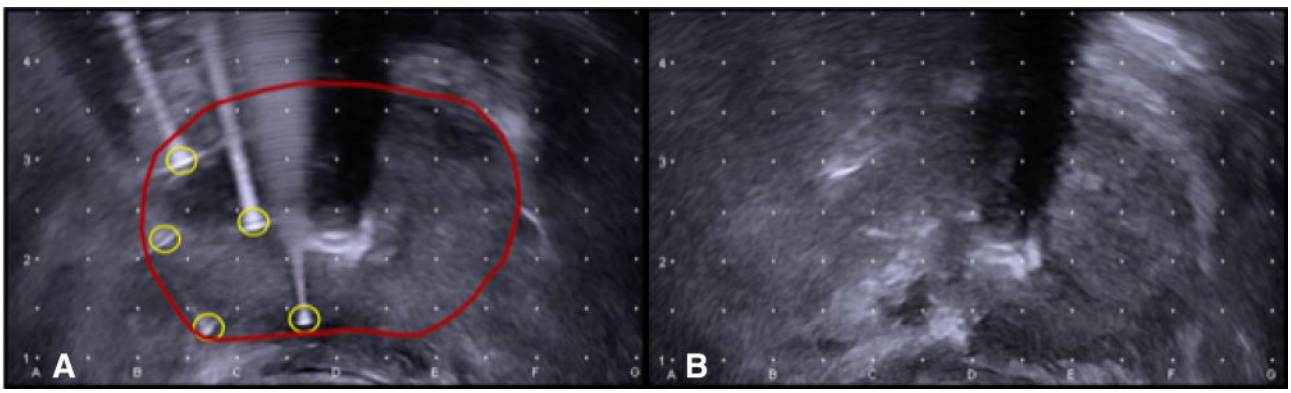

Fig. 3 **a** Axial ultrasound image showing placement of five IRE electrodes (yellow circles) positioned in the posterior right apex of the prostate (red); **b** Ultrasound image showing post treatment destruction in the expected area. ©The Authors

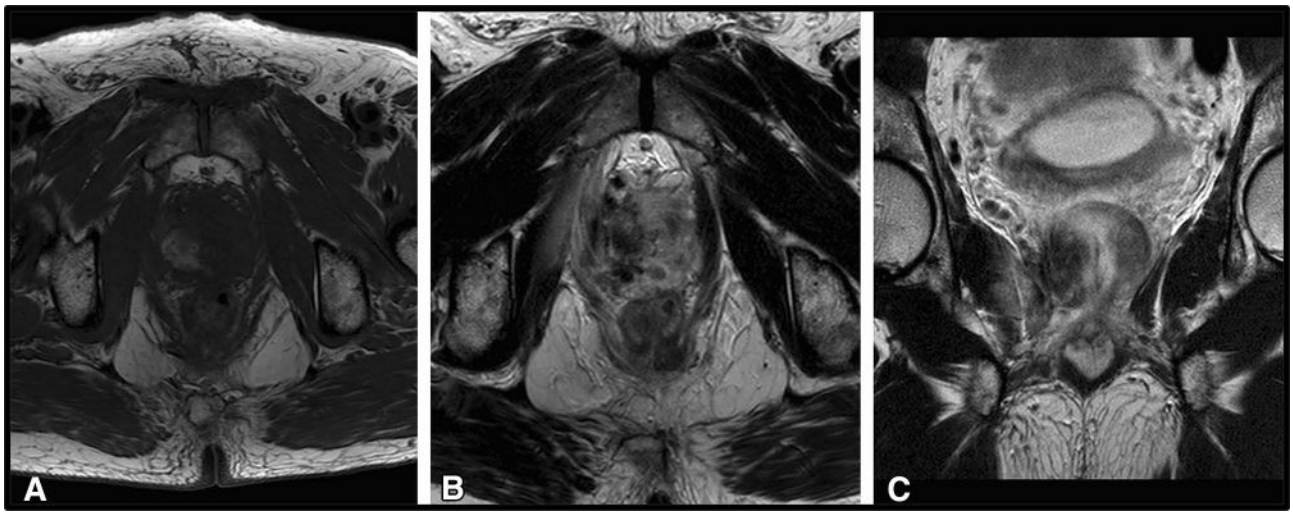

Fig. 4 One-week post-IRE ablation mpMRI images—**a** T1 axial image, **b** T2 axial image, **c** T2 coronal image—all showing oedema and haemorrhage in the right posterior apex. ©The Authors

frequency or incontinence (Clavien–Dindo 2). There were no cases of Clavien–Dindo grade 3 complications. No perioperative complications were recorded.

All 50 patients in this study consented to undergo QoL evaluation and completed at least 12-month follow-up questionnaires (Fig. 5). A significant decline in urinary QoL was observed at 6-week post-treatment but this recovered by 3 months and thereafter. There was no statistically significant difference in QoL at baseline and 12-month post-treatment ($P=0.063$). All patients were dry before treatment, two (4%) patients required one pad at 3 months and only one (2%) patient required one pad at 12 months. No patient required a pad 24 months after treatment. Forty patients were leak free prior to treatment. Of these patients, 33 (83%) remained leak-free at 3 months, four (10%) patients leaked about once a week and only three (7%) leaked more than once a week. No patient leaked more than once a day. At 12 months, 38 (95%) of patients were leak-free and only two (5%) leaked about once a week.

No significant difference was observed in the bowel QoL domain between baseline and 12 months; EPIC score of 96 at baseline and 98 at 12 months ($P=0.066$). No rectal injuries or fistulae were recorded in this cohort.

In terms of sexual function, there was a small but significant difference between sexual QoL domain scores at baseline versus 12 months; median EPIC sexual score was 65 at baseline and 59 at 12-month post-treatment ($P=0.001$). Of patients that were potent pre-IRE ablation, 94% (30/32)

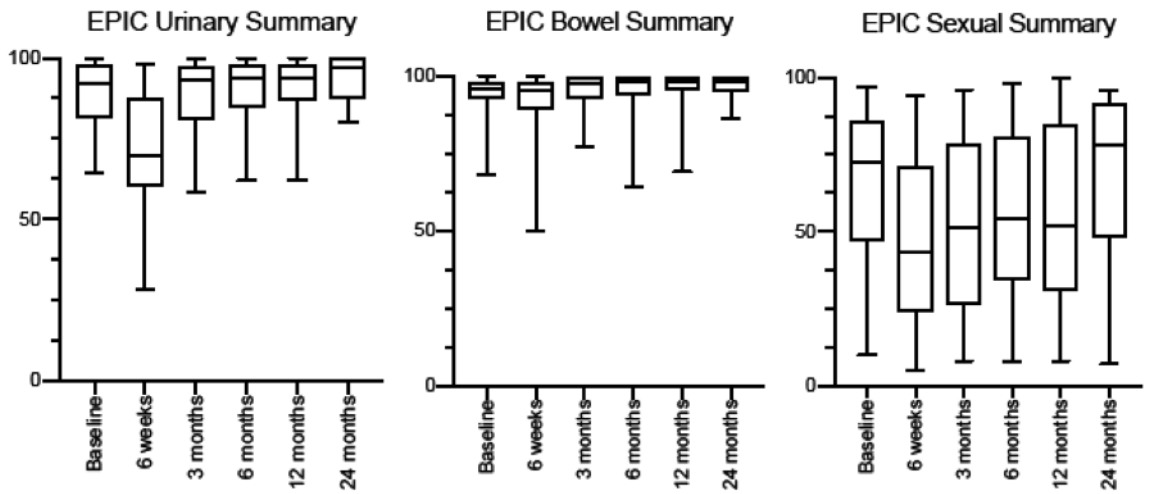

Fig. 5 QoL outcomes after primary IRE, measured using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire including urinary, sexual and bowel domains. ©The Authors

remained potent sufficient for sexual intercourse post-IRE ablation at 12-month post-treatment.

A total of 14 patients were treated in the anterior segment of the apex, 23 in the posterior segment, while 13 patients were treated in both. No significant difference was observed between anterior and posterior ablation in terms of urinary incontinence ($P=0.439$), urinary leakage ($P=0.642$) and erections sufficient for intercourse ($P=0.894$) post treatment.

Oncological outcomes

Post treatment PSA, mpMRI and biopsy findings are summarised in Table 2. Compared with baseline PSA (median PSA 6.25 ng/mL; IQR 4.35–8.9 ng/mL), the median PSA at 12 months decreased by 71% to 1.7 ng/mL; (IQR 0.84–3.35 ng/mL).

Forty (80%) patients had undergone follow-up TPB at the time of analysis. The remaining patients had either refused biopsy (against the urologist's recommendation) due to reassuring mpMRI and PSAs or were awaiting biopsy. Only one patient (2.5%) had in-field recurrence at 12 months. Out-of-field recurrence occurred in eight (20%) of patients. Of patients with out-field failure, all had low volume Gleason 3 + 4 PCa. Overall, 31/40 (78%) patients were free of significant disease after initial IRE. Of patients that had greater than 3-year follow-up; the failure free survival at 3 years was 90% (36/40).

Salvage treatment for patients with residual disease

Of nine patients with residual disease, five had a repeat IRE procedure for out-of-field recurrence. Four patients opted for salvage whole-gland treatment for residual PCa. One had low-dose-rate brachytherapy, while three underwent salvage robot-assisted radical prostatectomy (RARP). The median follow-up since RARP was 9 months. All patients were pad-free by 6-month follow-up. All patients had negative margins; two patients had organ-confined disease (pT2), while one patient had extraprostatic extension (pT3a).

Table 2 Oncological outcomes

PSA nadir	1.8 (0.84–3.35)
mpMRI at 6 months ($n=50$)	
Clear	43
In-field lesion	7
Out-field lesion	0
Biopsy results ($n=40$)	
Median (IQR) number of cores	30 (25–32)
Median (IQR) positive cores	1 (0–2)
Significant in-field disease, *n* (%)	1 (2.5%)
Significant out-field disease, *n* (%)	8 (20%)
Low-volume, Gleason 6 tumour, *n* (%)	13 (32.5%)
Whole gland free of significant cancer at 12 months, *n* (%)	31 (77.5%)

Discussion

This study demonstrates that IRE can be safely used as a FA modality in the distal apex with minimal impact on QoL and acceptable oncological control. With the increasing interest in focal ablative therapies for PCa, this paper provides valuable evidence for the utilisation of IRE in the prostatic apex. With regard to the use of FA in the distal apex, there is concern regarding the increased risk of damage to the urethral sphincter, particularly with thermal based FA modalities. Hence recent FA studies have excluded patients with distal apical lesions [3, 12]. It has been observed that post-cryotherapy and post-HIFU recurrences often occur in the distal apex, where the surgeon has attempted to protect the urethral sphincter [13].

The *al la carte* approach is a novel concept that proposes that a selection of different energy modalities be utilised for FA according to the intraprostatic cancer location [6]. There are several FA modalities currently available and each appear to have specific advantages in different locations within the prostate [6, 7]. Posterior tumours are well accessible by a transrectal or transperineal approach and hence can be treated by a number of different modalities. HIFU is the most utilised modality in this prostate segment and a recent large prospective study showed that it had a favourable failure free survival rates of 99%, 92% and 88% at 1, 3 and 5 years, respectively [3].

Anterior lesions are more easily accessible by transperineal needle-based energies. A recent prospective trial of patients treated with cryotherapy for predominantly anterior lesions showed that a failure-free survival of 90.5% at 3 years and a 0% incontinence rate [12].

Regarding apical lesions, non-thermal technologies such as vascular-targeted photodynamic therapy (VTP) and focal brachytherapy (FBT) have been recommended. They minimise damage outside the targeted area thus they may spare the urethral sphincter in apical disease [6, 7]. FBT has been demonstrated in recent studies to cause minimal urethral toxicity in men treated at the prostatic apex [14, 15]. In addition, VTP has also been shown to have minimal urethral toxicity and is considered suitable for ablation at the apex [16–18]. Given this, it would be expected that other non-thermal energies may be used in the prostatic apex with minimal QoL impact and acceptable oncological outcomes. IRE ablates tissue via a non-thermal mechanism, inducing cell membrane destruction leading to cell death. IRE has been demonstrated to have

tissue selectively and minimal urethral toxicity, but no study has investigated its use in the distal apex [8–10, 19].

This present study showed that there was no significant difference in urinary function at baseline and 12-month post-IRE ablation. Only one patient (2%) required one pad daily at 12 months for incontinence; however, this was no longer required at 24-month follow-up. Furthermore, there was no impact on bowel function and no fistulae were noted. There was a slight but significant decrease in sexual function observed in the study (EPIC sexual summary score 65 at baseline and 59 a year after treatment). Of men that were potent post treatment, 94% retained erections sufficient for intercourse 12-months post-IRE. This data demonstrates that IRE for the ablation of apical tumours is safe and has a minimal impact on patient QoL.

Oncological outcomes demonstrated reliable apical ablation with a very low rate of in-field residual disease at the apex (2.5%) and a relatively low rate of outfield residual disease (20%). The patients with out-field failure all had low volume Gleason 3 + 4 PCa and this likely represents tumour missed on initial biopsy and mpMRI. While these are acceptable short-term oncological results, they are worse than recent IRE studies treating the entire prostate [9, 10]. The majority of patients in this series had intermediate-risk PCa as low-risk disease is managed with active surveillance in our institution. Furthermore, as treatment is based on the lesion volume, there was no specific prostate volume threshold [20].

Limitations of this study include that it is a small retrospective analysis of a prospective cohort registry with only short to medium term follow-up (median 44 months). A recent study of FBT by King et al. reported a higher long-term risk of metastasis and Prostate Cancer-Specific Mortality at 10–12 years compared to whole gland therapy, thus reinforcing the need for long-term comparative outcome data before definitive conclusions regarding the safety of IRE are possible [21]. Long-term 10–15-year metastasis and survival outcomes from RCTs such as the ongoing PART study in the UK are needed before FA can be concluded to have equivalent oncologic safety to primary whole gland therapy. In addition, it should be noted that not all patients underwent an initial TPB, therefore, reducing the accuracy of comparison with the post treatment biopsy. As the apex is a difficult area to target with transrectal biopsies, larger PCa may have been misinterpreted and led to treatment failure. Moreover, this was a single-centre study which included the initial learning curve of the single surgeon.

Nevertheless, the main aim of this study was to assess whether treatment of distal apex with IRE was feasible, safe and had minimal QoL impact. A further prospective trial would be beneficial to confirm these results.

Conclusion

Focal ablation using IRE for PCa in the distal apex appears safe and feasible with acceptable early QoL and oncologic outcomes. A prospective, multicentre study with long-term follow-up is recommended to provide more robust evidence before this can be considered a standard treatment option.

Author contributions AB: project development, data collection, manuscript writing/editing, data analysis. AA: manuscript writing/editing, data analysis. MS: project development, manuscript writing/editing, data analysis. AB: data collection. A-MH: data collection, ethics. DB: data collection. TC: data collection, ethics. JT: manuscript writing/editing. PS: project development, manuscript writing/editing.

Funding Funding was provided by Australian Prostate Cancer Research Centre-NSW and St. Vincent's Prostate Cancer Centre.

Compliance with ethical standards

Conflict of interest Prof. Phillip Stricker is a paid consultant to Angiodynamics. Dr. Alexandar Blazevski is a paid proctor to Getz Healthcare. All other authors have nothing to disclose.

Ethics approval/informed consent The board of the Human Research Ethics Committee of St. Vincent's Hospital (Sydney, Australia) approval prospective acquisition of patient-reported QoL outcomes (HREC approval SVH 13/018) after institutional review. The analysis and data collection were performed following the Declaration of Helsinki after written informed consent was obtained from all patients.

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Re: 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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Eur Urol Oncol 2019; Epub ahead of print. doi: 10.1016/j.euo.2019.04.008

Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/31103721

Editorial Comment: There is increasing interest in focal ablative therapy as a means of treating unifocal or limited focality early stage prostate cancer. Improved imaging and biopsy techniques have allowed intraprostatic localization of prostate tumors and attempts at partial gland destruction. In this report the authors present a well standardized cohort of men treated for intermediate risk localized prostate cancer with magnetic resonance imaging guided focal ablation using irreversible electroporation. Electroporation works through destruction of the cell membrane by electrical current, resulting in cell death without a great deal of thermal energy dispersion. Men were treated between 2014 and 2017 and the data were entered into a prospective registry. Only men achieving 1-year followup (123 patients) and posttreatment biopsy (101) are included in the study.

The authors report that in-field recurrence was noted in 9.7% of all men treated, while out-of-field recurrence was seen in 12.7%. On changing technique to include a 10 mm margin of ablation around the magnetic resonance imaging demonstrable tumor the in-field recurrence dropped to 2.7% and out-of-field recurrence remained at 12.1%, indicating that improved tumor control can be achieved through improved margin control. Overall, complication rates were low, although just over 20% of men complained of short-term side effects, predominantly urinary, and approximately 25% of men reported significant reduction in potency, with mean EPIC (Expanded Prostate Cancer Index Composite) sexual function score declining from 65 to 50 points during the first year of followup.

Strengths of the study appear to be standardized rigorous selection criteria, uniform followup and recording, and use of targeted and transperineal template mapping biopsies at 1 year to determine efficacy. The latter point is critical as the true efficacy of ablative therapy can likely be determined only if patients are adequately sampled after treatment.

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Suggested Reading

Valerio M, Dickinson L, Ali A et al: Nanoknife electroporation ablation trial: a prospective development study investigating focal irreversible electroporation for localized prostate cancer. J Urol 2017; **197:** 647.

Murray KS, Ehdaie B, Musser J et al: Pilot study to assess safety and clinical outcomes of irreversible electroporation for partial gland ablation in men with prostate cancer. J Urol 2016; **196:** 883.

van den Bos W, Jurhill RR, de Bruin DM et al: Histopathological outcomes after irreversible electroporation for prostate cancer: results of an ablate and resect study. J Urol 2016; **196:** 552.