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Focal Therapy of Prostate Cancer Index Lesion With Irreversible Electroporation. A Prospective Study With a Median Follow-up of 3 Years

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Full-length article available at https://doi.org/10.1097/JU.0000000000002970.

Study Need and Importance: Focal therapy (FT) for prostate cancer (Pca) is a therapeutic approach aiming for tumor control while minimizing the side effects that can be associated with radical treatments. Irreversible electroporation (IRE) is a nonthermal tissue ablation technology based on the emission of short electrical pulses that allows treatment on any part of the prostate with a security margin. The widespread use of multiparametric MRI (mpMRI) and the development of ultrasound-MRI fusion systems for targeting biopsies allow the implementation of FT programs. Nevertheless, there is still a lack of long-term results concerning its ability to achieve both cancer control (defined as absence of tumor on treated areas) and preserve functional results, especially using IRE. To our knowledge this is the first prospective study published with all patients selected based on a combination of mpMRI and a transperineal systematic and targeted biopsy using an ultrasound-MRI fusion system (Koelis System) with no patients lost to follow-up. Patients were selected if they had a biopsy-proven low- to intermediate-risk Pca concordant with lesions visible on mpMRI. All procedures were performed by the same surgeon.

What We Found: FT using IRE is a reliable, safe, and effective procedure for treating Pca with almost 90% probability of achieving tumor control in the treated volume at 3 years. There seems to be a risk of recurrence over time in nontreated areas (see Figure).

Continence was preserved in all patients and potency in 94% of those previously potent.

Limitations: Single center; small sample (41 patients); 80% underwent control biopsy and most patients had low risk-Pca (International Society of Urological Pathology grade 1-2).

Interpretation for Patient Care: FT using IRE is a minimally invasive therapeutic option for patients with visible lesions on mpMRI with minimal side effects. At least, it could delay radical treatments of patients on active surveillance. A close follow-up is needed.

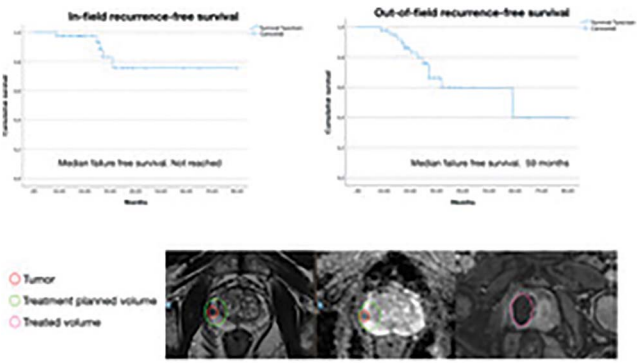

Figure. Kaplan-Meier curves showing in-field and out-of-field recurrence-free survival.

https://doi.org/10.1097/JU.0000000000002970
Vol. 209, 261-270, January 2023
Printed in U.S.A.

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Focal Therapy of Prostate Cancer Index Lesion With Irreversible Electroporation. A Prospective Study With a Median Follow-up of 3 Years

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Purpose: Our aim was to assess oncologic, safety, and quality of life–related outcomes of focal therapy with irreversible electroporation in men with localized prostate cancer.

Materials and Methods: This was a single-center, phase II study. Inclusion criteria: prostate cancer International Society of Urological Pathology grade 1-2, prostate specific antigen ≤15 ng/ml, ≤cT2b. Patients were selected based on multiparametric magnetic resonance imaging and transperineal systematic and targeted magnetic resonance imaging–ultrasound fusion–guided biopsy. Ablation of index lesions with safety margin was performed. Primary end point was cancer control, defined as the absence of any biopsy-proven tumor. A control transperineal biopsy was planned at 12 months and when suspected based on prostate specific antigen and/or multiparametric magnetic resonance imaging information. Quality of life was assessed using Expanded Prostate Cancer Index Composite Urinary Continence domain, International Index of Erectile Function, and International Prostate Symptom Score.

Results: From November 2014 to July 2021, 41 consecutive patients were included with a median follow-up of 36 months. Thirty patients (73%) had International Society of Urological Pathology grade 1 tumors, 10 (24%) grade 2, and 1 (2.4%) grade 3. Recurrence was observed in 16 of 41 (39%) of the whole cohort, and 16 of

Submitted January 28, 2022; accepted August 31, 2022; published September 8, 2022.
Support: The study was partially funded by the CUN Prostate Center (Clínica Universidad de Navarra).
Conflict of Interest: The Authors have declared that no competing interests exist. BML has received personal fees and nonfinancial support from GSK, Astellas Pharma, Werfen, and Jannsen, outside of the submitted work.
Ethics Statement: This study received Institutional Review Board approval (IRB No. ESTU-0028/13/UN0021).
Author Contributions: B. Miñana López was the coordinating principal investigator, underwent all irreversible electroporation procedures, and wrote manuscript drafts. B. Miñana López, G. Andrés Boville, G. Barbas Bernardos, F. Villacampa Aubá, L. Labairu Huerta, F. Ramón de Fata Chillón, X. Ancizu Marckert, and M. Torres Roca accrued patients and collected data. B. Miñana López, G. Andrés Boville, G. Barbas Bernardos, F. Villacampa Aubá, F. Ramón de Fata Chillón, X. Ancizu Marckert, M. Torres Roca, and F. Díez-Caballero Alonso performed the transperineal MRI-ultrasound fusion–guided biopsies. J. Sanz Ortega and M. Abengozar Muela reviewed pathology samples. G. Gallardo Madueño, A. Alcázar Peral, and A. Benito Boíllos reviewed diagnostic and control multiparametric MRIs. All Authors contributed to writing and approval of this report.
Data Availability: Research data are stored in an institutional repository under dedicated institutional review board. Requests for specific analyses or data will be considered by the Executive Board of CUN prostate Center following publication of the manuscript for researchers who provide a methodologically sound proposal. Data include (1) access to all the individual participant data collected during the trial, after de-identification; and (2) the study protocol, statistical analysis plan, and analytic code. Proposal should be directed to bminana@unav.es. To gain access, data requestors will sign a data access agreement.
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https://doi.org/10.1097/JU.0000000000002970
Vol. 209, 261-270, January 2023
Printed in U.S.A.

33 (48.4%) who underwent biopsy. In-field recurrence was detected in 5 (15%) and out-of-field in 11 (33.3%). Ten of 41 (24.6%) including 3 of 5 (60%) with in-field recurrences had significant tumors (Gleason pattern 4-5; more than 1 core or any >5 mm involved). Median recurrence-free survival was 32 months (95% CI 6.7-57.2). Twenty-six patients (63.4%) were free from salvage treatment. All patients preserved urinary continence. Potency was maintained in 91.8%.

Conclusions: Irreversible electroporation can achieve satisfactory 3-year in-field tumor control with excellent quality of life results in selected patients.

Key Words: electroporation, multiparametric magnetic resonance imaging, image-guided biopsy, prostatic neoplasms

Prostate cancer (Pca) is the most prevalent cancer in men, with an increasing detection rate owing to the widespread use of PSA testing. Pca is usually diagnosed at a mean age of approximately 70 years, and more than 50% of patients are classified into low- to intermediate-risk groups, leading to a potential risk of overdiagnosis and overtreatment.[1] Whole-gland treatment with radical prostatectomy (RP) or radiotherapy (RT) can be associated with poor functional outcomes, with significant rates of urinary incontinence and erectile dysfunction.[2]

Focal therapy (FT) is considered a promising investigational approach for patients with localized low- or intermediate-risk Pca. It involves ablation of cancer areas while preserving most of the prostatic tissue, thus minimizing the side effects associated with radical treatments.[3]

Although multifocality observed in Pca has been considered a limitation of this approach, it is assumed that clinically significant disease is usually limited to the index lesion, which is often visible on multiparametric MRI (mpMRI).[4-6] Therefore, patient selection relies on the information provided by mpMRI and a combination of transperineal systematic and targeted biopsies, ideally using MRI-ultrasound fusion systems.[7]

Irreversible electroporation (IRE) is a tissue ablation technology based on the emission of short electrical pulses that allows accurate ablation within a predefined targeted area, avoiding thermal damage to adjacent structures, such as bowel, urethra, and/or neurovascular bundles.[8,9] Other main advantage is that it permits personalized multiple zone treatments. Previous studies have confirmed acceptable short-term functional and oncologic results.[10-14]

We present 3 years outcomes from a prospective phase II study of men with localized low- to intermediate-risk Pca who underwent primary IRE at a single institution.

MATERIAL AND METHODS

Study Design

This single-center, prospective, phase II study was approved by the Institutional Review Board (IRB No. ESTU-0028/13/UN0021). This study is considered within the IDEAL framework to introduce and assess surgical innovation stages 2a and 2b. Written informed consent was obtained from all the participants.

Eligible patients were men (age >18 years) with biopsy-proven low- to intermediate-risk localized Pca, PSA level ≤15 ng/mL, International Society of Urological Pathology (ISUP) grade 1-2, clinical stage ≤T2 b. Participants were excluded if they had undergone any previous treatment for PCa.

All patients were selected based on mpMRI information reported by three expert radiologists who utilized the standardized Prostate Imaging–Reporting and Data System (PI-RADS) classification.

All patients underwent transperineal MRI-ultrasound fusion–guided biopsy. The Koelis Trinity system in most patients, and the Preirus HI-RVS were used.

The biopsy protocol included a combination of systematic and targeted samples adapted to prostate volume, consisting of a wide sampling of the bilateral peripheral zone, the anterior fibromuscular stroma, 2 cores from each lobe transition zone, and at least 2 samples from any suspected PI-RADs 3-5 lesions.

A pathology review was performed on all biopsies by 2 expert uropathologists.

Cancer-positive cores had to be concordant with lesions observed on mpMRI, with no signs of extracapsular extension or lymph node involvement. Lesions selected for treatment on mpMRI, 1 or multiple, should ideally be located 5 mm from the neurovascular bundles, bladder neck, or external urinary sphincter to minimize the risk of compromising functional results.

IRB approved 3 exceptions assuming they were aligned with the rationale of the study and patients would have a close follow-up: 2 patients with no visible tumor on mpMRI with positive core location identified and 1 with a small ISUP 3 lesion.

The primary end point was cancer control, defined as the absence of any biopsy-proven tumor. The secondary end points were changes in erectile function, urinary continence, and urinary tract symptoms. Safety assessments of perioperative (30 days) and short-term (12 months) procedure-related adverse events were recorded from all patients using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[15] Postoperative events were graded using the modified Clavien-Dindo classification.[16]

A control mpMRI was carried out 4-6 weeks after the procedure to check for appropriate lesion coverage. This was considered satisfactory if the ablated zone comprised the tumor volume defined by both the ADC map and

positive biopsy location, with a security margin of at least 10 mm (Figure 1). The mpMRI was repeated at 12 months and annually thereafter. Control PSA was obtained at 3, 6, and 12 months after IRE and then every 6 months.

A per-protocol transperineal biopsy (systematic and targeted if any lesion was visible) was planned at 12 months, and per-case when persistently rising PSA and/or suspicious lesions (PI-RADS scores of 4 and 5) on mpMRI were observed.

Oncologic outcomes were analyzed in all patients who had a minimum follow-up of 12 months. Any Pca found on follow-up biopsy was considered treatment failure. A significant Pca was considered if any Gleason pattern 4-5 (ISUP grades 2-5) or when a high-volume ISUP grade 1 (more than 1 core involved and/or any core with more than 5 mm tumor) was detected. An in-field recurrence was considered when tumor was located within the treated volume with a margin of 10 mm. Out-of-field recurrence was considered when tumor was detected in the untreated lobe or more than 10 mm beyond the treatment margin.

Quality-of-life and functional outcomes were evaluated using validated questionnaires. Urinary tract symptoms were assessed using International Prostate Symptom Score (IPSS), urinary continence was assessed using the Expanded Prostate Cancer Index Composite (EPIC) Urinary Continence domain (23, 26, 27, 28; range 0-100) and erectile function was assessed using the International Index of Erectile Function (IIEF5) Questions 1-5 (range 0-25). Questionnaires were completed at baseline and at 4 weeks, 6 months, and 12 months postoperatively. Patients with at least 6 months of follow-up were included. Normal erectile function was defined as the proportion of patients with erections sufficient for penetration or an IIEF5 score >22. Normal urinary continence was defined as the absence of any security pad or an EPIC urinary continence score of >85 (supplementary Material, https://www.jurology.com).

Procedure Description

All IRE procedures were performed under general anesthesia by a single urologist (BML) using an IRE device and 18-gauge electrodes (Nanoknife).

Monopolar electrodes were placed transperineally around the index lesion under biplanar transrectal ultrasound guidance using a 5×5 mm brachytherapy template grid. Safety margins of 10 mm were used, and a 5 mm distance was applied from the rectum, bladder neck, neurovascular bundles, external sphincter, and urethra whenever possible. The number and active tip length of the electrodes were dependent on the size and location of the target lesion. The distances between all the electrodes were measured in the transrectal ultrasound axial plane. The device was programmed to deliver 90 pulses with a voltage setting of 1,500 V/cm and a pulse length of 90 ms. Pulse delivery was calculated using device software based on the active electrode tip length and the distances between the electrodes to obtain an optimum electrical field between 20 and 45 A.

The patients were discharged on the day after the procedure with oral antibiotics for a week. The urethral catheter was removed 24 hours after the procedure.

Statistical Analysis

Statistical analysis was performed using SPSS Mac version 28. Discrete and continuous variables were displayed as means (standard deviations), whereas categorical variables were presented as frequencies and percentages. Kaplan-Meier estimates of time-to-event outcomes are described with 95% confidence intervals (95% CI). Wilcoxon's signed rank test (2-tailed) was used to assess statistically significant differences in paired continuous variables when comparing 2 temporal sets (basal vs 12 months). Statistical significance was set at $P = .05$.

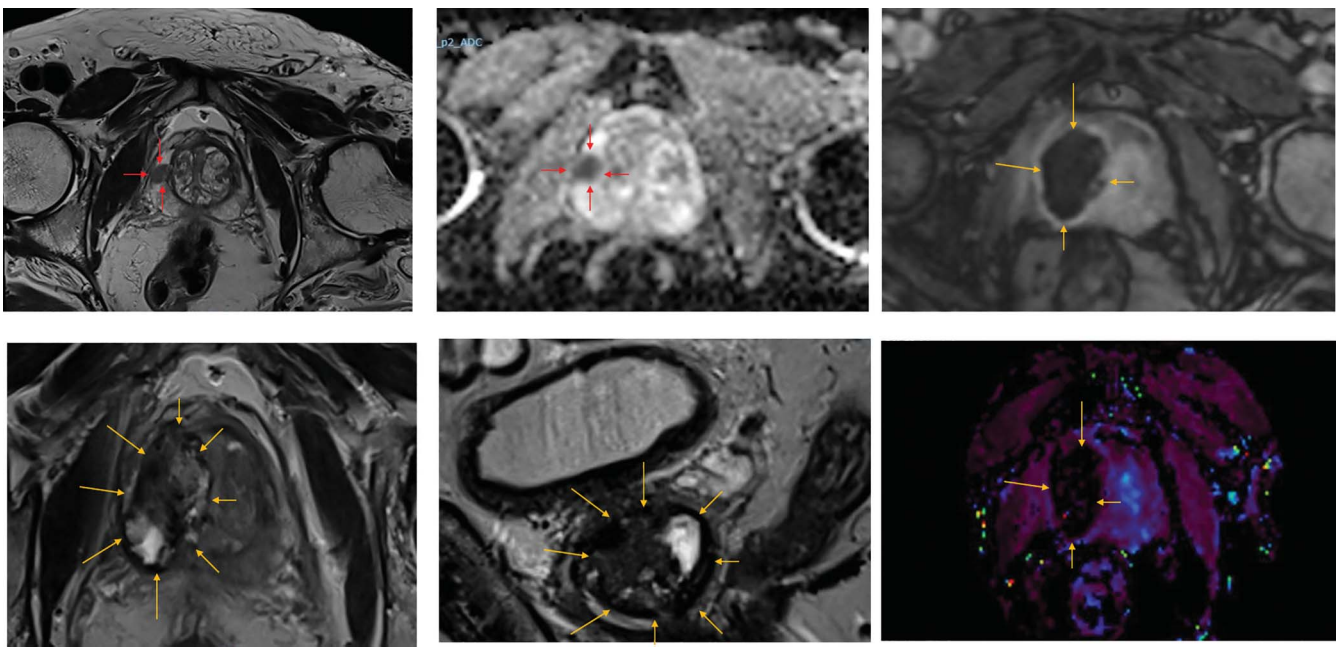

Figure 1. Example of standard treatment control. Tumor located in right peripheral zone treated with a safety margin >10 mm confirmed by a multiparametric MRI 3-5 weeks after the procedure. Arrows delineate both tumor and treated volume.

Table 1. *Patients' Baseline Characteristics and Procedure-related Information*

Baseline characteristics	
Patients, No.	41
Age, mean (SD), y	65.8 (8.34)
Follow-up, median (IQR), mo	35 (21)
Preoperative PSA, mean (SD), ng/ml	6.9 (2.76)
Prostate volume, mean (SD), cc	52.3 (20.4)
Biopsy cores, mean (SD), No.	26.09 (5.74)
Percentage positive cores, mean (SD), %	11 (8.37)
Targeted foci, No. (%)	
1	36 (87.5)
2	5 (11.9)
MRI/biopsy concordance, No. (%)	
Yes	39 (95.12)
No	2 (4.87)[a]
ISUP grade pretreatment, No. (%)	
1	30 (73.17)
2	10 (24.3)
3	1 (2.43)
Procedure-related information	
Procedure duration, mean (SD), min	58.47 (11.9)
Ablation laterality, No. (%)	
Unilateral	31 (75.6)
Bilateral	10 (24.3)
Ablation on axial plane, No. (%)	
Anterior	17 (41.4)
Posterior	24 (58.5)
Ablated volume, mean (SD), cc	8.12 (4.76)
Apex treated, No. (%)	
Yes	23 (56)
No	18 (44)
Percentage PSA reduction at 3 mo, mean (SD)	46.11 (26.5)
Hospital stays, mean (SD), d	1.04 (0.21)
Urethral catheter, mean (SD), h	25.7 (8.2)

Abbreviations: IQR, interquartile range; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging—Reporting and Data System; PSA, prostate specific antigen; SD, standard deviation.
[a] No PI-RADS >2 on MRI.

Table 2. *Safety Results: Recorded Adverse Events (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) and Postoperative Complications According to Clavien-Dindo Classification*

Adverse events (CTCAE)			
	Perioperative (≤30 days)	1-6 mo	>6 mo
Any event, No.	50	9	8
Patients with any event, No. (%)	17 (41.4)	7 (17.7)	7 (17.07)
AUR, No. (grade)	4 (2)	0	0
Dysuria, No. (grade)	15 (1)	0	0
Hematuria, No. (grade)	15 (1)	0	0
Hemospermia, No. (grade)	13 (1)	1 (1)	0
UTI, No. (grade)	1 (2)	0	0
Incontinence, No. (grade)	0	0	0
Hypospermia, No. (grade)	0	6 (1)	6 (1)
Erectile dysfunction, No. (grade)	3 (3)	3 (3)	3 (3)
Clavien-Dindo complications grade, No. (%)			
0		37 (90.2)	
1		2 (4.8)	
2		0	
3a		2 (4.8)	
>3a		0	

Abbreviations: AUR, acute urinary retention; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; UTI, urinary tract infection.

RESULTS

From November 2014 to July 2021, 41 consecutive patients met all eligibility criteria and were included in the final analysis, with a median follow-up of 35 months. Baseline patient characteristics, procedure-related information, safety, and oncologic and functional outcomes are displayed in Tables 1-3, respectively. None of the patients was lost to follow-up.

The mean age of the cohort was 65.8 years (SD 8.34) with a mean preoperative PSA of 6.9 ng/mL (SD 2.76). The mean number of cores taken was 26.09 (SD 5.74) with 11% of cancer-positive cores.

All patients (95.1%), except 2, had a visible lesion on MRI corresponding to the Pca-positive cores on prostate biopsy. Two patients (4.8%) were treated based on the location of positive cores with no PI-RADS ≥3 lesions on MRI.

A total of 36 patients (87.5%) had 1 isolated Pca focus treated and 5 (11.9%) had 2 ablated foci.

Table 3. *Oncologic and Functional Results*

Oncologic results		
MRI postoperative control satisfactory, No. (%)	36	(87.8)
Prostate volume ablated, mean (SD), cc	8.12	(4.76)
Percentage prostate volume ablated, mean (SD)	17.94	(13.34)
Percentage PSA reduction, mean (SD)	46.11	(26.5)
Control transperineal biopsy, No. (%)	33/41	(80.4)
Pca recurrence (only biopsied), No. (%)	16/33	(48.4)
In-field	5/33	(15.1)
Out-of-field	11/33	(33.3)
Pca recurrence (whole cohort)	16/41	(39)
In-field	5/41	(12.1)
Out-of-field	11/41	(26.8)
Overall time to recurrence, median (95% CI), mo	32	(6.89-57.1)
In-field time to recurrence	Not reached	
Out-of-field time to recurrence, median (95% CI), mo	59	(23.95-105.9)
ISUP grade of recurrent tumors, No. (%)		
1	1.8	(53.3)
2	3	(20)
3	4	(26.6)
4	1	(2.4)
Significant recurrent tumor, No. (%)		
In-field	3/5	(60)
Out-of-field	7/11	(63)
Salvage treatment-free survival, No. (%)	26	(63.4)
Treatment after progression		
Active surveillance	1/16	(6.25)
Radical prostatectomy	10/16	(62.5)
External beam radiotherapy	4	(25)
HDR brachytherapy	1	(6.25)
Pathological stage after prostatectomy, No. (%)		
pT2	5	(50)
pT3a	3	(30)
pT3b	2	(20)
Cancer control after salvage treatment, No. (%)	14/15	(93.3)
Overall biochemical control, No. (%)	39	(95.12)
Overall cancer-specific survival, No. (%)	41	(100)
Functional results		
Preoperative potency (IIEF5 score >22), No. (%)	37	(90.2)
Preoperative continence (EPIC Urinary score >85), No. (%)	41	(100)
Erectile function preservation, No. (%)	34/37	(91.8)
Overall continence rate, No. (%)	41/41	(100)

Abbreviations: CI, confidence interval; EPIC, Expanded Prostate Cancer Index Composite; HDR, high dose rate; IIEF5, International Index of Erectile Function; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; Pca, prostate cancer; PSA, prostate specific antigen; SD, standard deviation.

The ablation was limited to 1 lobe in 31 cases (75.6%) but was extended to both lobes to assure the security margin or for treating bilateral tumors in 10 (24.4%). The mean volume ablated was 8.12 cc (SD 4.76) corresponding to a 17.9% of the prostatic volume.

We had no system errors during the procedure, which had a mean duration of 58.4 min (SD 11.9). All patients, except 2 who developed acute urinary retention (AUR), were discharged from the hospital the day after the procedure, with the urethral catheter successfully removed. Two patients experienced an AUR after discharge. Only 2 (4.8%) Clavien-Dindo grade 3 (AUR) complications occurred.

One patient (2.4%) had perioperative acute bacterial prostatitis, 14 (34.1%) had transient grade 1 hematuria, and 15 (36.5%) had grade 1 dysuria. Six patients (14.6%) developed persistent hypospermia. None of the patients had urethral or bladder neck strictures.

Fifty adverse events were recorded in 17 cases (41.4%). Most were transient grade 1 (84%) or grade 2 (12.5%), and only 2 patients had grade 3 (erectile dysfunction).

Functional Results

Continence outcomes at baseline remained unchanged at 12 months in all patients. Thirty-seven out of 41 (90.2%) patients had satisfactory erections before the procedure, which was maintained in 34 (91.8%). We observed no significant differences between the baseline and 12 months results for EPIC urinary continence ($P = .141$). In contrast, a statistically significant worsening of IIEF5 score ($P = .026$) and an improvement in IPSS ($P = .003$) were detected, without clinical significance (Figure 2).

Oncologic Results

A mean reduction in PSA of 46.1% (SD 26.5) at 3 months was observed.

Postoperative MRI confirmed that the targeted zone was ablated within the preplanned security margins in 36 (87.8%) patients. Four patients who underwent MRI showed insufficient ablation coverage and all developed in-field recurrences.

A total of 33 (80.4%) at risk underwent a control transperineal biopsy, 20 (48.7%) per protocol, and 13 (31.7%) because of a rising PSA. The remaining 8 (19.5%) refused biopsy because of a low and stable PSA with normal mpMRI.

Pca recurrence was detected in 16/33 (48.4%) biopsied patients: 5 (15.1%) in-field, 11 (33.3%) out-of-field, and 1 in both. If we consider the whole cohort 16/41 (39%) had tumor recurrences (12.1% in-field and 26.8% out-of-field). The median failure-

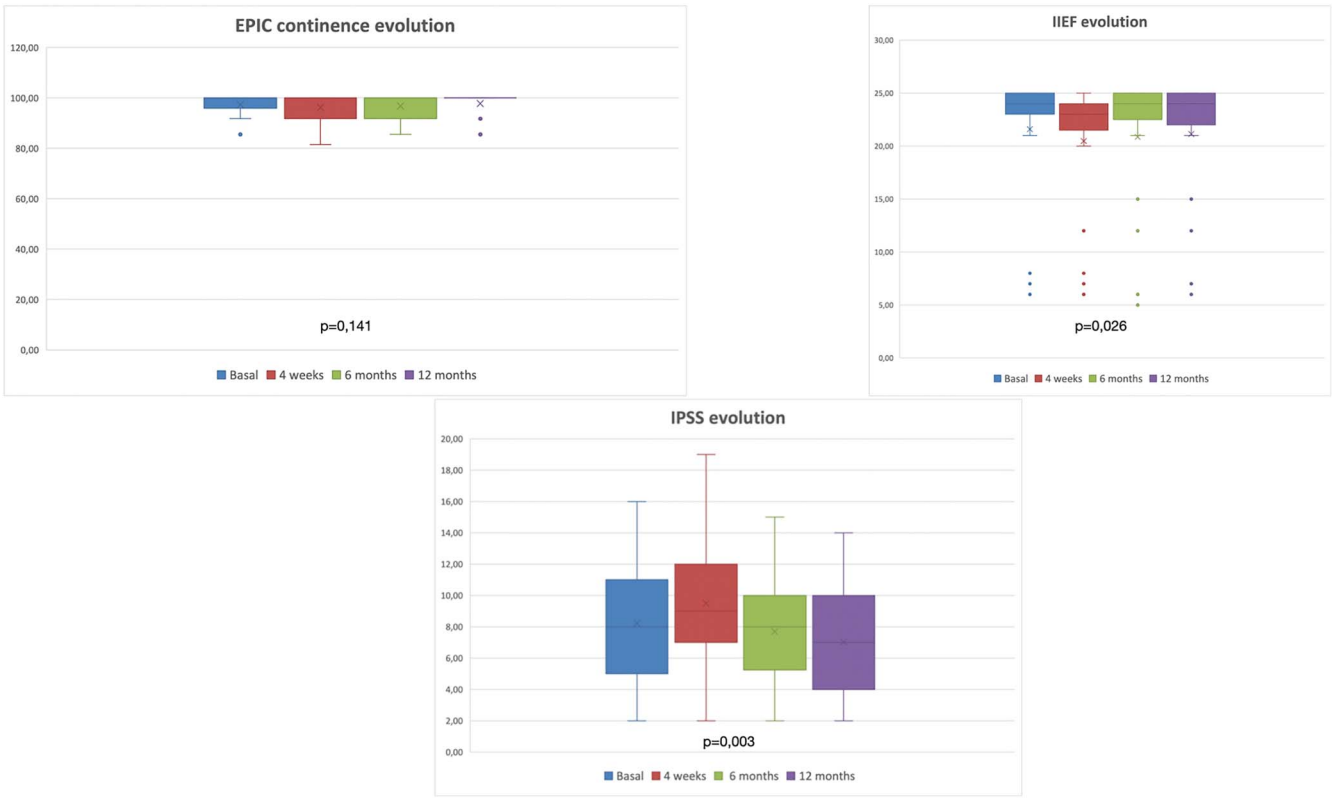

Figure 2. Functional outcomes. Expanded Prostate Cancer Index Composite (EPIC) Urinary Continence domain (23, 26, 27, 28), International Index of Erectile Function (IIEF5) Erectile Function domain (Questions 1-5), and International Prostate Symptoms Score (IPSS).

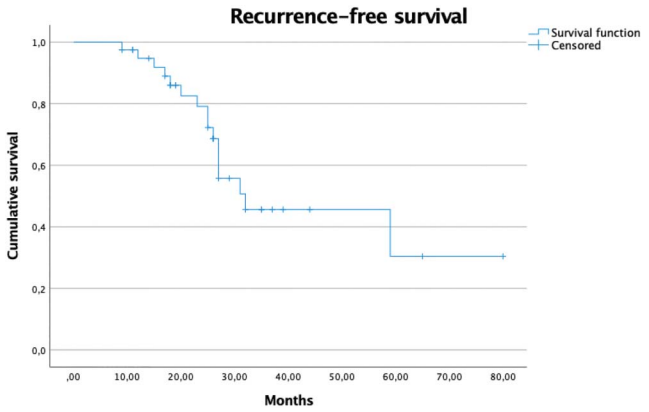

Figure 3. Kaplan-Meier curve showing overall recurrence-free survival. Recurrence was defined as any biopsy-proven tumor.

free survival (FFS) was 32 months (IC95% 6.89-57.1; Figure 3). The in-field median FFS was not reached, while the out-of-field median FFS was 59 months (IC95% 23.95-105.9 months; Figure 4).

Four of 5 patients with in-field recurrence (80%) were suspected at the first control MRI. All patients had tumors located close to external sphincter or the bladder neck.

The pathological characteristics of recurrent tumors were: 8 (53.3%) ISUP grade 1, 3 (20%) grade 2, 4 (26%) grade 3, and 1 (2.4%) grade 4. Significant cancer was observed in 10 patients (62.5%): 3 of 5 (60%) in-field and 7 of 11 (63%) out-of-field.

Overall, 26 patients (63.4%) were free of salvage treatment. One patient (6.25%) underwent active surveillance, four (25%) underwent external beam radiotherapy, 1 (6.25%) underwent high dose rate brachytherapy, and the remaining 10 (62.5%) underwent RP. Of those treated with RP, pathological stage was pT2 in 5 (50%), pT3a in 3 (30%), and pT3b in 2 (20%). No patient was re-treated with FT. One patient with an ISUP 3 pT3b tumor had biochemical recurrence, with no evidence of lesions on positron emission tomography ^{68}Ga prostate-specific membrane antigen. One patient is on adjuvant androgen suppression after RT. Cancer control after salvage treatment has been achieved in 14 of the 15 (93.3%) patients.

DISCUSSION

Although 1 larger cohort of patients treated with IRE has been published,[17] to our knowledge, this is the only prospective study with all patients selected with transperineal MRI-ultrasound fusion–guided biopsy, with no patients lost to follow-up.

Our results confirmed that IRE can be safely applied without significant adverse events. Urinary continence was preserved in all patients and erectile function in 91.8% confirming previously reported experiences that showed an impairment rate between 0%-24% at 12 months. It should be emphasized that this cohort represents a set of highly selected and motivated patients with 90.2% showing normal preoperative potency compared to 59%-83% in other series.[10,11,13,14]

In addition to achieving excellent functional results, FT must demonstrate good oncologic control. If we consider only patients who undergone control biopsy, 48% of tumor recurrences were observed, 15% in-field. Nevertheless, patients who refused a control biopsy had low and stable PSA with normal mpMRI and our experience, coinciding with others, show a negative predictive value of control biopsy with normal MRI of around 90%, all tumors being ISUP grade 1.[17,18] Therefore, we can consider the whole cohort showing a 39% of recurrences (12% in-field) a representative result. Significant tumors were detected in 24.3%, corresponding to an FFS rate of significant Pca at 3 years of 75.6%.

We agree that a security margin of at least 9 mm seems to provide the best tumor control, as has been shown by Le Nobin et al and might explain why others achieved less satisfactory results.[11,17,19] In our experience, most in-field recurrences could be suspected on the first control mpMRI, suggesting targeting failures that can be attributed to an attempt to avoid any lesion on the urethral sphincter or bladder neck.

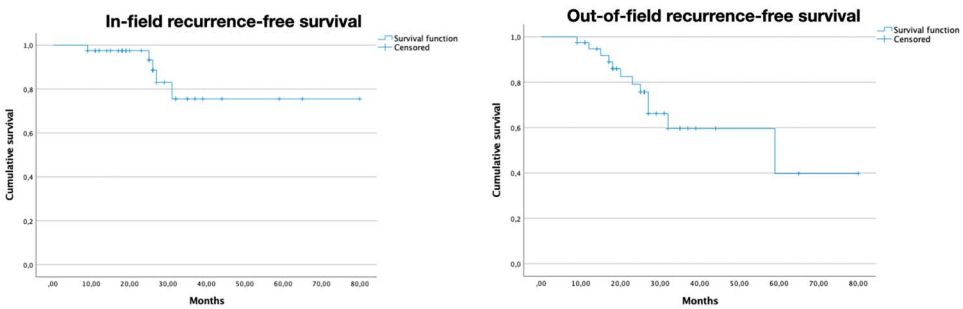

Figure 4. Kaplan-Meier curve showing separated in-field and out-of-field recurrence-free survival. Recurrence was defined as any biopsy-proven tumor.

We observed a 26.8% out-of-field recurrence rate, bringing out the problem of multifocality that can be synchronous or metachronous, and is considered a major limitation of FT. Selecting patients for FT implies discarding aggressive tumors in untreated areas, and this can only be addressed by combining mpMRI and transperineal targeted and systematic biopsies.

Eight patients (19.5%) developed a new tumor in the remaining prostatic tissue during follow-up, and all of them could be detected due to a rising PSA with the appearance of new lesions on mpMRI in most cases. Tumor recurrences were considered significant in 62.5%, including a 29% ISUP grade 3-4. The likelihood of developing a new tumor in the untreated volume seems to be a time-dependent event, with a median time of 59 months.

Overall, 15 patients (36.5%) underwent salvage treatment, and cancer control was achieved in 39 out of 41 (95.12%), showing the necessity of a close follow-up.

This study has some limitations: small sample size; 73% of patients had ISUP grade 1 and almost 20% of patients refused per-protocol control biopsy. A longer follow-up is needed to gain more insight into the oncologic results.

CONCLUSIONS

We confirmed that IRE delivered to the index lesion is a safe procedure that preserves functional results in almost all patients when carefully selected. This technique can achieve satisfactory in-field tumor control, but nontreated areas must be closely monitored over time.

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EDITORIAL COMMENTS

Organ-sparing treatment with focal therapy can offer an attractive treatment for well-selected patients with clinically localized prostate cancer (PCa) with reduced morbidity relative to whole-gland treatments (radical prostatectomy or radiation). However, treatment with focal therapy is complicated by the multifocality of

PCa and dependence upon MRI visibility. Irreversible electroporation (IRE) is a novel technology capable of tumor ablation via local delivery of electrical pulses to disrupt cancer cell membranes which is under investigation for focal management of PCa.

The authors report results of a prospective phase II trial evaluating IRE for localized PCa in 41 patients. They report low complication rate and favorable preservation of continence and erectile function. Of patients who underwent posttreatment biopsy (33/41), 48% had cancer recurrence and 15% had in-field recurrence. However, half of the biopsy recurrences were <5 mm Gleason Grade Group 1 cancers. Only 8 (24.2.%) patients had Gleason Grade Group 2 or higher cancer, which is comparable to 22.5% clinically significant cancer recurrence reported in one of the largest prospective series of IRE.[1]

Despite the prospective nature of this study, there are several limitations to consider. The majority (~70%) of patients in this cohort had low-risk PCa, which is a major limitation given low mortality and guideline recommendations for active surveillance in this group. Additionally, 37% of patients progressed to salvage treatment within 3 years, albeit many were for out-of-field recurrence and low-grade disease.

Long-term oncologic control with preservation of continence and erectile function are the primary goals of focal therapy. IRE has shown promise, although there is a moderate risk of recurrence and salvage treatment. As IRE technique and patient selection are refined, it will be essential to evaluate existing and novel end points including the avoidance of definitive therapy and its subsequent morbidity given the relative low risk of metastasis and cancer-specific mortality of PCa.

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The authors prospectively evaluated focal therapy (FT) with irreversible electroporation (IRE) through an established protocol to obtain minutely precise detail on cancer control and quality of life impact. Their approach should be commended for the solid inclusion of imaging, control biopsies, and functional outcomes assessment. That being said, the manuscript harbors a common major limitation of the pioneering FT series, which is the inclusion of ISUP 1 patients in patient selection. It has been shown that FT does not yield oncologic benefits and active surveillance should be preferred for these patients.[1]

Forty-one patients were included in their protocol and recurrence was observed in 39% of the cohort with over 80% of patients with control biopsies and 15% of in-field recurrence at a median of 3 years of follow-up. These results plea, once again, for the revaluation of FT interventions to be combined with limited systemic pinpoint therapy to control the prostatic microenvironment.[2] Moreover, 20% of the treated population refused control biopsies on the ground of a stable PSA and no MRI lesion, although a per-protocol mandatory biopsy was intended. That approach was demonstrated in a previous FT study[3] to be harboring false-negatives, which weakens the solidity of outcomes.

Although the strict selection of patients for FT remains the cornerstone of the technique beyond any energy attributes, the fruit one harvests from the tree in the authors' work is that IRE was able to provide sound ablative treatment in both anterior and posterior zones of the gland: 41.4% and 58.5% of patients, respectively, in their series. Furthermore, 56% of patients received apical IRE treatment with both adequate complication profile and limited impact on functional outcomes. The idea of having a single energy source with the possibility of being deployed at any prostatic anatomical location opens an interesting and perhaps more cost-adapted path for further diffusion of partial gland ablation.

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REPLY BY AUTHORS

The Editorial Comments consider patient selection criteria as a weakness of this study, but it was designed to assess focal therapy (FT) as a concept and irreversible electroporation (IRE) as ablative technology. The ethics committee considered it mandatory to include low- to intermediate-risk patients to minimize the risk of tumor progression during the study. We have demonstrated that IRE can achieve good tumor control within the treated volume (85%-88%) with minimal side effects.

Although 20% refused biopsy control due to a normal MRI and a low and stable PSA, this has shown a high negative predictive value for discarding significant tumors.[1]

A significant number of patients with low/intermediate-risk recurrence underwent radical salvage therapy because they considered recurrence a treatment failure and decided to switch to definitive treatment. After salvage surgery, a pathological stage pT3 was detected in 50% of these patients.

In our opinion, we are now into a new paradigm with more precise pretreatment tumor characterization, based on information coming from MRI and a combination of targeted and systematic biopsies using MRI-ultrasound fusion systems. Although this will improve selection of candidates for active surveillance, it will necessarily lead to a significant increase of patients treated with FT. This is supported by level 1 evidence demonstrating that FT reduces the risk of conversion to radical treatments compared to active surveillance with minimal morbidity and with the prostate clinically free of tumor in a high proportion of patients (60% in our study).[2] This can be perceived as safer and more attractive for well-informed patients.[3]

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