Radiology

Image-guided Irreversible Electroporation of Localized Prostate Cancer: Functional and Oncologic Outcomes

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Conflicts of interest are listed at the end of this article.

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Background: Irreversible electroporation (IRE) is a nonthermal ablative method based on the formation of nanoscale defects in cell membranes leading to cell death. Clinical experience with the technique for treatment of prostate cancer remains limited.

Purpose: To evaluate urogenital toxicity and oncologic outcome of MRI–transrectal US fusion–guided IRE of localized prostate cancer.

Materials and Methods: In this prospective study, men with biopsy-proven, treatment-naive, low- to intermediate-risk prostate cancer (prostate-specific antigen [PSA], ≤15 ng/mL; Gleason score, ≤3 + 4; clinical stage, ≤T2c; lesion size at multiparametric MRI, ≤20 mm) underwent focal MRI/transrectal US fusion–guided IRE between July 2014 and July 2017. Primary end point was the urogenital toxicity profile of focal IRE by using participant-reported questionnaires. Secondary end points were biochemical, histologic, and imaging measures of oncologic control. Analyses were performed by using nonparametric and χ^2 test statistics.

Results: Thirty men were included (median age, 65.5 years); mean PSA level was 8.65 ng/mL and mean tumor size was 13.5 mm. One grade III adverse event (urethral stricture) was recorded. The proportion of men with erection sufficient for penetration was 83.3% (25 of 30) at baseline and 79.3% (23 of 29; $P > .99$) at 12 months. Leak-free and pad-free continence rate was 90% (27 of 30) at baseline and 86.2% (25 of 29; $P > .99$) at 12 months. Urogenital function remained stable at 12 months according to changes in the modified International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms, or ICIQ-MLUTS, and the International Index of Erectile Function, or IIEF-5, questionnaires ($P = .58$ and $P = .07$, respectively). PSA level decreased from a baseline median value of 8.65 ng/mL (interquartile range, 5–11.4 ng/mL) to 2.35 ng/mL (interquartile range, 1–3.4 ng/mL) at 12 months ($P < .001$). At 6 months, 28 of 30 participants underwent posttreatment biopsy. The rate of infield treatment failure was 17.9% (five of 28) as determined with multiparametric prostate MRI and targeted biopsies at 6 months.

Conclusion: After a median follow-up of 20 months, focal irreversible electroporation of localized prostate cancer was associated with low urogenital toxicity and promising oncologic outcomes.

Online supplemental material is available for this article.

The potential risk of prostate cancer overdiagnosis and treatment has increased in recent years after the widespread implementation of prostate-specific antigen (PSA) testing. Yet most randomized clinical trials have failed to show a survival benefit in patients undergoing radical treatment for low- to intermediate-risk prostate cancer (1–4). Known complications related to whole-gland therapies combined with advances in tumor detection and risk stratification strategies for prostate cancer (eg, multiparametric prostate MRI, image-guided targeted biopsies) have led to a transition from total organ extirpative surgery to organ-preserving focal therapies (5).

The aim of focal therapy in the treatment of prostate cancer is to achieve oncologic control while reducing the adverse effects of whole-gland therapies. Among various techniques for focal tumor ablation, irreversible electroporation (IRE) is particularly favorable for the treatment of prostate tumors. It is a nonthermal ablative method based on the formation of nanoscale defects in cell membranes leading to consequent cell death (6). Because of the preservation of the endoneural architecture and the proliferation of Schwann cells following IRE, as shown in several animal studies, this technique allows nerves to attain histologic and functional recovery (7–10). Therefore, IRE has gained interest from both health care professionals and patients with prostate cancer. However, despite the great clamor around this technique, clinical evidence to support this therapy in the treatment of localized prostate cancer remains poor and clinical studies are limited.

We hypothesized that nonthermal ablation by using IRE could achieve high rates of tumor control while minimizing urogenital toxicity (eg, erectile dysfunction and urinary incontinence) that are otherwise associated with radical therapies. The purpose of this study was to assess urogenital toxicity and oncologic outcome of MRI–transrectal US fusion–guided IRE for the focal treatment of

Abbreviations

CI = confidence interval, IRE = irreversible electroporation, IQR = interquartile range, PSA = prostate-specific antigen

Summary

MRI–transrectal US fusion–guided irreversible electroporation is a safe and effective procedure for patients with localized low- to intermediate-risk prostate cancer with promising midterm results, both in terms of urogenital toxicity and oncologic control.

Key Points

- Following irreversible electroporation (IRE) treatment of prostate cancer, no residual cancer was found in 23 of 28 (82%) of study participants at 6 months after targeted prostate biopsy.
- Prostate-specific antigen levels decreased from 8.65 ng/mL to 2.35 ng/mL at 12 months ($P < .001$) following IRE of the prostate.
- IRE of the prostate was associated with a leak-free and pad-free continence rate of 96.3% and stable urogenital function at 12 months.

study participants with localized low- to intermediate-risk prostate cancer.

Materials and Methods

Study Design and End Points

This prospective phase II study was approved by the institutional review board (EA4/052/13). Written informed consent was obtained from all participants. This study was not supported by any public or private entity and authors had sole control over the data and information submitted for publication. The primary end point of the study was to determine the incidence of erectile dysfunction and urinary incontinence following focal IRE. Secondary end points were biochemical, histologic, and imaging measures of cancer control.

Study Population

Eligible participants were men (age >18 years) with biopsy-proven, treatment-naive, low- to intermediate-risk nonmetastatic prostate cancer (PSA level, ≤15 ng/mL; Gleason score, ≤3 + 4; clinical stage, ≤T2c; lesion size at multiparametric prostate MRI, ≤20 mm). Inclusion and exclusion criteria were as follows: Men could enter the study if they had a transperineal template biopsy, an MRI–US fusion–guided biopsy, or a standard transrectal US–guided biopsy (≥10 cores). Cancer-positive cores had to reflect and be concordant in tumor localization with a high-quality multiparametric prostate MRI showing localized prostate cancer with no signs of extracapsular extension or lymph node metastases. Participants were excluded if they had undergone previous radiation therapy for prostate cancer, previous or concomitant androgen suppression therapy, or previous focal therapy of the prostate. Up to 50 participants could be included in the study during a recruitment time of up to 3 years. Between July 2014 and July 2017, 324 men presented on their own initiative or through their treating urologists to our outpatient clinic for minimally invasive tumor therapy and were assessed for eligibility. During the 3 years of recruitment time, 30 consecutive men meeting the aforementioned eligibility criteria underwent focal IRE of the prostate (Fig 1).

IRE Procedure and Early Assessment of Ablation

The same multidisciplinary team of radiologists (B.G., with more than 20 years of experience in image-guided tumor ablation) and urologists (C.S., with more than 20 years of experience in urology oncology including image-guided brachytherapy) performed all procedures. The investigators were aware of the clinical indication as well as all clinical data relating to the patient to be treated. Each participant was put under general anesthesia and deep muscle paralysis. After induction of general anesthesia, participants were placed in lithotomy position and a transurethral urinary catheter was positioned. All participants received perioperative antibiotics. The IRE procedures were performed by using a commercially available IRE generator (NanoKnife; Angiodynamics, New York, NY). The interventional technique was previously described in detail in a technical note addressing the use of MRI–transrectal US–fusion technique for electrode placement in 10 participants included in our study without reference to or consideration of any data about the safety or effectiveness of the therapy itself (11).

Briefly, monopolar electrodes were inserted transperineally and positioned around the target lesions under image guidance by using an MRI–transrectal US–fusion technique. After confirmation of correct electrode position and measurement of interelectrode distances in both the transverse and the sagittal plane, IRE pulses were delivered for all electrode pairs. The IRE protocol included a total of 90 pulses with a pulse length of 70 μsec to achieve a current flow of 20–50 A between each electrode pair. After energy delivery, the electrodes were carefully removed and the urinary catheter was left in place. The urinary catheter was removed 2–10 days after the procedure, depending on the size of the ablation zone and its distance to the intraprostatic urethra.

To assess perfusion changes within the predetermined target volume as a surrogate of complete ablation, participants underwent transrectal contrast material–enhanced US of the prostate by using the MRI–transrectal US–fusion technique the day before and the day after IRE. A detailed description of the procedure is provided in Appendix E1 (online).

Assessment of adverse events and functional outcomes.— Adverse events were recorded by using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (13). Functional data were collected for all participants by using participant-completed questionnaires at baseline as well as at 6, 12, and 24 months after IRE. Questionnaires included the International Index of Erectile Function, or IIEF-5, a five-item questionnaire developed to diagnose the presence and severity of erectile dysfunction (14), and a modified version of the International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms, or ICIQ-MLUTS, covering five items about urinary leakage and pad use (15). For IEF-5, higher values indicate a better condition, whereas for ICIQ-MLUTS, high scores designate a worse condition.

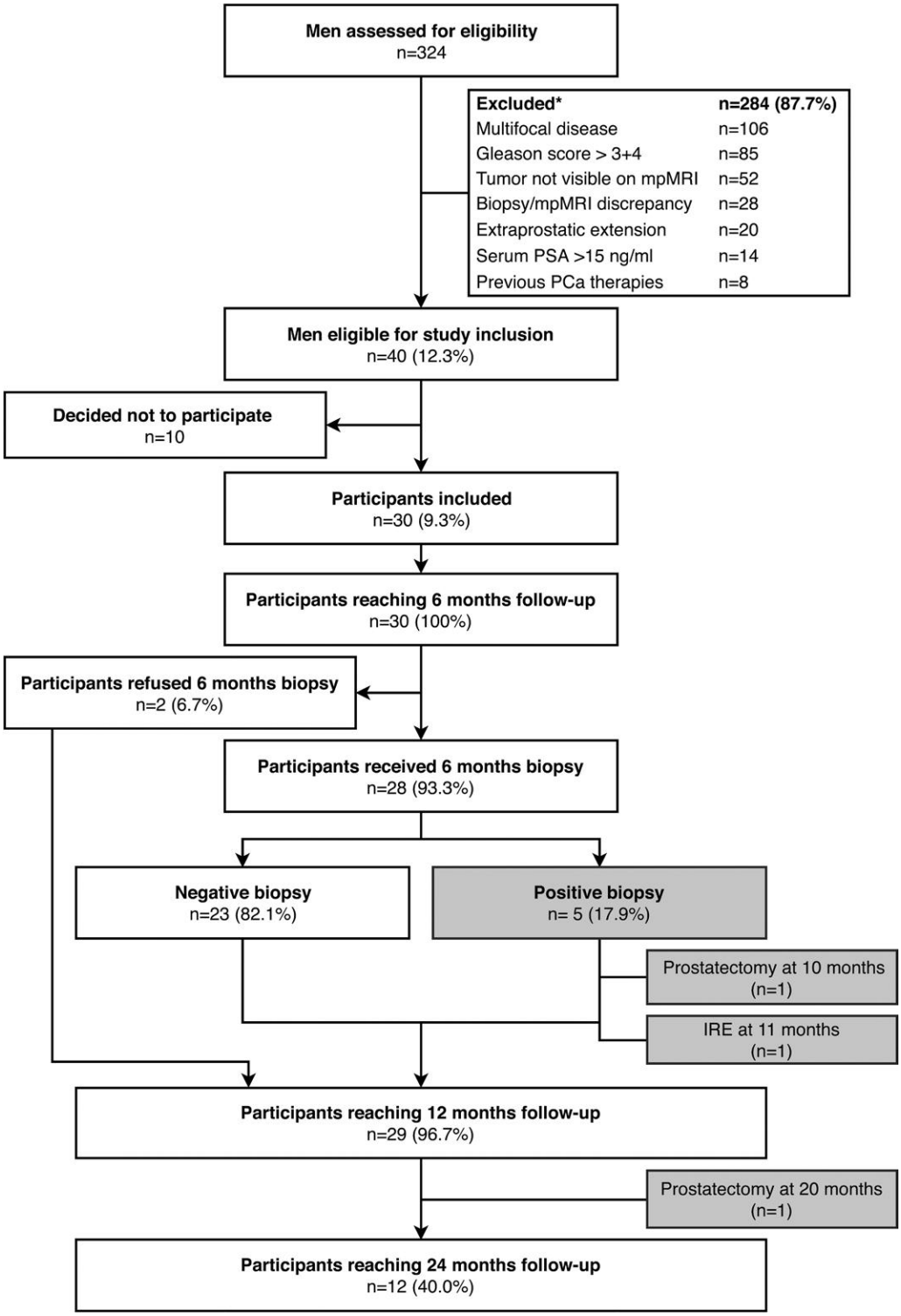

Figure 1: Study flowchart. IRE = irreversible electroporation, mpMRI = multiparametric MRI, PCa = prostate cancer, PSA = prostate-specific antigen. * indicates that multiple exclusion criteria may apply for same participant.

Oncologic outcomes.—PSA measurements were performed 6 months after IRE and every 3 months thereafter. At 6 months, multiparametric prostate MRI (Magnetom Skyra; Siemens, Erlangen, Germany) was performed to assess the presence of residual disease in the treated parts and the untreated parts of the prostate. Multiparametric prostate MRI was reviewed by one radiologist (B.H., with more than 20 years of experience in urogenital MRI) who was not blinded to the clinical data of the participants. At the 6-month follow-up visit, participants underwent MRI-guided transrectal targeted in-bore biop-

sies of the ablation zone and the border of the ablation zone with 16–18-gauge needles. Two to four cores were taken from each participant. Additional targeted biopsies were performed in case of lesions greater than or equal to Prostate Imaging Reporting and Data System, or PI-RADS, category 3 found elsewhere in the prostate. Any prostate cancer found in a core obtained within or at the border of the ablation was defined as in-field residual disease. Any prostate cancer found in a core obtained outside the target volume was designated as out-of-field residual disease. After 6-month biopsy and regardless of its result, all participants were regularly monitored. Follow-up protocol included PSA measurements at 3-month intervals and multiparametric prostate MRI at 12 months after IRE (or earlier in case of a suspicious increase in PSA level).

Statistical Analysis

Statistical analysis was conducted by using SPSS Statistics (version 25; IBM, Armonk, NY) and the R statistics package (version 3.4.2; R Foundation, Vienna, Austria). Discrete and continuous variables are displayed as median and interquartile range (IQR), whereas categorical variables are displayed as frequencies and percentages. Two-tailed Wilcoxon signed rank test was used to evaluate variation between baseline, 6-month, and 12-month follow-up, including the IEEF-5 questionnaire results. McNemar χ^2 test was performed for intraindividual comparisons between baseline and follow-up for binary variables. Confidence intervals (CIs) were calculated by using the Clopper-Pearson method for binomial proportions. According to the Bonferroni method, a P value $\leq .016$ was considered to indicate statistical significance to correct for multiple testing.

Results

Study Population

Baseline participant characteristics and treatment parameters are summarized in Table 1. The median age of the cohort was 65.5 years (IQR, 60–68.8 years) and median baseline PSA level was 8.65 ng/mL (IQR, 5–11 8.65 ng/mL). Median tumor size was 13.5 mm (IQR, 9.2–17 mm). According to National Comprehensive Cancer Network criteria, four of 30 (13.3%) and 26 of 30 (86.7%) participants were considered at low and intermediate risk, respectively. Prostate biopsies were performed as follows: 20 of 30 (66.7%) participants underwent standard transrectal US–guided biopsy, where three of these 20 (15%) participants underwent an additional MRI-guided biopsy due to a negative transrectal US–guided biopsy and a lesion suspicious for cancer at multiparametric prostate MRI. Seven of 30 (23.3%) participants underwent MRI–US fusion–guided biopsy and three of 30 (10%) participants underwent transperineal template biopsy. The median number of cores taken was 12 (IQR, 12–14.8). The median number of cancer-positive cores was three (IQR, one to three). At multiparametric prostate MRI, all participants had a visible lesion corresponding to the cancer-positive cores of the prostate biopsy. According to PI-RADS version 2, 16 of 30 (53.3%) lesions were classified as PI-RADS category 4, while the remaining 14 of 30 (47.7%) were classified as PI-RADS category 5 (16).

Table 1: Baseline Participant Characteristics and Treatment Parameters

Characteristic	Finding
No. of participants	30
Age (y)	65.5 (60–68.8)
Prostate-specific antigen level (ng/mL)	8.65 (5–11)
Tumor size (mm)	13.5 (9.2–17)
Gleason score*	
3 + 3	7/30 (23.3)
3 + 4	23/30 (76.7)
NCCN risk group*	
Low	4/30 (13.3)
Intermediate	26/30 (86.7)
High	…
Tumor location at multiparametric MRI*	
Posterolateral peripheral zone	14/30 (46.7)
Posteromedial peripheral zone	4/30 (13.3)
Anterior fibromuscular stroma	4/30 (13.3)
Anterior transitional zone	3/30 (10)
Posterior transitional zone	3/30 (10)
Anterior peripheral zone	2/30 (6.7)
PI-RADS version 2 score*	
PI-RADS 4	16/30 (53.3)
PI-RADS 5	14/30 (47.7)
No. of electrodes per participant*	
3	2/30 (6.7)
4	27/30 (90)
5	1/30 (3.3)
Procedure time (min)	74.5 (55–86)
Catheterization (d)	2 (2–10)

Note.—Unless otherwise specified, data are medians, with interquartile ranges in parentheses. NCCN = National Comprehensive Cancer Network, PI-RADS = Prostate Imaging Reporting and Data System.

* Data are numerators and denominators, with percentages in parentheses.

Periprocedural Results and Adverse Events

All participants underwent unifocal ablation. The size of ablation zone depended on tumor size (Fig 2). Two participants were treated by using three electrodes and one participant with a large ventral tumor required five electrodes; all other participants were treated by using four IRE electrodes. Median procedure time was 74.5 minutes (IQR, 55–86 minutes). Urinary catheter removal was performed after a median of 2 days (IQR, 2–10 days).

Overall, among 30 participants, six (20%; 95% CI: 8%, 39%) adverse events were recorded: two grade I events (6.7%; 95% CI: 0.8%, 22%), three grade II events (10%; 95% CI: 2%, 27%), and one grade III event (3.3%; 95% CI: 0%, 17%). Three participants had a postoperative urinary tract infection; all were successfully treated with oral antibiotic therapy by the referring urologist. Two participants reported intermittent self-resolving hematuria following IRE. One participant developed a urethral stricture requiring surgical bladder neck incision and urethrotomy 3 months after IRE procedure. No participant deaths or serious adverse events were recorded.

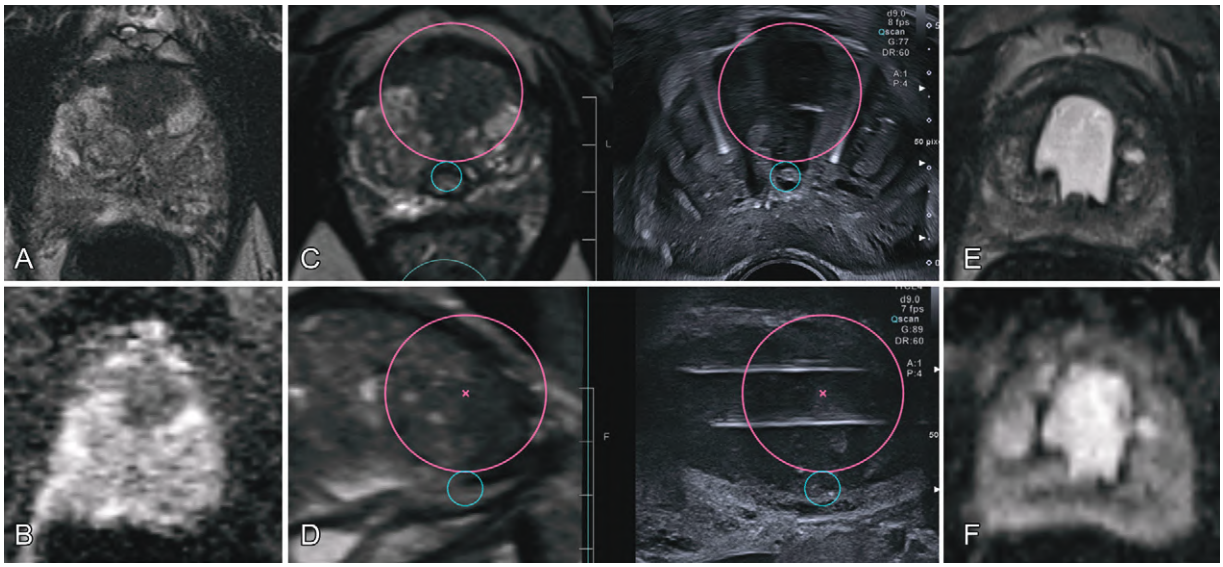

Figure 2: Images in a 68-year-old man with ventrally located Gleason score 3 + 3 tumor treated with irreversible electroporation. *A, B,* Images of baseline unenhanced axial T2- and diffusion-weighted MRI show ventrally located tumor. *C, D,* Unenhanced axial and sagittal MRI–transrectal US–fusion images obtained during procedure show accurate electrode placement in both transverse and sagittal plane to ensure complete enclosure of tumor marked with spherical volume of interest (large pink circle). Small blue circle is anatomic landmark used for image fusion indicating urethra. *E, F,* Images of follow-up unenhanced T2- and diffusion-weighted MRI at 6 months show large fluid-filled defect in anterior aspect of gland with no residual suspected diffusion restriction. Participant experienced prostate-specific antigen level reduction of 60%. Biopsy at 6 months confirmed absence of residual tumor.

Functional Outcomes

In terms of urogenital toxicity and functional outcomes, all participants replied to the questionnaires at baseline and follow-up, and no participant was lost to follow-up. Among 30 participants, 30 (100%), 29 (96.7%), and 12 (40%) participants reached 6-month, 12-month, and 24-month follow-up, respectively. One participant underwent radical prostatectomy 10 months after IRE due to in-field residual disease and rising PSA and was hence excluded from further analysis. The proportion of participants with leak-free continence was 90% (27 of 30; 95% CI: 73%, 98%) at baseline, 83.3% (25 of 30; 95% CI: 65%, 94%; $P = .47$) at 6 months, and 86.2% (25 of 29; 95% CI: 68%, 96%; $P > .99$) at 12 months. Pad-free continence was 96.7% (29 of 30; 95% CI: 83%, 100%) at baseline, 93.3% (28 of 30; 95% CI: 78%, 99%) at 6 months, and 96.5% (28 of 29; 95% CI: 82%, 100%) at 12 months. All 12 participants who reached 24-month follow-up were leak-free and pad-free continent (12 of 12, 100%; 95% CI: 74%, 100%). The mean modified ICIQ-MLUTS questionnaire score increased initially from a baseline score of 0.17 to 0.67 at 6 months ($P = .21$) and then decreased again to 0.3 at 12 months ($P = .58$).

The proportion of participants with erections sufficient for penetration decreased from 83.3% (25 of 30; 95% CI: 65%, 94%) to 66.7% (20 of 30; 95% CI: 47%, 83%; $P = .07$) at 6 months and then increased again to 79.3% (23 of 29; 95% CI: 60%, 92%; $P > .99$) at 12 months. All 12 participants available for 24-month follow-up reported erections sufficient for penetration. Use of phosphodiesterase type 5 inhibitors increased from 6.7% (two of 30; 95% CI: 0%, 22%) at baseline to 20% (six of 30; 95% CI: 8%, 39%) at 6 months and decreased again to 10.3% (three of 29; 95% CI: 2%, 27%) at 12 months. Median IIEF-5 score showed an initial decrease from 21 (IQR, 16–24) at baseline to 19 (IQR, 12–22) at 6 months ($P = .04$) indicating a slight reduction in erectile function, but showed a gradual return to baseline at 12 months (median, 20; IQR, 12–23; $P = .07$) and 24 months (median, 22.5; IQR, 18.5–25; $P = .40$) (Fig 3).

Biochemical, Imaging, and Histologic Outcomes

Biochemical, imaging, and histologic outcomes are summarized in Table 2. In terms of cancer control, median serum PSA level decreased from a baseline value of 8.65 ng/mL (IQR, 5–11.4 ng/mL) to 2.70 ng/mL (IQR, 1.1–4.1 ng/mL) at 6 months ($P < .001$), 2.35 ng/mL (IQR, 1–3.4 ng/mL) at 12 months ($P < .001$), and 2.35 ng/mL at 24 months ($P = .002$) corresponding to a decrease of 69%, 72%, and 73%, respectively. Early postprocedural transrectal contrast-enhanced US 1 day after ablation showed complete ablation in 29 of 30 participants (96.7%) (Fig 4). In one participant, postprocedural contrast-enhanced US showed only a small perfusion defect with incomplete coverage of the target volume. This finding was confirmed with multiparametric prostate MRI, and the participant was scheduled for a second IRE ablation. At 6 months, two participants refused posttreatment biopsy. Both showed no evidence of residual disease or new lesions suspicious for cancer at multiparametric prostate MRI and both experienced a decrease in PSA level after 6 months greater than 70%. At histopathologic analysis, no residual prostate cancer was found in 23 of 28 participants (82.1%; 95% CI: 63%, 94%). In-field residual disease was found in five of 28 participants (17.9%; 95% CI: 6%, 37%), including three participants who harbored clinically insignificant cancer (Gleason score, ≤3 + 3; cancer core length, ≤3 mm) and two participants who harbored clinically significant cancer.

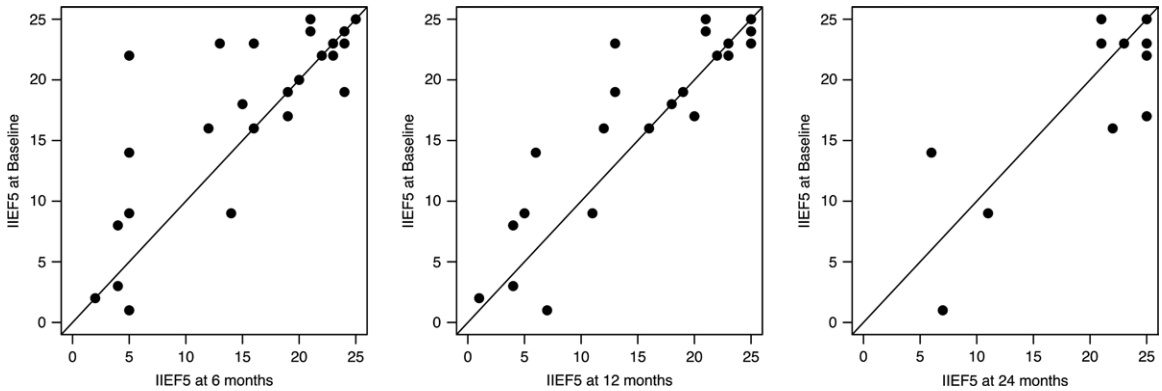

Figure 3: Pairwise scatterplots show variations in sexual function at 6-month, 12- month, and 24-month follow-up after focal irreversible electroporation as assessed with International Index of Erectile Function-5 (IIEF-5) questionnaire. Two-tailed *P* values were reported for Wilcoxon signed ranks test comparing baseline and 12-month median scores. Median baseline versus 6-, 12-, and 24-month scores: 21 (interquartile range [IQR], 16–24) versus 19 (IQR, 12–22; *P* = .04) versus 20 (IQR, 12–23; *P* = .07) versus 22.5 (IQR, 18.5–25; *P* = .40).

Table 2: Biochemical, Imaging, and Histologic Outcomes

Parameter	Finding
Prostate-specific antigen level (ng/mL)	
Baseline	8.65 (5–11)
6-mo visit	2.70 (1–4)
12-mo visit	2.35 (1–3)
24-mo visit	2.35 (1–3)
Early contrast material–enhanced US at 1 day*	
Complete ablation	29/30 (96.7)
Insufficient ablation	1/30 (3.3)
Multiparametric MRI at 6 mo*	
No residual disease	27/30 (90)
In-field residual disease	3/30 (10)
New out-of-field lesions	2/30 (6.7)
Biopsy at 6 mo*	
In-field failure	5/28 (17.9)
Out-of-field failure	0/28 (0)
Clinically significant cancer	2/28 (7.1)
Clinically insignificant cancer	3/28 (10.7)
Follow-up	
Follow-up (mo)	20 (14–29)
In-field failure*	5/30 (16.7)
Out-of-field failure*	2/30 (6.7)
Participants requiring second IRE*	1/30 (3.3)
Participants requiring radical prostatectomy*	4/30 (13.3)

Note.—Unless otherwise specified, data are medians, with interquartile ranges in parentheses. IRE = irreversible electroporation.
* Data are numerators and denominators, with percentages in parentheses.

Two participants with unsuspicious multiparametric prostate MRI of the treated lobe underwent additional targeted biopsies of two new equivocal lesions in the untreated side of the prostate depicted at 6 months after multiparametric prostate MRI. None of these lesions turned out to be cancerous at histopathologic analysis.

Follow-up and Oncologic Outcomes beyond the 6-month Biopsy

The median follow-up for the entire cohort was 20 months (IQR, 14–29 months). Among the five participants with histologic proof of residual disease, two participants with clinically significant cancer underwent radical prostatectomy due to increasing PSA level at 10 months and 24 months after IRE, respectively. One of the three participants with clinically insignificant cancer at 6-month biopsy underwent a second treatment with focal IRE and showed no biochemical or histologic evidence of residual disease thereafter. The remaining two participants with clinically insignificant cancer at 6-month biopsy are still under active surveillance. In three of these five participants with residual disease at 6-month biopsy, multiparametric prostate MRI at 6 months showed suspicious areas at the border of the ablation zone. In the remaining two participants, residual prostate cancer was not detectable at 6-month multiparametric prostate MRI. Both participants who refused posttreatment biopsy showed stable PSA level less than 2 ng/mL and no evidence of residual disease during follow-up or new lesions suspicious for cancer at 12-month multiparametric prostate MRI. Two of 23 participants (8.7%) with no evidence of biochemical, imaging, and histologic residual disease at 6 months experienced a biochemical relapse during follow-up. In both participants, multiparametric MRI and MRI–transrectal US–guided fusion biopsy confirmed the presence of new, out-of-field, clinically significant prostate cancer and both participants underwent radical prostatectomy 25 months and 33 months after IRE.

Discussion

The purpose of this study was to assess urogenital toxicity and oncologic outcome of MRI-transrectal US fusion–guided irreversible electroporation (IRE) for the focal treatment of study participants with localized low- to intermediate-risk prostate cancer. At 12 months after the procedure, 96.3% (26 of 27) of participants remained pad-free and leak-free continent.

One participant developed a new mild stress urinary incontinence that remained persistent at 12-month follow-up. In terms of preservation of sexual function, 95.8% (23 of 24) of participants with good baseline sexual function reported erections sufficient for penetration at 12 months. Questionnaires administered to assess participant reported urogenital function remained stable at 12 months (P = .58 and P = .07, respectively). The rate of in-field treatment failure was 17.9% (five of 28) as determined by using multiparametric prostate MRI and targeted biopsies at 6 months. Among the five participants with residual disease in the ablated lobe, three participants harbored clinically insignificant prostate cancer (Gleason score, ≤3 + 3; cancer core length, ≤3 mm) and two participants had clinically significant prostate cancer (Gleason score >3 + 3; cancer core length, >3 mm).

There was one grade III adverse event in our cohort due to a urethral stricture requiring surgical bladder neck incision and urethrotomy 3 months after IRE. Urethral strictures are known complications after both radical prostatectomy (incidence of 0.4%–32%) and focal therapy (incidence of 1%–31%) (17,18). Based on the limited data currently available in the literature, IRE seems not to be immune to this complication. Both Murray et al (19) and Valerio et al (20) reported one case of urethral stricture requiring transurethral resection or dilation in their cohort of participants. In terms of preservation of urogenital function, our results are in good agreement with those obtained by other groups. Valerio et al (20) reported no change in pad-free and leak-free continence between baseline and 12-month follow-up and only a slight reduction in terms of absolute erectile function (75% vs 69%). It should also be emphasized that the majority of our study participants (21 of 30, 70%) had tumors localized in the dorsal aspect of the prostate in close proximity to the neurovascular bundles, and nine of 30 participants (30%) had an apical tumor close to the external urinary sphincter. This is in contrast to the cohort of Valerio et al (20), in which only participants with ventrally located tumors were included.

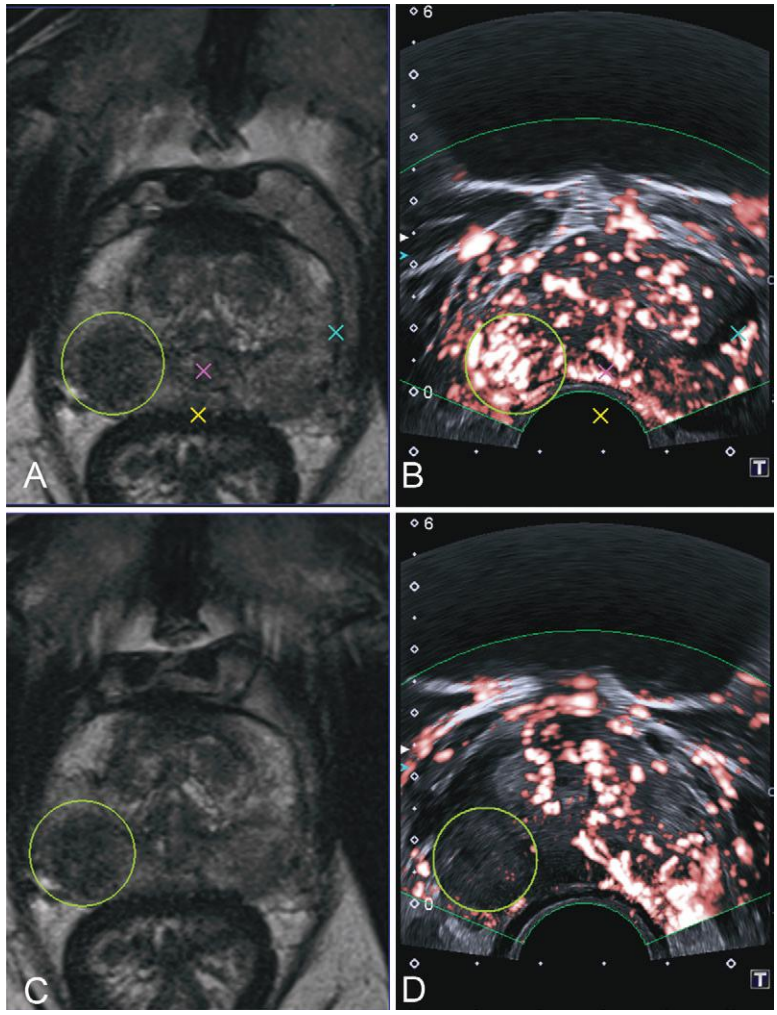

Figure 4: Images in a 63-year-old man with Gleason score 3 + 4 prostate cancer. Representative images of contrast-enhanced US imaging by using MRI–transrectal US fusion technique before and 1 day after irreversible electroporation (IRE). Tumor is marked with spherical volume of interest (green circle). Three small Xs are anatomic landmarks used for image fusion indicating urethra, dorsal boundary, and lateral boundary of gland. *A, B,* Preoperative contrast-enhanced US images show focal area of hyperperfusion corresponding to tumor in right peripheral zone. *C, D,* Postoperative contrast-enhanced US images 1 day after IRE show large perfusion defect corresponding to ablation zone. At 6-month follow-up, participant showed prostate-specific antigen level reduction of 70%. Both multiparametric MRI and targeted biopsy confirmed absence of residual tumor.

Our rate of local tumor control is consistent with those reported by previous studies. Both Murray et al (19) and van den Bos et al (21) reported a rate of in-field treatment failure of 16%, which is slightly better than ours. Less favorable results have been reported by Valerio et al (20), who described in-field residual disease in 38.9% of participants. This discrepancy is most probably attributable to the fact that Valerio et al treated only participants with tumors located in the ventral aspect of the prostate (20), which are particularly challenging to treat (22).

One major strength of our study is the comparatively long follow-up that allowed us to evaluate the clinical course of our participant cohort beyond the time of 6-month biopsy. After a median follow-up of 20 months, four participants (four of 30, 13%) underwent salvage prostatectomy. The fact that two of them had no sign of residual disease in the treated lobe at 6-month biopsy and no lesions suspicious for cancer at 6-month multiparametric prostate MRI corroborates the importance of a standardized follow-up following focal therapy.

Participants remain at high risk of developing new tumors in the residual gland, despite being free of visible macroscopic disease 6 months after focal therapy. All four participants who underwent radical prostatectomy during follow-up were treated with a curative intent and none of them displayed distant metastases. The use of transrectal contrast-enhanced US 1 day after IRE allowed us to identify the only case of incomplete ablation, but has not proved useful in the detection of residual disease after IRE.

Our study had several limitations. First, our sample size was small. Second, there was a large amount of attrition in the follow-up at 1 year and 2 years. The majority of participants had a follow-up visit prior to 24 months, and only 12 of 30 participants (40%) were available for a follow-up visit at 24 months. This severely limits the value of our results in terms of oncologic outcome. Third, at each participant's 6-month visit, the untreated prostate lobe was only subject to targeted biopsies for lesions greater than or equal to Prostate Imaging Reporting and Data System, or PI-RADS, category 3 at multiparametric prostate MRI. Systematic sampling during follow-up was only performed in case of raising levels of prostate-specific antigen with no visible tumors at multiparametric prostate MRI, which may cause an underestimation of out-of-field residual disease.

Our results suggest that focal irreversible electroporation is a safe and effective procedure for participants with localized prostate cancer, confirming the durability of the favorable outcomes both in terms of urogenital function preservation and oncologic control after a median follow-up of 20 months. Future research should aim to reproduce these results in multicenter trials with larger number of participants and to develop standardized criteria for participant selection and treatment delivery.

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