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Evaluation of clinical and mpMRI findings of irreversible electroporation therapy for the treatment of localized prostate cancer: Preliminary results

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ABSTRACT

Objective: To evaluate early clinical and multiparametric prostate magnetic resonance imaging (mpMRI) results of irreversible electroporation (IRE) efficiency in treatment of localized prostate cancer.

Material and methods: For the patients in whom IRE was performed for local ablation, mpMRI was used for the sixth month follow-up. These images were compared with the mpMRI images obtained before the procedure. We performed transperineal fusion biopsy to patients with diagnosis of localized prostate cancer. We treated the eligible ones with IRE. Six of them have completed their 6-month follow-up period. We compared preoperative prostate specific antigen (PSA), international prostate symptom score, international index of erectile function (IIEF), and mpMRI of these patients with those obtained at the sixth month of follow-up. Side effects experienced by the patients were evaluated as well.

Results: We had 10 patients who received IRE treatment. Six patients completed their sixth month-follow-up and came for control visits. At the end of 6 months, the mean decrease in PSA level was 73%. IIEF results were seen not to have changed significantly. On mpMRI, diffusion restriction was seen to have disappeared except for one patient, and Prostate Imaging Reporting Data System scores were decreased.

Conclusion: We concluded that early clinical and mpMRI results for IRE in the focal ablative treatment of localized prostate cancer were gratifying. As an ambulatory procedure with a low incidence of side effects, we look forward to seeing the long-term results of IRE treatment.

Keywords: Focal ablation; IRE; prostate cancer; treatment.

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Introduction

Prostate cancer is the most commonly seen cancer in men. We mostly encounter the localized form of prostate cancer.[1] Prostate specific antigen (PSA) is frequently used in line with changing disease trends during the last 20 years. There are two frequently used curative treatment systems for localized prostate cancer: radical prostatectomy and radiotherapy. They have significant side effects such as erectile dysfunction and urinary incontinence that complicate the decision-making process when choosing the treatment options.[2]

As is the case in the treatment for other types of cancer, focal ablative treatments are used as viable alternatives in localized prostate cancer as well. The most significant advantage of these methods is their ability to eliminate the tumor without hindering the integrity of the organ in the areas they are identified. Today, we have many focal ablative treatment methods in use.[3] Among these, irreversible electroporation (IRE) has a unique place. The procedure is applied with two or more electrodes by disrupting the permeability of cellular membranes with repetitive sequential electrical currents. Thus, tissue ablation can be

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achieved without causing a thermal effect in the targeted area.[4,5]

In this study, we aimed at investigating the efficiency of IRE in the treatment of localized prostate cancer. We performed multiparametric prostate magnetic resonance imaging (mpMRI)-fusion biopsy and after establishing the diagnosis of localized prostate cancer with biopsy, we applied IRE to lesions that could be localized with mpMRI. We made the attempt to compare the clinical and mpMRI results of the patients who had completed six months of follow-up.

Material and Methods

Verbal and written consents of the patients were obtained after explaining them the details of the procedure and ethical committee approval was received from the TOBB ETU Clinical Research (KAEK-118/096). We performed at least three core targeted biopsies from each suspicious lesions which Prostate Imaging and Reporting and Data System (PI-RADS) ≥ 3. Also we performed 12 core systematic biopsy of each patient (Figure 1). Pathologic evaluation revealed significant cancer if core length of cancer is bigger than 50%, Gleason score bigger than 3 + 3, and more than one core. The patients who were included in our study had the diagnosis of adenocarcinoma with prostate-MR fusion system biopsy performed perineally. Targeted transperineal fusion biopsy protocol was used for this purpose. Bioject™ (D&K Technologies, Barum, Germany) software was used for prostate mapping to be used in transperineal biopsy; the same mapping was later utilized for IRE treatment (Figure 2). We treated our first patient in January 2020. mpMRI and prostate-specific membrane antigen-based positron emission tomography/computed tomography were used for clinical staging of our patients.

MRI Method

For the patients in whom IRE was performed for local ablation, mpMRI was used for the sixth month follow-up. These images were compared with the mpMRI images obtained before the procedure, and the evaluation was based on PI-RADS Steering Committee (version 2.1) criteria. By making comparisons with previous mpMRI results, changes that are secondary to the treatment, lesions that are considered to be residual malignancies at this level, and lesions outside the treatment focus that raised the suspicion for residual malignancy were separately reported. All mpMRI equipment harbors three plane small field of view (FOV) T2A, axial diffusion-weighted imaging, and dynamic contrast enhanced (DCE) imaging. All the patients were screened with 3T (Ingenia, Philips Medical System, Netherlands). Diffusion-weighted images were obtained with "b" values of 0, 1,500 s mm^{-2} and to decrease kurtosis effects, apparent diffusion coefficient (ADC) maps were created from b = 0, 200, 1,000 s mm^{-2} values. For DCE imaging, all patients were administered with 0.2 mL kg^{-1} gadoterate meglumine (Dotarem, Guerbet, Roissy, France) at a rate of 3 mL s^{-1} intravenously. 44-Channel spine coil and 32-channel phased-array body coil were used for imaging. The images were evaluated for diffusion restriction on diffusion-weighted images, ADC hypointensity, and early arterial contrast enhancement on dynamic contrast-enhanced images in favor of residual lesion positivity at the level of local treatment.

Main Points

- Focal ablative therapies are viable alternatives for the treatment of localized prostate cancer.
- Adding to IRE's success in the treatment of pancreatic and liver tumors, initial early results for prostate cancer were found considerably sufficient as well.
- IRE is a considerably new and effective procedure, and it will become a standard treatment for localized prostate cancers in the future.

IRE Procedure

Under general anesthesia with deep muscle relaxation effect, all patients entered the procedure in lithotomy position. Urethral catheters were placed for bladder drainage. Transrectal biplanar ultrasound (BK medical, Herlev, Denmark) probe and transperineal template were used. Three or four IRE electrodes

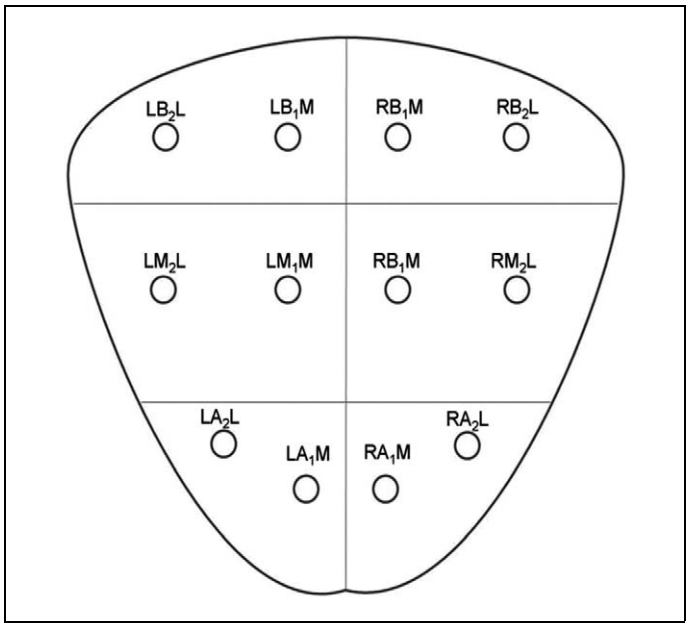

Figure 1. Scheme of 12 focal systematic prostate biopsy.

were placed at the periphery of the previously mapped lesion (Figure 3). The distance between the active electrodes was 1-2 cm. The distance between the electrodes and the depth they are placed were measured with biplanar ultrasound and entered into the IRE (Nanoknife, Angio-Dynamics, New York, USA) system. First, test current was delivered to test ideal current levels. Treatment dose was administered afterwards. Urethral catheter was kept in place for 1-3 days depending on the prostatic obstruction the patient was experiencing.

Results

IRE treatment was applied to 10 patients diagnosed as localized prostate carcinoma. Mean age of the patients was 59.7 (55-72) years, and their mean PSA level was 7.04 ng (4.1-10.5). Mean IIEF score of the patients before the treatment was 18.6 (9-26). Gleason scores and group grading values obtained after pathological examination are presented in Table 1. Six of these patients had 6 months of follow-up, and their results were included in this study. Due to the COVID-19 pandemic, delays were experienced in the follow-up of the other patients; therefore, they were excluded from the study. Three patients had more than one lesion, so the procedure was performed bilaterally for them. All the remaining patients underwent quadrant ablation procedure. As one of our patients had ongoing diffusion restriction during his sixth month follow-up visit, a repeat IRE procedure was performed. PSA values of the patients were measured every 3 months, and PSA was found to have decreased by 73% at the end of 6 months (Table 2). Urethral catheter was kept in place for 5 days in only two patients. It was retrieved on the next day in the other patients. In patients having benign prostate hyperplasia and specifically median lobe hypertrophy, urethral catheter was kept in place for a longer period and alpha blockers were prescribed. None of the patients experienced pain or bleeding during the post-operative period. Two hours after the procedure, the patients could have oral food intake and they were mobilized as early as possible. After the procedure, mean IIEF score of the patients at 6 months was 19 (8-26). None of the patients complained of newly developed urinary incontinence or erectile dysfunction during the follow-up visits performed 3 and 6 months after the procedure. MRI was performed at 6 months. Except for one patient, diffusion restriction at the site of IRE procedure was found to have disappeared and PI-RADS score was found to have decreased (Figures 4 and 5 and Table 2).

Discussion

Focal ablative therapies are viable alternatives for the treatment of localized prostate cancer. The rationale in focal tumor ablation is to preserve normal healthy tissues, vital structures like vessels and nerves in the vicinity of the tumor while eliminating the tumoral structure at the target with clear margins. One of the main advantages of the IRE technology is that it does

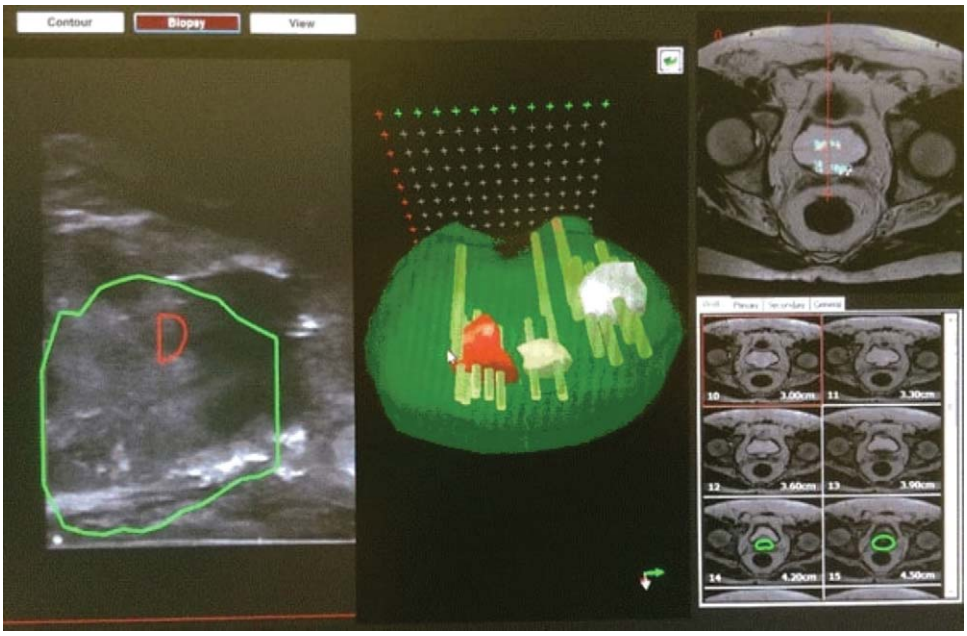

Figure 2. Transperineal MR fusion prostate biopsy.

Turk J Urol 2021; 47(4): 299-304
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not cause any thermal effect on structures having an adventitia layer.[6] So, it exerts a minimum effect on the vessels and nerves decreasing the rate of side effects bringing forward a significant advantage compared to other focal treatments.

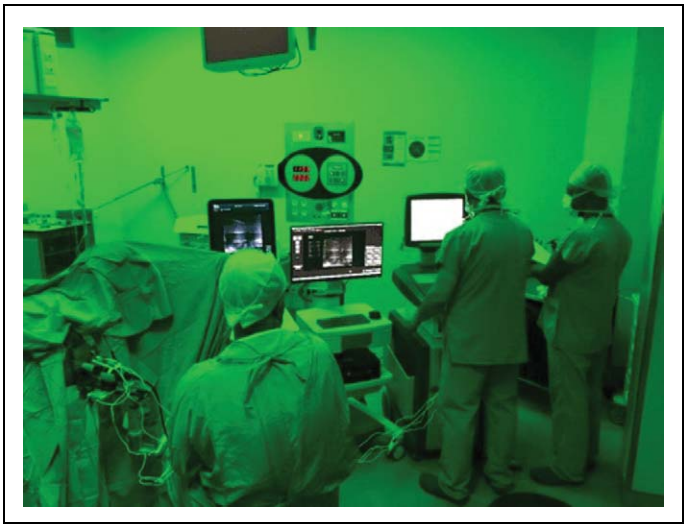

Figure 3. IRE procedure at the operation room.

Table 1. Patients Characteristics

Patient variables	Values
Age (years)	59.7 (55-72)
PSA (ng L^{-1})	7.04 (4.1-10.5)
Prostate volume (mL)	42.4 (24-65)
Gleason score (patient number)	
3 + 3 group I	4
3 + 4 group II	2
4 + 3≥ group III≥	4
IIEF	18.6 (9-26)
Clinical stage	
T1c	2
T2a	4
T2b	3
T2c	1
PI-RADS score	
1-2	2
3	4
4	7
5	3

PSA, prostate specific antigen.

The first application of IRE in prostate cancer was by Onik et al.[4] on 16 patients with localized prostate cancer. These patients did not experience side effects like erectile dysfunction or urinary incontinence. Following this, Valerio et al.[7] reported their IRE experience on 34 patients mentioning treatment failure in one patient. In a study by Van den Bos et al.,[5] 16 patients who were planned to undergo radical prostatectomy received IRE treatment 1 month prior to their operation. Pathological examination performed after radical prostatectomy demonstrated that the ablation was sufficient in the targeted areas and that there were not any skip lesions. In the largest biopsy-controlled study conducted to date, 123 patients diagnosed as localized prostate cancer were treated with IRE, control biopsy specimens were obtained from the treatment site at the end of 1 year and an ablation success of nearly 97% was obtained. In this study, urinary continence was achieved in 98.8% of the patients at the end of 12 months, and the potency was shown to not have changed in 76% of them. In this study, the specificity of mpMRI for diagnosing residual prostate cancer was 98%, while negative predictive value was found as 94%.[8]

Currently, organ preserving treatments are started to be regarded as standard treatments for breast, pancreas, liver, and kidney malignancies. Likewise, considering the burden they create for the patient and the healthcare system, radical procedures will have a limited place in the treatment of localized prostate cancers. In a recently conducted study, a randomization with radical prostatectomy or IRE was made in two similar groups with the same clinical features. In the comparisons of these patients performed after 12 months, there was not any difference between the groups with regard to oncological results, while IRE was significantly superior for urinary incontinence and erectile dysfunction.[9] For high-risk prostate cancers, the most ideal approach is radical prostatectomy; however, for medium- or low-risk prostate cancers, focal treatments should be considered as serious alternatives.

The aim in the treatment of localized prostate cancers is to eradicate the tumor completely. Among the imaging methods,

Table 2. Six-Month Follow-Up Results after the Procedure

Patient results	Values
PSA decrease rate (%)	73
IIEF	19 (8-26)
Continence rate (%)	100
PIRADS score reduction rate (%)	84
Unilateral/bilateral application	7/3

PSA, prostate specific antigen; IIEF: international index of erectile function.

mpMRI provides the most detailed information for prostate cancer. In the studies conducted so far, its diagnostic precision was found to be superior to standard biopsies.[10,11] Sufficient clinical information is obtained in the controls performed with MRI after the focal treatment of prostate cancer.[12,13] In our limited series, we showed the disappearance of diffusion restriction in all but one patient that have completed their 6 months of follow-up. Only in one patient, because of the diffusion restriction that persisted at the periphery of the lesion, a second IRE procedure was performed. In this patient, the largeness of the lesion site was perceived as the cause of the failed procedure. Together with the decrease in PSA levels, PI-RADS score reductions on MRI images are indicators of considerably favorable clinical response to treatment. In the continuation of this study, this evidence needs to be supported with pathological results as well. For this reason, we planned randomized biopsies

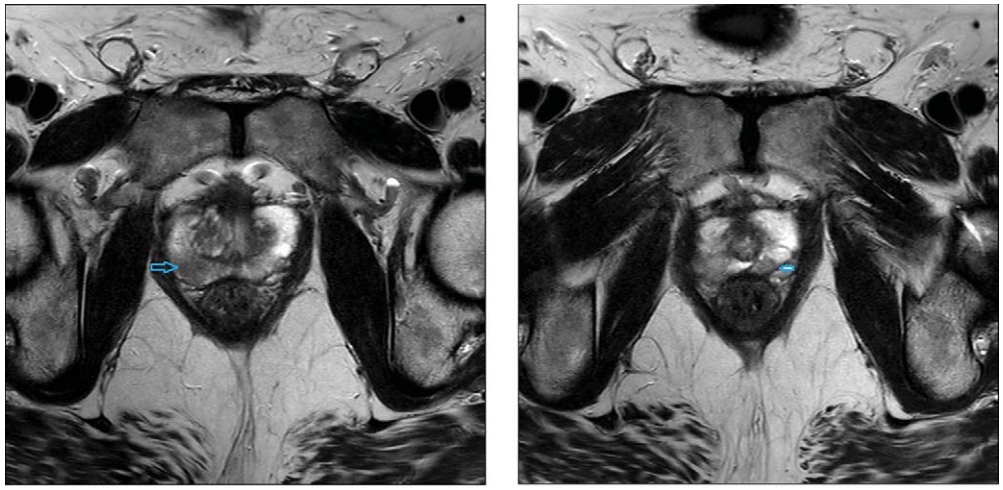

Figure 4. On mpMRI obtained before the IRE procedure, on the right peripheral zone, T2 hypointense area confirmed with Gleason score 4 + 3 lesion (a, large arrow), and on the left peripheral zone T2 hypointense area confirmed with Gleason score 3 + 3 lesion (b, small arrow).

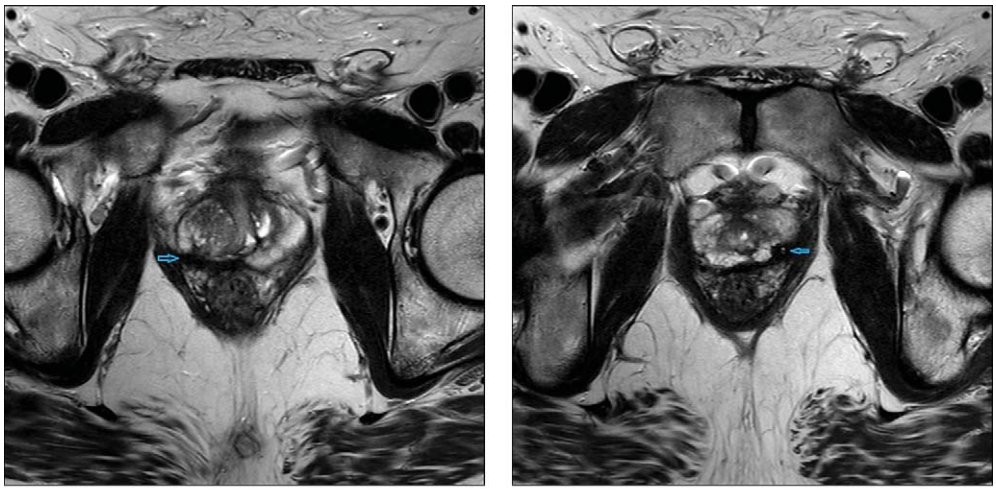

Figure 5. On mpMRI obtained after 6 months of the IRE procedure of the same patient, post-procedure suspicious fibrosis area on right peripheral zone (a, arrow), and post-procedure suspicious fibrosis area on left peripheral zone (b, arrow).

Turk J Urol 2021; 47(4): 299-304
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for all patients upon the completion of 1 year. Other limitations of this study are having a retrospective series with a single arm with limited number of patients. We think that IRE is a considerably new and effective procedure, and it will become a standard treatment for localized prostate cancers in the future.

The first focal ablation experience was with IRE in our clinic. Its ease of use and adaptability to transperineal prostate fusion biopsy system made IRE a first choice for us. Adding to its success in the treatment of pancreatic and liver tumors, initial early results with our limited number of patients with prostate cancer were found considerably sufficient as well. We are planning to see the long-term results in larger series of patients.

Ethics Committee Approval: Ethical committee approval was received from the TOBB ETU Clinical Research (KAEK-118/096).

Informed Consent: Written and verbal informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ş.A.A.; Design - Ö.A.; Supervision - N.Ç.T.; Resources - Ş.A.A.; Materials - P.G.K.; Data Collection and/or Processing - Ş.A.A.; Analysis and/or Interpretation - Ö.A.; Literature Search - Ö.A.; Writing Manuscript - P.G.K.; Critical Review - N.Ç.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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