Irreversible Electroporation for Prostate Cancer as Salvage Treatment Following Prior Radiation and Cryotherapy

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Salvage treatment options after localized primary treatment failure of prostate cancer are limited and associated with risk for serious complications. We report on the management details of a 57-year-old African American man treated with partial-gland ablation using irreversible electroporation following local recurrence after brachytherapy and prior salvage cryoablation. Therapeutic and functional outcomes were assessed by conventional means, including serum prostate-specific antigen values and prostate biopsy results.

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KEY WORDS

Prostate cancer • Salvage therapy • Irreversible electroporation • Focal therapy

In 1996, a 42-year-old African American man with a prostate-specific antigen (PSA) level of 14 ng/mL (level on repeat testing, 16 ng/mL) was diagnosed with prostate cancer. Pathology reports indicated Gleason score 6 (3+3) adenocarcinoma on the right side of the prostate, in clinical stage T1c. His American Urological Association (AUA) symptom score was reported as 1, and his erectile function score was reported as 3 out of 5 (reported on a 5-point scale, with 1 being no erections and 5 being normal erections without difficulty). He elected treatment with iodine-125 brachytherapy and neoadjuvant hormone suppression. Serial PSA levels showed appropriate response with a PSA nadir <1.0 ng/dL until 10 years after treatment, when he met criteria for biochemical failure. His PSA level was 1.1 ng/mL and results of a bone scan were negative. Transperineal prostate biopsy revealed Gleason score 6 (3+3) cancer in 1 of 16 cores, in the right anterior zone. His AUA score was 7, and his erectile function score was reported as 3 of 5. Salvage, partial-gland prostate cryoablation was offered and

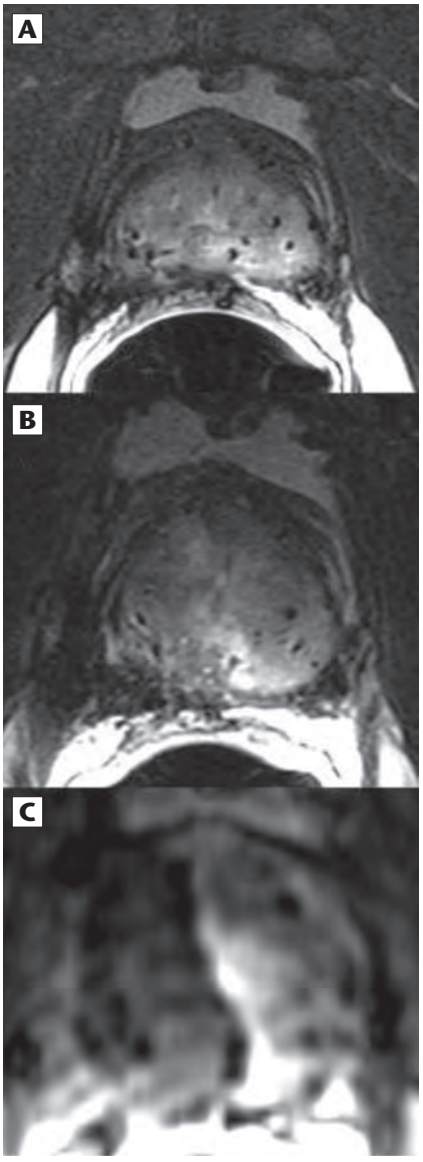

Figure 1. Axial magnetic resonance imaging of prostate 3 months before and 1 month after irreversible electroporation partial gland ablation applied to the right lobe. Preoperative T2-weighted imaging (A) demonstrates irregularity of the right side with generalized nonspecific low signal due to prior treatment and unspecified extraprostatic changes not correlated with histologic evidence of malignancy from biopsy. Postoperative T2-weighted images (B) demonstrate slight increase in prostate size due to inflammation or fewer endorectal balloon compression effects. Postcontrast images (C) reveal hemiablation effect of irreversible electroporation treatment to the right side with slight crossing of the midline below the urethra. No extraprostatic treatment effects were identified on these studies.

applied uneventfully to the right hemigland of the prostate, utilizing a urethral warmer and two freeze-thaw cycles. After cryoablation, no imaging was obtained to formally assess prostate gland treatment.

Two years after cryoablation, his PSA level had continued to rise (3.76 ng/mL) prompting repeat transrectal ultrasound (TRUS) biopsy of the prostate and seminal vesicles, results of which were negative (46 cores). His AUA symptom score was 14, and his erectile function score was reported as 1 of 5. He received dilations for a membranous urethral stricture. Five years after cryoablation, his PSA level was 4.5 ng/mL, and continued to elevate to 10.2 ng/mL, and then to 14 ng/mL. A digital rectal examination revealed an abnormality on the right side of the prostate. A repeat prostate biopsy was performed, revealing Gleason 7 (3+4) prostate cancer in 1 of 12 cores in the right lateral apex of the prostate. He then self-referred to our institution for salvage management options. He reported severe erectile dysfunction (score, 2 of 5) and weak urinary flow, cystoscopically confirmed as resulting from membranous urethral stricture.

Multiparametric magnetic resonance imaging (MRI) of the prostate showed a 17.6-mL prostate with heterogeneous signal changes consistent with prior treatment effect and artifacts from brachytherapy implants. A suspicious region was described as an asymmetric lesion on the right peripheral zone from the middle to the base of the gland (Figure 1). Heterogeneous signal was identified in the seminal vesicles, and the lymph nodes were described as nonsuspicious. The rectal wall was noted to be in close contact with the gland with evidence consistent with fibrosis. A bone scan revealed nothing remarkable.

A full discussion of management options was provided, including a referral to a colorectal surgeon for a discussion of potential surgical risks for rectal wall injury. The patient requested evaluation for candidacy for partial-gland ablation (PGA) therapy with irreversible electroporation (IRE). A confirmatory biopsy of the prostate and seminal vesicles was performed by the transperineal approach (38 cores), identifying Gleason score 7 (3+4) prostate cancer in two of four cores from the right anterior base, with a maximum of 7.7 mm in length and 20% of core involvement. The seminal vesicles were normal.

After the patient was counseled on the potential risks and gave informed consent, he was treated with IRE PGA applied to the right lobe of the prostate using five probes placed under TRUS guidance; a 5-mm clearance from the urethra, rectum, and bladder was utilized to avoid collateral tissue damage. Following cystoscopic evaluation of the urethra and bladder, treatment was applied using 90 pulses per electrode pair. Total voltage delivered between probe sets ranged from 1200 to 2160 V/cm. The procedure lasted 108 minutes. A urethral urinary drainage catheter was left in place for 24 hours after the procedure. The patient was able to urinate upon removal of the catheter.

Three months after IRE PGA, the patient's serum PSA level was undetectable (<0.05 ng/mL). Results of a traditional TRUS-guided prostate biopsy performed 4 months after treatment was negative for cancer, identifying only fibrosis and focal acute inflammation. Since treatment with IRE PGA, the patient has remained without biochemical recurrence (PSA <0.05 ng/mL) for 3.25 years. PSA levels after therapies are shown in Figure 2.

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related to prior treatment, as indicated by his preexisting stricture findings, or due to cumulative vascular damage to periurethral tissue. Rates of urethral stricture after primary and salvage radiotherapy and ablative techniques, including cryotherapy, range from 3% to 15%, dependent on time of follow-up.[15-18] As demonstrated by post-treatment contrast MRI studies, the IRE PGA therapy was applied close to the urethra but not circumferentially in order to avoid the risk of profound ischemic involvement. However, this finding also serves to highlight that the "tissue-sparing" properties suggested by studies in normal tissues are neither absolute nor necessarily universal to all tissue types.[7,19] Like any surgical intervention, care needs to be exercised when considering use of IRE near sensitive organ sites or in compromised tissues in which damage to these tissues may risk collateral dysfunction.[20]

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Measuring therapeutic outcomes following PGA therapies presents a major challenge, to such an extent that regulatory agencies do not allow the use of IRE or other ablation device technologies to be referred to as a "treatment" for oncologic conditions unless there is demonstrable proof of efficacy. The use of PSA dynamics as an outcome measure is problematic and has not been validated, yet it is a commonly used observatory metric. The study by Valerio and colleagues[13] using primary focal IRE for anterior gland ablation reported a roughly 50% decrease in median PSA by 6 months following PGA (6.1 ng/mL preoperatively and 3.2 ng/mL postoperatively). Similar changes have been identified with other modalities that employ hemiablation in the primary setting.[14,21,22] In the case presented, the profound change in PSA, we believe, is clinically meaningful due to the long duration of the undetectable PSA level; however, this finding needs to be placed in the context of multiple prior whole-gland therapies. Still, this finding is somewhat unusual, as it is rare to develop undetectable levels of PSA following whole-gland radiation or cryotherapy procedures.[2,3,21] In this patient's procedure, treatment was applied to only half of the prostate gland, and it was expected that PSA would remain detectable due to the untreated remnant of the gland. One possibility includes the formation of an immune response against prostate tissue or PSA generated from multiple therapies applied to this tissue. Such responses following surgical and ablative treatments have been described, although these responses are rare. In this case, we have no evidence to support this speculation with subsequent histology findings demonstrating only nonspecific inflammatory changes and severe fibrosis without viable prostatic glands in the biopsies from the left side of the prostate. Exploration of this hypothesis requires prospective and specific studies. Continued follow-up for this patient will include serial

MAIN POINTS

- Therapeutic options for locally recurrent prostate cancer after primary radiation treatment include hormone therapy, salvage prostatectomy, cryoablation, and high-intensity focused ultrasound. In appropriately selected patients, oncologic control may be reasonably achieved with salvage radical prostatectomy, but the rate of complications, including urinary incontinence, bladder neck strictures, and rectal injury, can be high.
- Salvage cryoablation of the prostate gland has emerged as a less invasive technique with similar effectiveness in local cancer control as salvage radical prostatectomy. However, failure following salvage therapies represents a unique challenge and the majority of men in this situation find themselves on hormone therapy.
- Irreversible electroporation (IRE) is an energy-based system that produces tissue ablation by means of short high-voltage electrical pulses that are delivered through metal needle electrodes preplaced within the tissue to be ablated. It can be used as a second-line salvage treatment modality in a patient with locally recurrent prostate cancer.
- Care needs to be exercised when considering use of IRE near sensitive organ sites or in compromised tissues in which damage to these tissues may risk collateral dysfunction.

serum PSA testing and further studies, such as prostate biopsy or imaging, considered in the case of biochemical or clinical evidence of recurrence.

It is important to note that this type of response may not be applicable to other patients, but it may hold promise for future trials of IRE in a salvage setting. It is worth noting that we and others have carefully performed IRE for local failure following radiation in selected cases and have not witnessed this form of response in those cases. Further accumulated experience will help to add to the understanding of IRE effects in previously radiated or otherwise ablated tissues, including the effects of serially repeated IRE procedures. Risks for identifiable adverse events such as urethral stricture disease, collateral injury, functional loss, and inflammatory and infectious complications require further evaluation. ■

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