12-29-2023

Irreversible electroporation as a focal therapy for localized prostate cancer: A systematic review

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Citation

Prabhakar, P., Avudaiappan, A. P., Sandman, M., Eldefrawy, A., Caso, J., Narayanan, G., & Manoharan, M. (2024). Irreversible electroporation as a focal therapy for localized prostate cancer: A systematic review. *Indian journal of urology : IJU : journal of the Urological Society of India*, *40*(1), 6–16. https://doi.org/10.4103/iju.iju_370_23

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Review Article

Irreversible electroporation as a focal therapy for localized prostate cancer: A systematic review

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ABSTRACT

Introduction: Irreversible electroporation (IRE) is a new and promising focal therapy for the treatment of localized prostate cancer. In this systematic review, we summarize the literature on IRE for prostate cancer published over the last decade.
Methods: PubMed and EMBASE were searched with the end date of May 2023 to find relevant publications on prostate cancer ablation using IRE. Original studies with focal IRE as the primary curative treatment which reported on functional or oncological outcomes were included. The bibliography of relevant studies was also scanned to identify suitable articles.
Results: A total of 14 studies reporting on 899 patients treated with IRE for localized prostate cancer were included. Of all the studies reviewed, 77% reported on recurrence within the zone of ablation, and it ranged from 0% to 38.9% for in-field and 3.6% to 28% for out-of-field recurrence. Although, a standardised follow-up protocol was not followed, all the studies employed serial prostate-specific antigen monitoring, a multiparametric magnetic resonance imaging, and a biopsy (6–12 months post-treatment). Across all the studies, 58% reported that the urinary continence returned to the pretreatment levels and 25% reported a minor decrease in the continence from the baseline at 12-months of follow-up. Erections sufficient for intercourse varied from 44% to 75% at the baseline to 55% to 100% at 12-months of follow-up across all the studies.
Conclusion: IRE, as a focal therapy, shows promising results with minimal complications and reasonably effective oncological control, but the data comparing it to the standard of care is still lacking. Future research should focus on randomized definitive comparisons between IRE, radical prostatectomy, and radiation therapy.

INTRODUCTION

Prostate cancer is the second most common solid tumor in men with an incidence of 1,414,259 new cases globally in the year 2020.[1] The standard of care for localized prostate cancer, depending on the International Society of Urological Pathology (ISUP) grade and the stage of the disease, has traditionally been active surveillance, radical prostatectomy (RP), and radiation therapy (RT). RP and RT have been the long-standing curative whole-gland approaches with the best possible oncological outcomes for patients with localized prostate cancer. However, these curative treatment options are associated with adverse quality-of-life outcomes such as urinary incontinence and sexual dysfunction. Therefore, newer advances in the field of prostate cancer have been directed towards focal therapy with an intent of balancing the patient's quality of life while treating the lesion effectively.

Focal ablation can cover a wide range of ablation strategies depending upon the location of the tumor within the prostate. The most common ablative strategies are focal, quadrant, hemiablation, and hockey-stick ablation [Figure 1].[2]

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_370_23

Received: 20.09.2023, **Revised:** 10.11.2023,

Accepted: 04.12.2023, **Published:** 29.12.2023

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

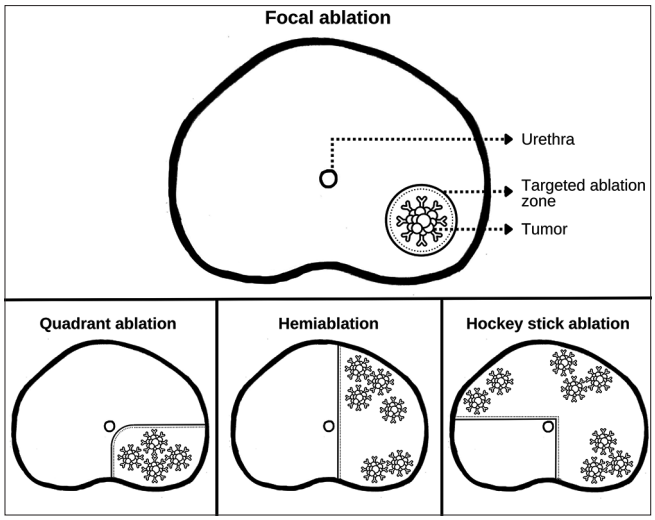

Figure 1: Types of prostate ablation

Focal therapies such as irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), cryoablation, radiofrequency ablation (RFA), photodynamic therapy (PDT), brachytherapy, and focal laser ablation (FLA) aim to preserve the noncancerous prostatic tissue as well as minimize the harm to the neurovascular bundles, urethra, urethral sphincter, and the rectum [Table 1].[3] Cryoablation, FLA, RFA, and PDT deliver localized thermal ablation but can cause nonselective injury to the tissues surrounding the target area, as they lack precision compared to the IRE. Focal therapies that rely on thermal ablation are also affected by the heat sink effect, when the area of ablation is too close to the blood vessels.[4] IRE is a relatively new focal therapy when compared to HIFU or cryoablation, which have been explored more extensively. When a cell is subjected to an electric field, a process called poration occurs, wherein nanopores are formed on the cell membrane. IRE utilizes repetitive electric pulses to create nanopores on the cell membrane and induces cell death due to membrane instability and disruption of the cellular homeostasis.[5]

HISTORY OF IRREVERSIBLE ELECTROPORATION

Nollet, in the 18th century, was the first to conduct an experiment on electroporation where he applied electrical current to the skin of an animal and observed the development of red spots.[6] Unknown to him at that time, this was the first scientific record of IRE. Following this, the principle of IRE was used to purify river water in the 19th century. High-voltage electrical pulses were found to kill bacteria and aid in the purification process without altering the temperature of the water.[7] Sale and Hamilton were the first to describe the phenomenon of IRE and how the mechanism of cell death was unrelated to a change in the temperature but was due to the irreversible damage to the cell membrane.[8-10] With this discovery, reversible electroporation was developed as one of the various methods to transfer DNA into eukaryotic cells.[11] Neumann *et al.* were the first to use electroporation to increase the membrane permeability to facilitate the transfer of DNA into mouse lyoma cells.[12] This led to the exploration of novel applications of electroporation such as electrochemotherapy where chemotherapeutic agents like bleomycin were administered using electroporation.[13-15] At this stage, the goal was to create temporary nanopores and IRE was considered as the upper electrical threshold beyond which cell death occurred due to irreversible membrane permeability.[16]

Davalos *et al.* in 2005 were the first to describe the use of IRE as a focal ablative procedure for the treatment of cancer.[17] Subsequently, multiple animal trials showed that the IRE was safe to use in close proximity to structures such as the bile duct, renal tissue, blood vessels, and hilar structures of the liver.[18-20]

PRINCIPLE BEHIND IRREVERSIBLE ELECTROPORATION

The ideal focal therapeutic approach for prostate cancer would selectively ablate the malignant cells while simultaneously preserving or minimizing the damage to the surrounding tissues. IRE is predominantly nonthermal and involves the application of a pulsed electrical field to create nanopores in the cell membrane. When the electrical field applied is beyond a certain voltage threshold, the process of poration becomes irreversible and causes membrane instability and induces cell death.[21] After the initial theories of using IRE as a focal therapy for prostate cancer, Onik *et al.* were the first to evaluate IRE in the prostatic tissue of canines. The study looked at the safety and efficacy of IRE and found that there was no heat-sink effect near the vascular tissues and the transition zone demarcating the normal from the ablated tissue was narrower as compared to the other focal ablative therapies.[22] Tsivian and Polascik were the first to evaluate the functional outcomes of low-energy direct current *in vivo* in a canine study. The study showed that the erectile function recovered between 4 and 23 days post-IRE of the prostate and the most common complication was hematuria which resolved spontaneously.[23] Onik and Rubinsky were one of the first to evaluate *in vivo* IRE in a cohort of 16 patients with organ-confined disease.[24] The post-IRE prostatic biopsy tissue was negative for cancer in all the patients.[24] Similar *in vivo* studies also showed that IRE was effective in ablating malignant cells within the targeted zone of ablation while preserving the nearby structures.[25-27]

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[28] PubMed and EMBASE were searched with the end date of May 2023 to find all the relevant publications regarding prostate cancer ablation using IRE. The search terms (Medical Subject

Table 1: Comparison of irreversible electroporation to other focal therapies

Focal therapy	Ablation principle	Approach	Periprocedural requirements	Advantages	Disadvantages
IRE	Low-energy electrical pulses cause cellular apoptosis through membrane instability	Transperineal	General anesthesia Muscle relaxant MRI or TRUS monitoring	Spares nearby neurovascular structures Can be applied to all segments of the prostate	Lacks long-term follow-up data
HIFU	High-energy ultrasound to thermally ablate tissue	Transrectal	General anesthesia	Least invasive focal therapy	Difficulty targeting anterior lesions Limited by large prostate glands
Cryotherapy	Freezing and thawing cycles cause cellular edema, crystal formation, and ischemia inducing apoptosis and necrosis	Transperineal	CT, TRUS, or MRI monitoring with thermoelectric thermometer	Active real-time monitoring Can treat large volumes	Lacks precision Difficult to target lesions in the apex, prostatic urethra, and bladder neck due to surrounding structures
PDT	Photosensitizers activated by targeted light form cytotoxic reactive oxygen species	Transperineal	General anesthesia Intravenous photosensitizer	Can be applied to all segments of the prostate	Lacks long-term follow-up data
FLA	High-energy lasers cause photothermal ablation	Transrectal or transperineal	Local anesthesia MRI-based temperature monitoring	Could potentially be performed in the office Active real-time monitoring	Limited by large prostate glands
RFA	Thermal ablation caused by frictional heating of cellular ions induced by high-frequency alternating current	Transperineal	General/spinal anesthesia TRUS	Active real-time monitoring	Lacks long-term follow-up data

IRE=Irreversible electroporation, HIFU=High-intensity focused ultrasound, PDT=Photodynamic therapy, FLA=Focal laser ablation, RFA=Radiofrequency ablation, MRI=Magnetic resonance imaging, TRUS=Transrectal ultrasound, CT=Computed tomography

Heading [MeSH] and non-MeSH) used were "irreversible electroporation" OR "IRE" OR "focal therapy" OR "focal ablation" AND "prostate" OR "PCa."

Articles were eligible if they were original studies (prospective, retrospective, and randomized trials) reporting on IRE as the primary therapy used to treat localized prostate cancer. The main outcome measures evaluated, aside from the treatment with IRE, were (1) functional outcomes (urinary incontinence or sexual function) and (2) oncological outcomes. Whole-gland treatment with IRE was excluded, as were case reports or series and review articles. In addition, articles that evaluated IRE as a salvage treatment option were also excluded. The search was also limited to articles that were published in English language and involved human patients only. Our initial search identified a total of 971 articles. After excluding duplicates, 345 articles remained. Articles were then shortlisted based on titles and 88 studies were selected to be screened for eligibility [Figure 2]. The eligibility assessment was performed by two separate authors (PP and APA). Full-text articles were reviewed and finally 14 studies were included in the review. The relevant study characteristics were extracted along with the functional and oncological outcomes and are summarized in Tables 2-4.

RESULTS

IRE has predominantly been evaluated in patients with low-to-intermediate risk localized prostate cancer.[42-44] Patient selection for IRE depends upon a number of factors such as tumor foci, prostate-specific antigen (PSA) levels, Gleason score, volume of the disease, and the clinical stage. Tay *et al.* conducted a Delphi consensus project that included 47 expert panelists on focal therapy and focused on three main domains for patient eligibility.[45] The three domains were role of biopsy/imaging, disease factors, and patient factors. In the biopsy/imaging domain, multiparametric magnetic resonance imaging (mpMRI) was the agreed upon standard tool for imaging among the expert panel with the MRI-TRUS fusion biopsy as the preferred method of biopsy.[45] Focal therapy was recommended for individuals with a PSA of ≤10 ng/ml, Gleason score ≤4 + 3 (ideal Gleason score is 3 + 4), and cancer foci of <1.5 ml (<3 ml if confined to one hemi-gland).[45]

In the studies reviewed, the highest median baseline PSA value was 8.65 ng/ml reported by Collettini *et al.* Across all the studies, there were a total of 912 patients with prostate cancer. The ISUP grade 2 was the most common in 550 patients (60.3%).[35] The patient distribution among the other grades was ISUP 1 with 183 patients (20.1%), ISUP 3 with 148 patients (16.2%), ISUP 4 with 23 patients (2.5%),

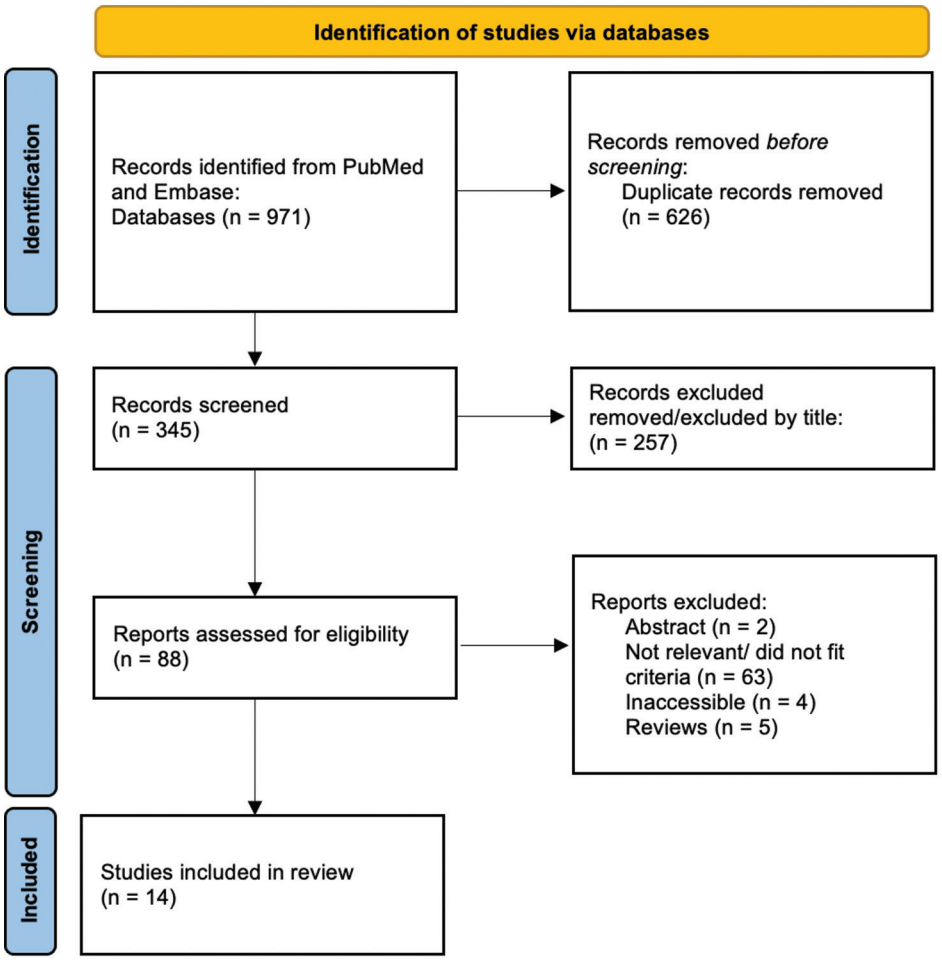

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart for study inclusion

and ISUP 5 with 8 patients (0.9%) [Table 2].[26,29-40,46,47] All the patients across all the studies underwent mpMRI and biopsy for grading and localization of the lesion prior to the procedure.

FUNCTIONAL OUTCOMES

The major functional outcomes evaluated by most of the studies which assessed the safety and efficacy of IRE for localized prostate cancer were urinary continence and sexual potency. The most commonly used validated questionnaires for the functional assessment were Expanded Prostate Cancer Index Composite, International Index of Erectile Function, and International Prostate Symptom Score [Table 3].[26,31-35,37,38,40,47]

Multiple studies have shown that IRE, as a focal therapy, reduces the functional morbidity as compared to the standard of care (RP and RT) in patients with intermediate-risk prostate cancer.[16,34] Valerio *et al.*, in one of the earlier studies evaluating IRE, reported a potency rate of 95% (19/20) and urinary continence rate of 100% (24/24) without any rectal dysfunction over a 6-month follow-up period [Table 3].[29] In studies which followed the patients serially with multiple visits, urinary incontinence was more pronounced from 6 weeks to 3 months in the postoperative period. Murray *et al.* assessed the safety and clinical outcomes in a cohort of 25 patients. The self-reported patient outcomes showed that the urinary function varied from a baseline of 77% (17/22) to 81% (13/16) at 6 months and 88% (15/17) at 12 months and similarly the erectile function varied from 59% (13/22) at the baseline to 65% (11/17) [Table 3].[30] Scheltema *et al.* conducted a propensity-score matched analysis and evaluated urinary and sexual functions based on the pad usage and erections sufficient for intercourse, respectively.[33] Over the 12-month follow-up, the pad-free urinary continence changed from 98% at the baseline to 96% and the erections sufficient for intercourse dropped from 69% at the baseline to 56%.[33] Collettini *et al.*, in their study evaluating the functional outcomes of 30 patients post-IRE, found that the leak-free continence rate was 86.2% (25/29) at 12-months follow-up compared to 90% (27/30) at the baseline.[35] Pad-free continence was 96.7% (29/30) at the baseline and 96.5% (28/29) at 12-months follow-up and the patients with erections sufficient for penetration reduced from 83.3% (25/30) at the baseline to 79.3% (23/29) at the 12-months follow-up.[35] Blazevski *et al.* in their study

Table 2: Study characteristics for all the articles within this review

Study	Study design	Population	Mean±SD/median (IQR)		ISUP grade, *n* (%)	Biopsy
			Age (years)	Baseline PSA (ng/mL)		
Valerio *et al.*[29]	Retrospective	34	65±6	6.1 (4.3–7.7)	ISUP 1: 9 (26) ISUP 2: 19 (56) ISUP 3: 5 (15) ISUP 4: 1 (3)	Targeted/template mapping
Ting *et al.*[26]	Retrospective	25	67 (60–71)	6.0 (4.3–8.6)	ISUP 1: 2 (8) ISUP 2: 15 (60) ISUP 3: 8 (32)	Targeted/template mapping
Murray *et al.*[30]	Prospective	25	63.1 (59.3–67.6)	4.3 (3.3–5.6)	ISUP 1: 18 (72) ISUP 2: 6 (24) ISUP 3: 1 (4)	Targeted/TRUS guided
Valerio *et al.*[31]	Prospective	19	60 (53–66)	7.75 (5.5–10.03)	ISUP 1: 8 (42.1) ISUP 2: 11 (57.9)	Template mapping
Scheltema *et al.*[32]	Prospective	60	68±7.0	6.0±3.3	ISUP 1: 8 (13) ISUP 2: 40 (67) ISUP 3: 10 (17) ISUP 4: 2 (3)	Template mapping
Scheltema *et al.*[33]	Prospective	50	67 (62–73)	5.9 (3.3–7.3)	ISUP 1: 8 (16) ISUP 2: 33 (66) ISUP 3: 9 (18)	Transrectal/transperineal mapping
van den Bos *et al.*[34]	Prospective	63	67 (61–71)	6 (3.2–8.4)	ISUP 1: 9 (14.3) ISUP 2: 38 (60.3) ISUP 3: 16 (25.4)	Transrectal/transperineal mapping
Collettini *et al.*[35]	Prospective	30	65.5 (60–68.8)	8.65 (5–11)	ISUP 1: 7 (23.3) ISUP 2: 23 (76.7)	Transperineal template, MRI-US fusion, transrectal US guided
Giganti *et al.* (2019 [36]	Retrospective	30	63 (60–67)	6.4 (5–8.8)	ISUP 1: 7 (23) ISUP 2: 20 (66.7) ISUP 3: 3 (10)	N/A
Blazevski *et al.*[37]	Prospective	123	68 (62–73)	5.73 (3.8–8.0)	ISUP 1: 12 (9.8) ISUP 2: 88 (71.5) ISUP 3: 23 (18.7)	TTMB, MRI-targeted
Blazevski *et al.*[38]	Prospective	50	68 (63–71)	6.25 (4.35–8.9)	ISUP 1: 5 (10) ISUP 2: 37 (74) ISUP 3: 6 (12) ISUP 4: 2 (2)	Transperineal/transrectal template biopsy
Geboers *et al.*[39]	Retrospective	217	67 (62–72)	6.2 (4.4–8.9)	ISUP 1: 28 (13) ISUP 2: 141 (65) ISUP 3: 35 (16) ISUP 4: 12 (5) ISUP 5: 2 (1)	Transperineal/transrectal template
Yaxley *et al.*[40]	Retrospective	64	72 (51–87)	6.1 (0.77–25%)	ISUP 1: 4 (6.3) ISUP 2: 33 (51.6) ISUP 3: 15 (23.4) ISUP 4: 6 (9.4) ISUP 5: 6 (9.4)	Transperineal
Wang *et al.*[41]	Prospective	109	67 (62–73)	9.0 (6.0–12.7)	ISUP 1: 47 (43.1) ISUP 2: 45 (41.3) ISUP 3: 17 (15.6)	Transperineal cognitive fusion and systematic template-guided

SD=Standard deviation, IQR=Interquartile range, TRUS=Transrectal ultrasound, MRI=Magnetic resonance imaging, ISUP=International Society of Urological Pathology, TTMB=Transperineal template mapping biopsy, US=Ultrasound, N/A=Not available, PSA=Prostate-specific antigen

with the largest patient cohort and a 12-month follow-up, examined the functional outcomes and found that the pad-free incontinence, leak-free incontinence, and the potency rates were 98.8% (80/81), 93.3% (70/75), and 76% (40/53), respectively.[37] In the most recent study by Yaxley *et al.*, at 12-months of follow-up, none of the patients had urinary incontinence and 85.7% (24/28) retained sexual function which was adequate for intercourse.[40] Across all the studies reviewed, most reported that the urinary continence returned to the pretreatment rates and only a handful of studies reported a minor decline in the continence rates from the baseline at the 12-month follow-up [Table 3].[30,33,37,38]

ONCOLOGICAL OUTCOMES

IRE has been proven to be effective in ablating significant cancers, however, the multifocal nature of the prostate cancer can cause challenges.[43] Oncological outcomes, across all the studies, were measured as recurrence within the field and outside the field of ablation along with a decrease in the PSA levels post-IRE. The longest median follow-up period was 44 months reported by Blazevski *et al.* Seven studies evaluated the outcomes at 12-month post-IRE and the shortest follow-up period (6 months) was reported in one of the older studies by Valerio *et al.* [Table 4].[29,31,33,34,38-40,47] The

Table 3: Functional outcomes

Study	Urinary continence post-IRE	Postprocedural sexual function	Complications
Valerio *et al.*[29]	Urinary continence (6 months): 24/24 (100%)	Sexual potency: 19/20 (95%)	CTCAE I: 12 (35%) CTCAE II: 10 (29%)
Ting *et al.*[26]	Pad free (baseline): 100% Pad free (6 weeks): 94% Pad free (3 months): 94% Pad free (6 months): 100% Leak free (baseline): 67% Leak free (6 weeks): 53% Leak free (3 months): 65% Leak free (6 months): 67%	Erections sufficient for intercourse (baseline): 44% Erections sufficient for intercourse (6 weeks): 38% Erections sufficient for intercourse (3 months): 47% Erections sufficient for intercourse (6 months): 56%	Clavien–Dindo 1: 5 (20%) Clavien–Dindo 3: 1 (4%)
Murray *et al.*[30]	Urinary function (score≥17) Baseline: 17/22 (77%) 6 months: 13/16 (81%) 12 months: 15/17 (88%)	Erectile function (score≥22) Baseline: 13/22 (59%) 6 months: 7/16 (44%) 12 months: 11/17 (65%)	30-day period Clavien–Dindo 1: 6 Clavien–Dindo 2: 7 Clavien–Dindo 3: 1 90-day period Clavien–Dindo 1: 0 Clavien–Dindo 2: 1 Clavien–Dindo 3: 1
Valerio *et al.*[31]	Pad free (baseline): 16/16 (100%) Pad free (12 months): 16/16 (100%) Leak free (baseline): 16/16 (100%)	Erections sufficient for penetration (baseline): 12/16 (75%) Erections sufficient for penetration (12 months): 11/16 (69%)	CTCAE I: 14 CTCAE II: 19
Scheltema *et al.*[32]	Pad free (baseline): 58/60 (97%) Pad free (6 months): 57/60 (95%) Pad free (12 months): 58/60 (97%)	Erections sufficient for penetration (baseline): 40/60 (66%) Erections sufficient for penetration (12 months): 27/40 (68%)	N/A
Scheltema *et al.*[33]	Pad free (baseline): 100% Pad free (6 weeks): 89% Pad free (3 months): 98% Pad free (6 months): 100% Pad free (12 months): 100%	Erections sufficient for intercourse (baseline): 69% Erections sufficient for intercourse (6 weeks): 40% Erections sufficient for intercourse (3 months): 54% Erections sufficient for intercourse (6 months): 49% Erections sufficient for intercourse (12 months): 56%	Clavien–Dindo 1: 11 Clavien–Dindo 2: 7
van den Bos *et al.*[34]	Pad free (6 months): 44/45 (98%) Pad free (12 months): 45/45 (100%) EPIC urinary (baseline): 92 EPIC urinary (3 months): 91 EPIC urinary (6 months): 93 EPIC urinary (12 months): 94	Erections sufficient for intercourse (baseline): 31/44 (70%) Erections sufficient for intercourse (3 months): 24/44 (55%) Erections sufficient for intercourse (6 months): 20/43 (46%) Erections sufficient for intercourse (12 months): 10/19 (55%) EPIC sexual (baseline): 66 EPIC sexual (3 months): 50 EPIC sexual (6 months): 54 EPIC sexual (12 months): 48	CTCAE I: 24% CTCAE II: 11%
Collettini *et al.*[35]	Pad free (6 months): 28/30 (93.3%) Pad free (12 months): 28/29 (96.5%) Pad free (24 months): 12/12 (100%) Leak free (6 months): 25/30 (83.3%) Leak free (12 months): 25/29 (86.2%) Leak free (24 months): 12/12 (100%)	Erections sufficient for penetration (6 months): 25/30 (83.3%) Erections sufficient for penetration (12 months): 23/29 (79.3%) Erections sufficient for penetration (24 months): 12/12 (100%)	CTCAE I: 2 CTCAE II: 3 CTCAE III: 1
Blazevski *et al.*[37]	Pad free (12 months): 80/81 (98.8%) Leak free (12 months): 70/75 (93.3%)	Sexual potency (12 months): 40/53 (76%)	Clavien–Dindo 1: 22% Clavien–Dindo 2: 9%
Blazevski *et al.*[38]	Pad free (baseline): 50/50 (100%) Pad free (3 months): 48/50 (96%) Pad free (12 months): 49/50 (98%) Leak free (baseline): 40/40 (100%) Leak free (3 months): 33/40 (83%) Leak free (12 months): 38/40 (95%)	EPIC sexual (baseline): 65 EPIC sexual (12 months): 59 Erections sufficient for intercourse (12 months): 30/32 (94%)	Clavien–Dindo 1: 10 (20%) Clavien–Dindo 2: 9 (18%)
Yaxley *et al.*[40]	Urinary incontinence (0%)	Sexual potency (baseline): 28/50 (56%) Sexual potency (12 months): 24/28 (85.71%)	Clavien–Dindo>2: 1
Wang *et al.*[41]	IPSS (baseline), median (IQR): 9 (4–15) IPSS (6 months), median (IQR): 4.5 (2–9.5)	IIEF-5 (baseline), median (IQR): 2 (1–18) IIEF-5 (6 months), median (IQR): 2 (0.5–12.5)	Clavien–Dindo 1: 33 (30.3%) Clavien–Dindo 2: 7 (6.4%) Clavien–Dindo 3: 1 (0.9%)

CTCAE=Common terminology criteria for adverse events, IQR=Interquartile range; EPIC=Expanded Prostate Cancer Index Composite, IIEF=International Index of Erectile Function, IPSS=International Prostate Symptom Score, N/A=Not available

median pre-treatment PSA, among the articles reviewed, ranged from 4.3 to 8.65 ng/ml. The method of recording follow-up PSA values varied and were either presented as median values in six studies and the rest reported the median PSA nadir [Table 4].[26,29-31,33-35,37-40,47] Across all the studies, a reduction in the PSA levels was noted at the follow-up

Table 4: Oncological outcomes

Study	Prostate volume (cc), mean±SD/ median (IQR)	Safety margin (mm)	Outcomes	Post-IRE PSA, median (IQR)	Post-IRE follow-up and monitoring	Follow-up time (months), median (IQR)
Valerio *et al.*[29]	42.4±14.6	3–5	N/A	3.4 (1.9–4.8)	Contrast-enhanced MRI at 1 week PSA every 3 months mpMRI at 6 months	6 (1–24)
Ting *et al.*[26]	43 (32–60)	5	In-field recurrence: 0 Adjacent to the field (<10 mm): 5/24 (21%) Out-of-field recurrence: 2/24 (8%)	2.2 (1.0–5.0)	T2-weighted MRI at 1 week PSA at 3 and 6 months mpMRI at 6 months TTMB at 7 months	8
Murray *et al.*[30]	40.5 (27.4–59)	5	In-field recurrence: 4/25 (16%) Out-of-field recurrence: 7/25 (28%)	2.2 (1.1–3.8)	PSA at 3 and 6 months MRI between 4 and 6 weeks TTMB at 6 months	10.9 (6.7–19.3)
Valerio *et al.*[31]	40 (29–51)	5	In-field recurrence: 7/18 (38.9%) No residual cancer: 11/18 (61.1%)	1.71 (1.33–4.67)	Contrast-enhanced MRI between 3 and 10 days Serial PSA at 6 weeks, 3, 6, 9, and 12 months mpMRI done at 6 months	12
Scheltema *et al.*[33]	35 (30–50)	N/A	Significant residual PCa: 13/44 (29.5%)	2.8 (0.9–4.5)	Serial PSA monitoring Transperineal biopsy at 12 months	12
Van den Bos *et al.*[34]	43 (30–60)	5–10	In-field PCa: 4/55 (7.3%) Out-of-field PCa: 2/55 (3.6%) Both in and out-of-field PCa: 2/55 (3.6%)	1.8 (0.96–4.8)	T2-weighted MRI at 1 week Serial PSA monitoring mpMRI at 6 months TTMB, TRUS, or targeted biopsy between 6 and 12 months	12
Collettini *et al.*[35]	N/A	N/A	In-field recurrence: 5/30 (16.67%) Out-of-field recurrence: 2/30 (6.7%) Required second IRE: 1/30 (3.3%) Required prostatectomy: 4/30 (13.3%)	6 months: 2.7 (1–4) 12 months: 2.35 (1–3) 24 months: 2.35 (1–3)	Serum PSA at 6 months and every 3 months mpMRI at 6 and 12 months TRUS biopsy at 6 months	20 (14–29)
Giganti *et al.*[36]	N/A	N/A	Tumor recurrence: 9/30 (30%) Required re-treatment: 4/30 (13%)	N/A	mpMRI within 10 days and at 6 months PSA every 3 months TTMB for rise in PSA or≥4 PIRADS	16 (6–24)
Blazevski *et al.*[37]	40 (30–60)	5–10	In-field lesion: 3/112 (2.6%) Adjacent-field lesion: 6/112 (5.4%) Out-of-field lesion: 11/112 (9.8%) Failure-free survival (3 years): 96.75% Metastasis-free survival (3 years): 68/69 (98.5%) Overall survival (3 years): 69/69 (100%)	3.48 (1.43–5.67)	PSA every 3 months for the first 2 years mpMRI at 6 months TTMB with targeted biopsy at 12 months	36 (24–52)
Blazevski *et al.*[38]	39 (30–60)	10	In-field recurrence: 1/40 (2.5%) Out-of-field recurrence: 8/40 (20%)	1.8 (0.84–3.35)	T2-weighted MRI within 7 days PSA every 3 months for the first 2 years mpMRI at 6 months Transperineal biopsy plus additional biopsy of the ablation zone and margins between 6 and 12 months	44 (30–60)
Geboers *et al.*[39]	42 (30–62)	5–10	Significant in-field PCa: 21/217 (9.7%) Significant out-of-field PCa: 14/217 (6.5%) Significant both in and out-of-field PCa: 4/217 (1.8%)	2.3 (1.3–4.7)	PSA every 3 months mpMRI at 6 months Template biopsy at 12 months	12

Contd...

Table 4: Contd...

Study	Prostate volume (cc), mean±SD/ median (IQR)	Safety margin (mm)	Outcomes	Post-IRE PSA, median (IQR)	Post-IRE follow-up and monitoring	Follow-up time (months), median (IQR)
Yaxley *et al.*[40]	40 (15–82)	5	Significant in-field PCa: 4/40 (10%) Significant out-of-field PCa: 5/40 (12.5%)	1.3 (0.07–7.20)	mpMRI at 6 months TTMB at 12 months	23 (3–39)
Wang *et al.*[41]	38.1±17.1	N/A	Significant in-field PCa: 1/100 (1%) Significant out-of-field PCa: 5/100 (5%)	1.1 (0.4–3.2)	PSA at 1 week, 1, 3, and 6 months MRI at 1 and 6 months Cognitive fusion targeted and systematic template-guided biopsy with 3 cores of the ablation zone at 6 months	6

IQR=Interquartile range, PSA=Prostate-specific antigen, TTMB=Transperineal template mapping biopsy, SD=Standard deviation, PIRADS=Prostate imaging reporting and data system, N/A=Not available, MRI=Magnetic resonance imaging, mpMRI=Multiparametric MRI, TRUS=Transrectal ultrasound, IRE=Irreversible electroporation, PCa=Prostate Cancer

as compared to the initial baseline values. Geboers *et al.* evaluated one of the largest (n = 217) retrospective cohorts and reported a change in the PSA levels from a median value of 6.2 ng/ml at the baseline to a nadir of 2.3 ng/ml at 12-months of follow-up.[39] Blazevski *et al.* assessed the outcomes in a cohort of 123-patients and found a decline in the PSA levels from a median baseline of 5.7 ng/ml to a nadir of 3.48 ng/ml.[37] Finally, in a more recent study, Yaxley *et al.*[40] recorded a decline in the PSA levels from a median of 6.1 ng/ml at the baseline to a nadir of 1.3 ng/ml at 12-months follow-up.

The majority of the studies characterized in-field recurrence as the presence of significant prostate cancer recurring within the zone of ablation and out-of-field recurrence as either adjacent to the ablation zone or at a different segment of the prostate on the per protocol biopsy performed post-treatment [Table 4].[33,39,40] Among the studies reporting in-field and out-of-field recurrence, the range was from 0% to 38.9% and 3.6% to 28%, respectively [Table 4].[26,29-31,33-40,47] Predominantly, two definitions were used to characterize significant prostate cancer at recurrence, with the first being an ISUP grade ≥1 recurrence with a mean core length of 6 mm or higher as reported by four studies.[26,35,39,40,48] Blazevski *et al.* in their two studies considered a Gleason score of ≥3 + 4 as significant cancer whereas the rest of the studies considered a score of ≥3 + 3 as significant prostate cancer.[30,31,34,35,41] For early follow-up and monitoring post-IRE, a contrast-enhanced MRI or T2-weighted MRI was obtained to evaluate the zone of ablation.[26,29,31,34,36,38] Some of the older studies reported by Valerio *et al.*, Ting *et al.*, and Van den Bos *et al.* obtained a MRI (contrast enhanced or T2 weighted) at 1 week posttreatment to evaluate the zone of ablation.[26,29,34] PSA levels were monitored serially in all the studies at a 3-monthly intervals with Blazevski *et al.* monitoring the PSA levels for a period of up to 2 years post-treatment.[26,29-41] All of the studies also required a mpMRI at 6 months post-IRE and most of them required a prostate biopsy at 12 months as part of the follow-up protocol [Table 4].[26,29-41]

On evaluating the distribution of patients among various ISUP Gleason grade groups among all the studies, maximum patients belonged to ISUP grade 2 with 405 patients. Patient distribution among the rest of the groups was as follows: ISUP 1 (136 patients), ISUP 3 (131 patients), ISUP 4 (23 patients), and ISUP 5 (6 patients).[26,29-40,46,47] Most studies had a minimum safety margin of 5 mm and the lowest margin was of 3–5 mm as reported by Valerio *et al.* in their 2014 study.[29] Three out of the 14 studies that reported oncological outcomes did not report on the margin of safety. The more recent studies have employed a 10-mm safety margin with at least a 5-mm margin when the electrode needle is placed close to vital structures [Table 4].[37-39]

COMPLICATIONS

The common acute complications or adverse events associated with IRE were urinary retention, hematuria, dysuria, and urinary tract infection (UTI). The incidence of urinary retention after IRE ranged from 5.6% to 26.3%, and the rate of UTI was between 9% and 11%.[26,29-31,34,35,37] The rate of hematuria and dysuria ranged between 6.7%–24% and 15%–26.3%, respectively.[26,29,31,34,35] Other infrequent complications were pain in the perineal area and in rare cases a urethral stricture (2%–5.2%) or rectourethral fistula (0.2%) were also reported.[42,44] All the reviewed studies recorded adverse events using the Clavien–Dindo or the Common Terminology Criteria for Adverse Events grading systems and predominantly grade 1 and grade 2 complications were reported across all the studies.[26,29-38,40,47] A single grade 3 complication each, during the period of the study, was reported by Ting *et al.* (non-ST elevation myocardial infarction), Murray *et al.* (epididymitis leading to abscess formation), and Collettini *et al.* (urethral stricture requiring urethrotomy).[26,30,35]

DISCUSSION

The current contemporary management options for patients with prostate cancer comprise of active surveillance, RP, and RT. Depending upon where the patient falls on the spectrum of disease severity, the treatment recommendations differ. While these treatment options provide the highest oncological outcomes, they do have certain pitfalls. Active surveillance protocols are ideal for low-risk prostate cancer with a small chance of progression. The drawback is that the concept of watchful waiting without any treatment can impact the mental status of the patient leading to anxiety and psychological stress from serial biopsies and PSA monitoring.[49,50] In comparison, radical treatment for low-risk prostate cancer can lead to undesired functional outcomes such as urinary incontinence and sexual dysfunction and in certain cases can result in overtreatment.[51] In this setting, IRE and the other focal therapies can help in addressing the shortcomings of both, the active surveillance and radical whole-gland treatment options.

Prostate cancer is multifocal in nature, but studies have shown that the disease progression is dependent on a single focus of cancer within the gland called the index lesion.[52,53] Liu *et al*. were among the first to identify that the disease progression for metastatic prostate cancer was influenced by a single precursor cell originating within the index lesion in the prostate gland.[54] Masterson *et al*. evaluated the role of tumor focality on disease progression and tumor aggressiveness and did not find a significant association.[55] Recent advances in imaging and biopsy modalities have vastly improved the ability to map the index lesion within the prostate.[43] mpMRI, in conjunction with targeted and mapping biopsies, has been shown to be accurate and reliable with detection rates over 90% in centers of excellence.[56] Furthermore, these diagnostic tests together have the ability to accurately (more than 90%) delineate clinically significant cancer within the various zones of the prostate.[56] This supports the rationale to use IRE to treat the index lesion within the prostate and influence disease progression.[57]

Focal therapies with thermal ablative techniques are susceptible to thermal or heat sink effects. If the zone of ablation is close to large vessels, there can be thermal fluctuations, thereby reducing the ablative efficacy.[4] IRE is not affected by the heat sink effect because the mechanism of inducing cell death is different from most of the other focal therapies (nonselective thermal cellular destruction).[16] Another advantage of IRE as a focal therapy is the ability to target lesions close to vital structures such as neurovascular tissue, the urethra, and the rectum with precision.[5,22] In contrast to thermal ablative modalities, IRE has a very narrow transition zone between the region of ablation and the normal tissue parenchyma.[51] The zone of ablation in IRE is sharply demarcated and a uniform necrotic and fibrotic tissue is present post-IRE.[58] Most studies employ a minimum safety margin of 5–10 mm with a 5-mm margin being reserved for lesions closer to the vital structures.[38-40] Van den Bos *et al*. showed that despite the high precision offered by IRE, a safety margin of 10 mm had lower in-field recurrences.[34] The IRE procedure can be monitored in real time using ultrasound which may not be possible for some of the other focal therapies. This is especially beneficial in an event of movement of the IRE procedure needles which can be repositioned into the target ablation zone again. The zone of ablation, during the short- and medium-term follow-up, can also be visualized on mpMRI and contrast-enhanced ultrasound.[36,59]

Very few post-procedural adverse events have been reported in patients with prostate cancer treated with IRE. The rates of urinary retention are similar to the other focal therapies such as HIFU (0.7%–35.7%), cryotherapy (8.5%), PDT (11.1%), and FLA (10.2%).[60-62] Similarly, the rates of UTI range between 0% and 17% for all the other focal therapies which is comparable to that reported among the reviewed IRE studies (9%–11%). Another infrequent early complication among the focal therapies was urethral stricture with a rate of up to 5.2% in the IRE studies as compared to 23.8% in HIFU and 3.2% in the cryotherapy groups.[61] Only one study in the IRE series reported a recto-urethral fistula (0.2%), whereas for the other focal therapies, the rate varied between 0% and 1%.[60]

A few studies explored the outcomes and feasibility of salvage treatments post-IRE and the use of IRE as a salvage treatment.[38-40,63-66] Primary treatment with IRE was not found to significantly alter the structural matrix or cause a cavity in the ablated zone. The ablated regions develop necrotic scar tissue without any distortion of the noncancerous tissues.[5] Studies examining the use of salvage robot-assisted RP following primary IRE did not find an increase in the surgical difficulty. Also, the oncological and functional outcomes were comparable to those seen in robot-assisted RP performed in the primary settings.[63,64] In addition, IRE is a safe and effective salvage treatment option for radio-recurrent localized prostate cancer and has been used as salvage treatment option following RP, RT, and other focal therapies successfully.[39,65,66]

Limitations

The studies included in this review were heterogeneous which limited the ability of a direct comparison or pooled analysis. Focal therapies such as IRE are also performed for low-risk prostate cancer and as such should only be used when the treatment is required. Another limitation is that the IRE is a newer experimental treatment modality and the patient cohorts are small. Also, the attrition to follow-up has further limited the available data evaluating its outcomes. In addition, IRE being a relatively new modality, is marred by the learning

curve which could negatively affect the oncological outcomes in the early learning phase. The other pitfall with IRE is the lack of 10-15 year long-term follow-up data to allow for ideal comparisons with the standard of care. Furthermore, there are no studies in the available literature comparing IRE to the standard of care in a randomized controlled trial setting.

CONCLUSION

IRE, as a focal therapy for prostate cancer, is still relatively new and the first human trial was reported in 2010, and the phase I–II trials were reported 2013 onwards. In addition, IRE as with any new treatment modality comes with a learning curve for physicians. Accordingly, the oncological and functional outcomes of IRE will potentially get better with time as the volume of patients undergoing the procedure increases. Similarly, the learning curve for IRE will also get shorter with time. Until recently, IRE was primarily used to treat low-risk and intermediate-risk prostate cancer but recent studies have included high-risk prostate cancer patients also.[38-40] This opens up the possibility to offer IRE to high-risk patients if they have favourable disease parameters amenable to focal ablation. Most of the studies evaluating IRE belong to the early experimental research stage. Despite this, the results demonstrate promising functional outcomes with minimal complications and reasonably effective oncological control, however, these are marred by a lack of comparison to the standard of care. Future research should focus on randomized definitive comparisons between IRE, RP, and RT.

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How to cite this article: Prabhakar P, Avudaiappan AP, Sandman M, Eldefrawy A, Caso J, Narayanan G, *et al*. Irreversible electroporation as a focal therapy for localized prostate cancer: A systematic review. Indian J Urol 2024;40:6-16.