NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for treating prostate cancer

Prostate cancer is often diagnosed before symptoms develop, but it may present with problems in passing urine or difficulties with sexual function. In this procedure, needles are inserted into the prostate and short electrical pulses of high-voltage current are passed through to create tiny holes in the cancer cells. The aim is to kill the cancer cells without damaging the structure of the prostate.

Contents

Abbreviations

Word or phrase	Abbreviation
American Urological Association	AUA
Common terminology criteria for adverse events	CTCAE
Erectile dysfunction	ED
Erection sufficient for intercourse	ESI
Expanded Prostate Cancer Index Composite	EPIC
High intensity focused ultrasound	HIFU
International Index of Erectile Function	IIEF-5
International Prostate Symptom score	IPSS
International Society of Urological Pathology	ISUP
Interquartile range	IQR
Irreversible electroporation	IRE
Prostate-specific antigen	PSA
Prostate cancer	PCa
Quality of life	QoL
Robot-assisted radical prostatectomy	RARP
Short form-12 questionnaire	SF-12
Transperineal template-guided prostate mapping biopsy	TTMB
Urinary tract infection	UTI
Vascular-targeted photodynamic therapy	VTP

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2022.

Procedure name

- Interventional procedure overview of irreversible electroporation for treating prostate cancer

Professional societies

- British Society of Interventional Radiology
- British Association of Urological Surgeons
- British Uro-oncology Group
- Royal College of Radiologists

Description of the procedure

Indications and current treatment

Prostate cancer is the most common cancer in men in the UK, with 50% of diagnoses in people aged 70 years and over. Most prostate cancers are either localised or locally advanced at diagnosis. Localised prostate cancer does not usually cause any symptoms, but some people might have some urinary problems or erectile dysfunction. Some people may not identify as men but may have a prostate.

The NICE guideline on prostate cancer describes recommendations for the diagnosis and management of prostate cancer. Current treatments for localised prostate cancer include active surveillance, radical prostatectomy, external beam radiotherapy, brachytherapy, and ablation of the whole gland using cryotherapy or HIFU. Hormone therapy (androgen deprivation or anti-androgens) is usually the primary treatment for metastatic prostate cancer, but is increasingly being used for locally advanced, non-metastatic disease.

What the procedure involves

The aim of irreversible electroporation is to destroy cancerous cells by subjecting them to a series of short electrical pulses using high-voltage direct current. This creates multiple holes in the cell membrane, irreversibly damaging the cell's homeostatic mechanisms and leading to cell death.

The procedure is done with the person under general anaesthesia. A neuromuscular blocking agent is essential to prevent uncontrolled severe muscle contractions caused by the electric current. A number of electrode needles (typically 3 to 5) are introduced transperineally and inserted into, and adjacent to, the tumour in the prostate using image guidance. A series of very short electrical pulses is delivered over several minutes to ablate the tumour. The electrodes may then be repositioned to extend the zone of electroporation until the entire tumour and an appropriate margin have been ablated. Cardiac synchronisation is used to time delivery of the electrical pulse within the refractory period of the heart cycle, to minimise the risk of arrhythmia.

Efficacy summary

Survival and recurrence

In a systematic review of 7,383 patients with prostate cancer, cancer-specific survival for IRE was 98% (95% CI 94% to 102%; 2 studies, n=48, median follow up 6 to 7 months; I^2=0%, p=0.966), overall survival was 99% (95% CI 98% to 101%; 3 studies, n=171, median follow up 6 to 36 months; I^2=0%, p=0.736), failure-free survival was 90% (95% CI 83% to 98%; 3 studies, n=575, median follow up 6 to 72 months; I^2=87.8%, p=0.000) and metastasis-free survival was 99% (95% CI 98% to 101%; 2 studies, n=146, median follow up 6 to 36 months; I^2=0%, p=0.665; Guo 2021).

In a case series of 429 patients with prostate cancer and 471 IRE treatments, there were recurrences in 10% (47/471) of treatments; 3 were in patients with Gleason scores of 6, 18 were in patients with Gleason scores of 7, and 26 were in patients with Gleason scores of greater than 7 (with higher scores indicating greater severity). Of these recurrences, 27 were in or adjacent to the IRE field (1 in a patient with Gleason 6 score, 10 in patients with Gleason 7 scores, and 16 in patients with Gleason scores greater than 7). Estimated recurrence-free survival at 5 years according to Kaplan–Meier analysis was 95% for low grade cancer (Gleason score 6), 85% for intermediate grade cancer (Gleason score 7) and 61% for high grade cancer (Gleason score >7; Guenther 2019).

In a case series of 123 patients, failure-free survival at 3 years after IRE was estimated at 97% in Kaplan–Meier analysis. Metastasis-free survival was 99% (68/69) at 3-year follow up and overall survival was 100% (69/69) at 3-year follow up (Blazevski 2020).

In a case series of 50 patients, failure-free survival in patients with greater than 3-year follow up was 90% (36/40; Blazevski 2021).

Biopsy outcomes

In the systematic review of 7,383 patients with prostate cancer, the pooled proportion of positive biopsy after procedure in patients with IRE was 24% (95% CI 18% to 31%; 5 studies, n=193; I^2=0%, p=0.734) with median follow up across studies ranging from 7 to 20 months (Guo 2021).

In the case series of 123 patients, 78% (79/102) of patients having biopsy were free of clinically significant cancer, 10% (10/102) had significant in-field disease and 13% (13/102) had significant in-field disease at 12-month follow up (Blazevski 2020).

In a non-randomised cohort study of 100 patients, 29.5% (13/44) of the people having biopsy had residual PCa at 12 months, and 1 patient was diagnosed with metastatic disease directly after IRE because of persisting elevated PSA (>10 nanograms/ml; Scheltema 2018a).

In a case series of 63 patients, 78% (79/102) of people having biopsy were free of clinically significant cancer, 16% (7/45) had significant in-field disease and 10% (4/41) had significant out-of-field disease at 6 to 12-month follow up (van den Bos 2018).

MRI outcomes

In the case series of 123 patients, 80% (90/102) of patients who had MRI had clear scans, 3% (3/112) had in-field lesions, 5% (6/112) had adjacent-to-field lesions, 10% (11/112) had out-of-field lesions and 5% (6/112) had both in and out-of-field lesions at 6-month follow up (Blazevski 2020).

In the case series of 63 patients, 86% (47/55) of patients who had an MRI were free of lesions, 7% (4/55) had in-field lesions, 4% (2/55) had out-of-field lesions and 4% (2/55) had both in-field and out-of-field lesions at 6-month follow up (van den Bos 2018).

In the case series of 50 patients, 86% (43/50) of patients who had an MRI were free of lesions, and 14% (7/50) had in-field lesions (Blazevski 2021).

Reduction in PSA

In the case series of 123 patients, there was a reduction in median PSA levels of 57% to 2.5 nanograms/ml (IQR 1.43 to 5.675 nanograms/ml) at 12-month follow up from an initial baseline value of 5.7 nanograms/ml (Blazevski 2020).

In the non-randomised comparative study of 100 patients, there was a reduction in median PSA of 51% (IQR 28 to 85%) to 2.8 nanograms/ml at 12-month follow up in patients who had IRE from a baseline value of 5.9 nanograms/ml (IQR 3.3 to 7.3; Scheltema 2018a).

In a case series of 63 patients, there was a reduction in median PSA of 70% to 1.8 nanograms/ml (IQR 0.96 to 4.8 nanogram/ml) at 6 to 12-month follow up from an initial baseline value of 6 nanograms/ml (IQR 3.2 to 8.4; Scheltema 2018b).

In the case series of 50 patients, there was a reduction in median PSA of 71% to 1.7 nanograms/ml (IQR 0.84 to 3.35) from a baseline value of 6.25 nanograms/ml (IQR 4.35 to 8.9; Blazevski 2021).

Safety summary

Recto-prostatic fistula

In the case series of 429 patients and 471 IRE treatments, recto-prostatic fistula was reported in 1 patient (Guenther 2019).

Bladder perforation

In the case series of 429 patients and 471 IRE treatments, bladder perforation by catheter recto-prostatic fistula was reported in 1 patient (Guenther 2019).

Severe prostatitis

In the case series of 429 patients and 471 IRE treatments, severe prostatitis was reported in 1 patient (Guenther 2019).

Permanent urinary retention

In the case series of 429 patients and 471 IRE treatments, permanent urinary retention was reported in less than 1% (4/471) of treatments (Guenther 2019).

Urinary incontinence

In the non-randomised comparative study of 100 patients, pad-free continence rates were 98%, 87%, 96%, 98% and 96% at baseline, 6 weeks, 3 months, 6 months, and 12 months respectively; these values increased to 100%, 89%, 98%, 100% and 100% respectively in those continent at baseline (Scheltema 2018a).

In the case series of 429 patients and 471 IRE treatments, 8% (12/155) of the evaluated patient IPSS (scored 0 to 35, whereby a higher score indicates more severe urinary symptoms) increased temporarily from below 8 to above 19 (severe symptoms) after IRE. In patients fully continent before IRE, no urinary incontinence was seen 12 months after IRE (Guenther 2019).

Erectile dysfunction

In the case series of 429 patients and 471 IRE treatments, there was a mean points change in IIEF-5 score (measured 5 to 25, whereby 5 indicates severe ED and 25 indicates no ED) of -8.7 points up to 18-months follow up, and a change of -3.9 points after 18-month follow up (p=0.045).

In the same study, 45% (56/124) of patients reported reduction of ED, 11% (14/124) experienced transient severe ED (which resolved in 12 months), and 3% (4/124) experienced ED that persisted for longer than 12 months (Guenther 2019).

In the non-randomised comparative study of 100 patients, ESI rates were 69%, 40%, 54%, 49% and 56% at baseline, 6 weeks, 3 months, 6 months and 12 months respectively; these values increased to 100%, 57%, 74%, 65% and 72% respectively in those potent at baseline (Scheltema 2018a).

In a case series of 63 patients, the median EPIC sexual function summary scores (scored 1 to 100, with 100 indicating greater sexual function) were 66 (IQR 47 to 85), 50 (IQR 27 to 75), 54 (IQR 29 to 72) and 48 (IQR 15 to 77) at baseline, 3 months, 6 months, and 12 months respectively ($p<0.001$ for significance between baseline and 6 months; van den Bos 2018).

In the same study, ESI rates were 70% (31/44), 55% (24/44), 46% (20/43) and 53% (10/19) at baseline, 3 months, 6 months and 12 months respectively. Impotence was present in 31% (8/26) of surveyed patients at 6 months, and 23% (3/13) at 12 months (van den Bos 2018).

In the case series of 60 patients, EPIC sexual domain scores were 60 (IQR 25 to 82), 52 (IQR 29 to 71), 46 (IQR 14 to 79) and 27 (IQR 2 to 79) for anterior segments at baseline, 3 months, 6 months and 12 months respectively, with a statistically significant difference between baseline and 6 months (p=0.03; Scheltema 2018b).

In the case series of 50 patients, EPIC sexual scores were 65, 46, 51,57, 59 and 76 at baseline, 6 weeks, 3 months, 6 months,12 months and 24 months respectively, with a statistically significant difference between baseline and 12 months after IRE (p=0.001; Blazevski 2021).

Other adverse events

Moderate

In the case series of 429 patients and 471 IRE treatments, 1 patient reported prostatitis, 1 patient reported proctitis, less than 1% (3/471) reported epididymitis,

1 patient reported pseudo post-vasectomy syndrome, and UTI was reported in 3% (12/471) of treatments (Guenther 2019).

In the case series of 123 patients, 9% (11/123) of patients reported Clavien-Dindo grade 2 complications, which included UTI, incontinence, and acute urinary retention (Blazevski 2020).

In the non-randomised comparative study of 100 patients,14% (7/50) reported Clavien-Dindo grade 2 complications, which included UTI and severe postoperative pain related to the indwelling catheter (Scheltema 2018a).

In the case series of 63 patients, 11% (7/63) reported CTCAE grade 2 complications, which included UTIs, more severe urgency or frequency complaints, epididymitis, incontinence in 1 patient at 6 months (which resolved within 12 months), and prolonged catheterisation because of urinary retention in 1 patient (van den Bos 2020).

In the case series of 50 patients, 18% (9/50) of patients reported Clavien-Dindo grade 2 complications, which included UTI, severe urgency or frequency, and incontinence (Blazevski 2020).

Mild

In the case series of 429 patients and 471 IRE treatments, mild haematuria was reported in 4% (18/471) of treatments, transient urinary retention was reported in 9% (43/471) of treatments and dysuria was reported in 7% (32/471) of treatments (Guenther 2019).

In the case series of 123 patients, 22% (27/123) of patients reported Clavien-Dindo grade 1 complications, which included perineal pain, haematuria, dysuria, and urgency or frequency (Blazevski 2020).

In the non-randomised comparative study of 100 patients, 22% (11/50) of patients reported Clavien-Dindo grade 1 complications, which included mild haematuria, urgency, and postoperative pain (Scheltema 2018a).

In a case series of 63 patients, 24% of patients reported CTCAE grade 1 complications, which included haematuria, dysuria, urgency or frequency complaints and perineal pain (van den Bos 2018).

In the case series of 50 patients, 20% (10/50) of patients reported Clavien-Dindo grade 1 complications, which included dysuria, haematuria, urgency, and postoperative pain (Blazevski 2020).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly happen, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse event: rectal injury.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to irreversible electroporation for treating prostate cancer. The following databases were searched, covering the period from their start to March 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with prostate cancer
Intervention/test	Irreversible electroporation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 6,658 patients (in which 828 patients had IRE) from 1 systematic review, 1 non-randomised comparative study and 5 case series (after accounting for patient overlap between studies).

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on irreversible electroporation for treating prostate cancer

Study 1 Guo (2021)

Study details

Study type	**Systematic review and meta-analysis**
Country	Australia, UK, Netherlands, Switzerland, USA, Germany, Russia, Romania, Slovenia, Italy, Turkey, China, France, Canada, Brazil, Israel, Sweden, Singapore, Belgium, Japan
Recruitment period	2001 to 2019
Study population and number	n=7,383 patients with prostate cancer across 56 studies (22 studies including 2870 patients on cryoablation, 19 studies including 3012 patients on high intensity focused ultrasound (HIFU), 8 studies including 768 patients on IRE and 7 studies including 733 patients on VTP).
Age and sex	IRE median age across all studies: 63 to 68 years
Patient selection criteria	Inclusion criteria: Randomised controlled trials (RCTs), prospective case series, and retrospective case series; use of CA, HIFU, IRE or VTP in a total or subtotal manner (focal, quadrant, hemi-ablation, etc.); (3) patients with biopsy-proved prostate cancer; outcomes including positive biopsy after procedure, biochemical recurrence-free survival, cancer-specific survival, overall survival, failure-free survival, metastasis-free survival; English language studies. Exclusion criteria: Duplicate studies, case reports, studies with fewer than 5 patients, conference abstracts, studies performed in salvage treatment setting.
Technique	Patients underwent either CA, HIFU, IRE, or VTP for treatment of prostate cancer.
Follow up	CA: median follow up 12 to 101.5 months HIFU: median follow up 6 to 127.5 months IRE: median follow up 6 to 72 months VTP: median follow up 6 to 48 months
Conflict of interest/source of funding	No conflicts of interest reported. Study funded by Scientific Research Starting Foundation for PhD/MD (Grant BJ-2019-135) and Scientific Research Foundation for Central Health Care (Grant 2020YB10).

Analysis

Study design issues: The systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers did a literature

search of PubMed, EMBASE, and the Cochrane Library to identify studies; disagreements were resolved through discussion.

Clinical efficacy was assessed through biochemical recurrence-free survival, cancer-specific survival, overall survival, failure-free survival, and metastasis-free survival. A random effects model was used to do a proportional meta-analysis, and statistically significant heterogeneity was assumed when I^2>50% and p value<0.1.

Funnel plots were constructed for each meta-analysis to detect publication bias, and Egger's test was used to assess publication bias statistically. A p value was regarded as statistically significant when less than 0.05. All analyses were done using STATA (version 14). The meta-analyses done in this study did not specify a time period for each outcome and included studies with differing lengths of follow up.

Other issues: Overlap with other Table 2 studies; Guenther (2019), Blazevski (2020), van den Bos (2018), Scheltema (2018b) and Blazevski (2021).

Most patients included in this study had procedures other than IRE.

Key efficacy findings

Number of patients included: 7,383 (CA: n=2870 across 22 studies, HIFU: n=3012 across 19 studies, IRE: n=768 across 8 studies, VTP: n=733 across 7 studies)

Proportion of positive biopsy following procedure

- CA (median follow up 12 to 101.5 months): 20% (95% CI 12 to 28%; 12 studies, n=1476; I^2 = 88.8%, p=0.000)
- HIFU (median follow up 6 to 127.5 months): 20% (95% CI 12 to 28%; 17 studies, n=2010; I^2 = 90.8%, p=0.000)
- IRE (median follow up 7 to 20 months): 24% (95% CI 18 to 31%; 5 studies, n=193; I^2 = 0%, p=0.734)
- VTP (median follow up 6 to 48 months): 36% (95% CI 29 to 44%; 7 studies, n=733; I^2 = 77%, p=0.000)

Cancer-specific survival

- CA (median follow up 44.4 to 101.5 months): 96% (95% CI 92 to 101%; 4 studies, n=274; I^2 = 83.7%, p=0.000)
- HIFU (median follow up 39 to 127.5 months): 98% (95% CI 97 to 100%; 4 studies, n=1867; I^2 = 70.3%, p=0.018)
- IRE (median follow up 6 to 7 months): 98% (95% CI 94 to 102%; 2 studies, n=48; I^2 = 0%, p=0.966)

Overall survival

- CA (median follow up 44.4 to 101.5 months): 93% (95% CI 86 to 99%; 4 studies, n=274; I^2 = 89.9%, p=0.000)
- HIFU (median follow up 39 to 127.5 months): 85% (95% CI 78 to 92%; 4 studies, n=1867; I^2 = 89.7%, p=0.000)
- IRE (median follow up 6 to 36 months): 99% (95% CI 98 to 101%; 3 studies, n=171; I^2 = 0%, p=0.736)

Failure-free survival

- CA (median follow up 58.5 to 63 months): 65% (95% CI 15 to 115%; 2 studies, n=95; I^2 = 97.5%, p=0.000)
- IRE (median follow up 6 to 72 months): 90% (95% CI 83 to 98%; 3 studies, n=575; I^2 = 87.8%, p=0.000)
- VTP (median follow up 6 to 48 months): 90% (95% CI 83 to 115%; 3 studies, n=374; I^2 = 80.6%, p=0.006)

Metastasis-free survival

- HIFU (median follow up 39 to 76.8 months): 95% (95% CI 93 to 98%; 3 studies, n=1855; I^2 = 80.1%, p=0.007)
- IRE (median follow up 6 to 36 months): 99% (95% CI 98 to 101%; 2 studies, n=146; I^2 = 0%, p=0.665)

Key safety findings

No safety outcomes reported.

Study 2 Guenther (2019)

Study details

Study type	**Case series**
Country	Germany
Recruitment period	2011 to 2016
Study population and number	n=429 patients with prostate cancer (471 IRE treatments)
Age and sex	Mean age 64±8 years
Patient selection criteria	Inclusion criteria: Patients with prostate cancer (all stages) who would potentially benefit from IRE-treatment of their PCa and who refused all types of standard therapy Exclusion criteria: Patients not well enough for total intravenous anaesthesia; patients with defibrillators.
Technique	IRE electrodes (AngioDynamics Inc., USA) were manually inserted through the perineum under ultrasound guidance without a brachytherapy grid. The IRE-field was planned in a way that it exceeded the macroscopic tumour extent by at least 8mm towards the centre of the prostate. Towards the capsule the electrodes were, whenever possible, placed within a couple millimetres inside the prostatic capsule. All treatments were carried out with the NanoKnife (AngioDynamics Inc., USA).
Follow up	4 months to 6 years
Conflict of interest/source of funding	None

Analysis

Follow up issues: Follow up MRI and PSA scores had a median time till last follow up data-point of 12 months. High rate of loss to follow up; of 429 patients that had IRE, 20% (44/429) of patients were lost to follow up after 6 months and 60% were lost to follow up after 12 months.

Routine follow up comprised PSA-tests and MRI scans. PSA-testing was recommended every 3 months in the first 2 years, then every 6 months and MRI was recommended after 1 day, at 3, 6, 12 months after IRE, then annually.

Study design issues: Retrospective case series. Biochemical recurrences were defined by a rise in PSA above the baseline value at 3 months after IRE with confirmation by multi-parametric MRI, and in some cases by additional biopsy or prostate specific membrane antigen PET or X-ray CT scans. All data was discussed by a board of urologists or oncologists and radiologists who had at least 10 years of experience in the field. Kaplan–Meier curves and analysis of oncological outcome was done with Prism GraphPad 5.

Urinary continence was primarily assessed by interviewing the patients concerning any involuntary loss of urine related to the IRE-treatment and the different forms of incontinence (such as stress, urge, overflow-incontinence).

ED was evaluated by 2 methods; standard IIEF-5 score before and after IRE (ranging from 5 to 25 where 25 represents no ED and 5 represents the most severe ED) and additional evaluation algorithm in which patients were asked whether they 1) had experienced any negative change in erectile function related to IRE and 2) were unable to have satisfactory intercourse and no spontaneous nocturnal erection. Patients in whom both statements were true were classified as having an IRE-related significant ED.

Study population issues: 123 out of 471 treatments (26.1%) were uni-lobar or focal (<50% volume ablation), 153 out of 471 (32.5%) were bi-lobar but did not involve the whole gland (50% to 90% volume ablation), and 134 out of 471 (28.5%) involved the whole gland (>90%). In 63 out of 471 (13.3%) patients treatment extent either could not be determined or patients were having treatment for recurrent disease.

According to the D'Amico Risk Classification, 312 out of 429 (66%) patients were high risk, 88 out of 429 (19%) were intermediate risk, and 25 out of 429 (5%) were low risk. In 4 patients D'Amico risk classification was impossible because of lack of biopsy. According to Gleason score cancer grading (with 6 as low grade, 7 as intermediate grade, 8 to 10 as high-grade cancer) 82 out of 429 patients had a Gleason score of 6, 225 out of 429 with a Gleason score of 7, and 113 out of 429 patients had a Gleason score of >7 (with no Gleason score available for 9 patients because of refusal of biopsy). Mean PSA at baseline across all patients was 10±250 nanograms/ml.

Other issues: Study also included in Guo 2021 systematic review.

Key efficacy findings

Number of patients analysed: 429 (471 treatments)

Recurrence (Kaplan–Meier analysis)

Clinical severity at baseline	Number of recurrences at 72 months (n=471 treatments)	Estimated % recurrence free survival at 72 months	Estimated % recurrence rate at 5 years (95% CI)
Gleason 6 (low grade)	3	94	5.6 (1.8 to 16.93)
Gleason 7 (intermediate grade)	18	85	14.6 (8.8 to 23.7)
Gleason >7 (high grade)	26	60	39.5 (23.5 to 61.4)

Recurrence in or adjacent to IRE field (Kaplan–Meier analysis):

Clinical severity at baseline	Number of recurrences at 72 months (n=471 treatments)	Estimated % recurrence free survival
Gleason 6 (low grade)	1	98 (64 months)
Gleason 7 (intermediate grade)	10	93 (72 months)
Gleason >7 (high grade)	16	75 (72 months)

Key safety findings

Rate of adverse events

Adverse events	% of treatments (n=471)
All mild events	**19.7 (93/471)**
Mild haematuria	3.8 (18/471)
Transient urinary retention	9.1 (43/471)
Dysuria	6.8 (32/471)
All moderate events	**3.8* (18/471)**
Prostatitis	0.2 (1/471)
Proctitis (uncertain genesis)	0.2 (1/471)
Epididymitis	0.6 (3/471)
Pseudo post vasectomy syndrome	0.2 (1/471)
Urinary tract infection	2.5 (12/471)
All severe or medically significant events	**1.5* (7/471)**
Permanent urinary retention	0.8 (4/471)
Recto-prostatic fistula	0.2 (1/471)
Bladder perforation by catheter	0.2 (1/471)
Severe prostatitis	0.2 (1/471)

***:** Correction of rounding errors in paper

Sexual dysfunction

Clinical outcome (n=124)	
Mean point reduction of IIEF-5 score by neurovascular bundle (NVB) involvement 12 months post IRE	None: -1.6 Left or right: -6.4 Both: -10.5
Mean point reduction in IIEF5 score by prostate ablation volume	<50%: -5.3 (-17.7%) 50-90%: -7.7 >90%: -11.1 (-37%)
Mean points reduction of IIEF5 score before and after 18 months post IRE	<18 months: -8.7 >18 months: -3.9 P value for significance = (0.045)
Subjective assessment of ED 12 months post IRE	Reduction of erectile function: 45% (56/124) Transient severe ED (resolved within 12 months):11.4% (14/124) Persistent severe ED (>12 months): 3% (4/124)

Urinary incontinence

IPSS score analysis revealed that in 7.7% (12/155) of the evaluated patients scores increased temporarily from below 8 to above 19 (severe symptoms) after IRE.

In patients fully continent before IRE, no urinary incontinence was seen 12 months after IRE or later during the observation period. In terms of urinary symptoms, 72.8% of evaluated patients reported no change or an improvement in quality of life and 27.2% reported a decrease.

Study 3 Blazevski (2020)

Study details

Study type	**Case series**
Country	Australia
Recruitment period	2013 to 2018
Study population and number	n=123 patients with localised apical prostate cancer
Age and sex	Median age 68 years (IQR 62 to 73 years)
Patient selection criteria	Inclusion criteria: Low (high-volume > 4 mm) to intermediate risk PCa according to D'Amico criteria; Gleason score ≤ 7 (ISUP ≤ 3); unilateral or midline anterior/posterior index tumour, allowing single targeted ablative therapy; PSA ≤ 15 ng/ml; life expectancy ≥ 10 years; no previous treatment for PCa; no previous androgen suppression treatment for PCa; minimum 12-month follow up; multiple lesions which can be encompassed in one treatment Exclusion criteria: Bilateral significant disease; metastatic disease; multiple lesions that cannot be treated within one treatment field
Technique	All patients underwent standardised focal irreversible electroporation (IRE) procedure performed by a single urologist using Nanoknife device (Angiodynamics, Inc., Queensbury, New York). All patients underwent a general anaesthetic with full muscle paralysis and also received IV antibiotics at induction. Safety margins of 5 or 10 mm from the targeted area were used to adjust for MRI volume underestimation. The number of electrodes placed was dependent on the size and location of the lesion.
Follow up	Median follow up 36 months (IQR 24-52 months)
Conflict of interest/source of funding	One author reports receiving consultant fees from Angiodynamics and proctor fees for training surgeons in IRE. Funded by Australian Commonwealth Department of Health and Ageing and the St.Vincent's Prostate Cancer Centre

Analysis

Follow up issues: All patients were followed up for a minimum of 12 months. Serial PSA levels were measured every 3 months for at least 2 years. Follow up multiparametric MRI was performed at 6 months and follow up (TTMB with additional targeted biopsies of the ablation zone and margins was performed at 12 months. Functional and QoL data were prospectively collected from patients who provided consent using the EPIC and the SF-12 questionnaires completed at baseline, at 6 weeks postoperatively, and 3, 6, 12, and 24 months postoperatively.

Study design issues: Single-centre retrospective analysis of predefined and prospectively collected data.

Significant PCa on follow-up biopsy was defined as Gleason score 3+ 4. A significant positive biopsy found within the targeted area was deemed in-field treatment failure and any found outside the target zone was designated as out-of-field failure. Initial analysis was done for the entire cohort, and then for patients after the treatment margin was increased and technical skills improved.

Failure-free survival was defined as progression to whole-gland or systemic treatment or metastasis or death and reported 3 years after initial treatment and was stratified for both the ISUP subgroup and the National Comprehensive Cancer Network risk category. Metastasis-free survival and overall survival were calculated at 1, 3, and 5 years after IRE.

Adverse events were recorded using the Clavien-Dindo classification (grouped 1 to 5, with 5 being the most severe).

Study population issues: According to the D'Amico Risk Classification, 11 out of 123 (%) patients were low risk, and 112 out of 123 (%) were intermediate risk. A total of 12 (9.8%) had (ISUP) grade 1, 88 (71.5%) had ISUP 2, and 23 (18.7%) had ISUP 3 (measured grades 1 to 5 with ISUP 5 being the most severe). Mean PSA at baseline across all patients was 5.7 nanograms/ml (IQR 3.8 to 8 nanograms/ml).

Other issues: The authors did analysis with all 123 patients and with exclusion of the first 32 patients to account for increased treatment margin to 10 mm and improved technique. Study also included in Guo (2021) systematic review and possible overlap with Blazevski (2021) which focuses solely on patients with apical prostate cancer.

Key efficacy findings

PSA and MRI outcomes

Outcome	All patients (n=123 for PSA, n=112 for MRI outcomes)	Excluding initial cohort (n=91 for PSA, n=80 for MRI outcomes)
Median PSA at 12-month follow up	2.5 nanograms/ml (IQR 1.43 to 5.675)	–
Median PSA nadir (IQR)	3.48 nanograms/ml (1.43 to 5.67) (n=123)	3.37 (1.04 to 5.7) (n=91)
MRI at 6 months – clear %	80 (90/112)	87.5
MRI at 6 months – in field lesion %	2.6 (3/112)	1.25 (1/80)
MRI at 6 months – Adjacent-to-field lesion %	5.4 (6/112)	3.75 (1/80)
MRI at 6 months – out-of-field lesion	9.8 (11/112)	7.5 (6/80)
MRI at 6 months – both in and out-of-field lesion	5.4 (6/112)	0

Biopsy outcomes

Outcome	% of all patients (n=102)	% of patients excluding initial cohort (n=74)
Significant in-field disease at 12 months	9.8 (10/102)	2.7 (2/74)
Significant out-of-field disease at 12 months	12.7 (13/102)	12.1 (9/74)
Whole gland free of clinically significant cancer at 12 months (%)	77.5 (79/102)	85.1 (63/74)

Survival outcomes

- Failure-free survival (estimated): 96.75%
- Metastasis-free survival: 98.5% (68/69) at 3-year follow up
- Overall survival: 100% (69/69) at 3-year follow up

Key safety findings

Rate of adverse events

Clavien-Dindo classification	Complications listed*	% incidence (n=123)
1	Perineal pain, haematuria, dysuria, urgency frequency,	22 (27/123)
2	Urinary tract infection, incontinence, acute urinary retention	9 (11/123)

*Rates for each individual complication are not reported

Study 4 Scheltema (2018)

Study details

Study type	Non-randomised comparative study
Country	Australia
Recruitment period	2013 to 2016
Study population and number	n=100 patients with prostate cancer (50 IRE versus 50 robot-assisted radical prostatectomy (RARP))
Age and sex	IRE: median age 67 years (IQR 62 to 73 years) RARP: median age 67 years (IQR 64 to 71 years)
Patient selection criteria	Patients receiving single ablative IRE or nerve-sparing robot-assisted radical prostatectomy (RARP); clinical stage T1c-T2b; low to intermediate-risk PCa (ISUP 1 to 3); written informed consent for QoL evaluation, minimum of 6 months follow up.
Technique	IRE was done by a single surgeon and was executed following the methods as described by Ting et al. (2016). A transurethral indwelling catheter was placed to drain the bladder before treatment. RARP was done by a single-surgeon (PS) employing the techniques described by Patel et al. and executed using the Da-Vinci Xi surgical system with 6 access ports (Intuitive Surgical Sunnyvale®, CA, USA).
Follow up	12 months
Conflict of interest/source of funding	One author reports receiving consulting fees from AngioDynamics. Funded by the Australian Commonwealth Department of Health and Ageing and the St Vincent's Prostate Cancer Centre.

Analysis

Follow-up issues: 88% (44/50) IRE patients had follow-up biopsies, 10% (5/50) refused and 1 patient was still awaiting biopsy at the time of analysis. Patient reported QoL data was also collected at baseline, 1.5, 3, 6, and 12 months after procedure. At 1.5, 3, 6, and 12 months, the response rate for questionnaires was 93%, 97%, 94% and 71% of the 100 patients, respectively.

Study design issues: Retrospective analysis of prospectively collected data (single centre). IRE patients were matched 1:1 to RARP patients using propensity score matching.

Rates of urinary continence (defined as pad-free continence) and ESI were compared between IRE and RARP up to 12 months. Oncological failure rates for IRE were defined by positive follow-up biopsies at 12 months with significant PCa (high-volume ISUP 1 or any 2 or 3). For RARP, this was defined as biochemical failure (PSA≥0.2 micrograms/litre) or the need for adjuvant radiotherapy within 12 months. Early surgical complications were classified as specified by the Clavien–Dindo classification (ranging from 1 to 5, with 5 being the most severe).

Study population issues: No statistically significant differences between the matched IRE and RARP populations. In the IRE group, 8 out of 50 patients (16%) had ISUP grade 1 biopsy, 33 out of 50 (66%) had ISUP grade 2 biopsy and 9 out of 50 (18%) had ISUP grade 3 biopsy. In the RARP group, 9 out of 50 patients (18%) had ISUP grade 1 biopsy, 31 out of 50 (62%) had ISUP grade 2 biopsy and 10 out of 50 (20%) had ISUP grade 3 biopsy. Median PSA was 5.9 micrograms/litre (IQR 3.3 to 7.3) for the IRE group and 6.3 micrograms/litre (IQR 4.3 to 7.7) for the RARP group.

Other issues: Study is also included in Guo (2021) systematic review.

Key efficacy findings

Number of patients analysed: 100 (50 IRE versus 50 RARP)

Oncological outcomes

Of the IRE patients who had biopsies at 12 months, 13 out of 44 (29.5%) had residual PCa. One patient was diagnosed with metastatic disease directly after IRE because of persisting elevated PSA (>10 nanograms/ml).

Median PSA after IRE: 2.8 nanograms/ml (IQR 0.9 to 4.5) – reduction of 51% (IQR 28% to 85%).

None of the RARP patients experienced biochemical failure (PSA ≥0.2 nanograms/mL) within the first 12 months of follow up.

IRE was superior to RARP in preserving ESI during the first 12 months of follow up. The absolute risk reduction to develop erectile dysfunction was 32%, 46%, 27% and 22% at 1.5, 3, 6, and 12 months, respectively.

Key safety findings

Rate of complications

Complication grade	IRE	RARP
Clavien-Dindo 1	11 (mild haematuria, urgency, and postoperative pain)	9 (urinary retention n=5, other complications not reported)
Clavien-Dindo 2	7 (urinary tract infection and severe postoperative pain related to the indwelling catheter)	5 (urinary tract infection n=4, postoperative anaemia requiring blood transfusion n=1).

Pad free continence

Follow up	Pad free continence % IRE (all)	Pad free continence % RARP (all)	Pad free continence % IRE (continent at baseline)	Pad free continence % RARP (continent at baseline)
Baseline (n=100)	98	98	100	100
6 weeks (n=93)	87	44	89	45

3 months (n=97)	96	75	98	77
6 months (n=94)	98	85	100	87
12 months (n=71)	96	84	100	86

IRE was superior to RARP in preserving pad-free UC during the first 12 months of follow up ($p<0.01$); The absolute risk reduction was 44%, 21%, 13% and 14% at 1.5, 3, 6, and 12 months, respectively.

ESI rate

Follow up	**IRE ESI % (all)**	**RARP ESI % (all)**	**IRE ESI % (potent at baseline)**	**RARP % (potent at baseline)**
Baseline (n=100)	69	68	100	100
6 weeks (n=93)	40	20	57	25
3 months (n=97)	54	22	74	28
6 months (n=94)	49	28	65	38
12 months (n=71)	56	36	72	50

Study 5 van den Bos (2018)

Study details

Study type	**Case series**
Country	Australia
Recruitment period	2013 to 2016
Study population and number	n=63 patients with organ confined prostate cancer
Age and sex	Median age 67 years (range 61 to 71 years)
Patient selection criteria	Inclusion criteria: Low to intermediate-risk PCa according to D'Amico criteria; Gleason score ≤7 (ISUP Grade ≤3); Unilateral or single midline anterior/posterior index tumour, allowing single targeted ablative therapy; Life expectancy ≥10 years. Exclusion criteria: No previous treatment for PCa; No previous androgen suppression/hormone treatment for PCa; follow up of less than 6 months.
Technique	All IRE procedures were done by a single urologist using an IRE device and 18-gauge electrodes (Nanoknife, AngioDynamics, Queensbury, NY, USA). All patients were given general anaesthesia with full-muscle paralysis and had prophylactic IV antibiotics at induction. An indwelling catheter was placed for urinary drainage. Safety margins of 5 or 10 mm from the targeted area were used to adjust for MRI lesion volume underestimation. The safety margin was increased to 10 mm after the first 10 cases. The number and active tip length of the electrodes was dependent on the size of the targeted lesion.
Follow up	6 to 24 months (outcomes reported up to 12 months)
Conflict of interest/source of funding	No conflicts of interest reported. Funded by the Australian Commonwealth Department of Health and Ageing and the St Vincent's Prostate Cancer Centre.

Analysis

Follow-up issues: Not all patients consented to have QoL evaluation during follow up (27% refused). 55/63 (87%) of primary patients had 6-month follow up with multiparametric MRI.45 out of 63 patients (71%) had had follow-up biopsy at the time of analysis, 3 refused follow-up biopsies and 15 patients were awaiting TTMB. Quality of life questionnaires were also completed at baseline, 6 weeks, and 3, 6 and 12 months postoperatively.

Study design issues: Retrospective single centre analysis. The QoL and functional data were prospectively collected from all patients who provided consent using the EPIC, including urinary, sexual and bowel domains and the AUA symptom score (scored 0 to 35 where higher scores indicate increased severity). The SF-12 health survey physical component summary and mental component summary scores were used to assess

overall health status.

Significant PCa on follow-up biopsy included high-volume Gleason sum score 6 (ISUP grade 1) with a core involvement of >5 mm/>50% maximum core volume or any core involvement with Gleason sum score of 7 to 10 (ISUP grades 2 to 5). A significant positive biopsy found within the targeted treatment area (or adjacent to the treatment area) was determined as in-field treatment failure and any found outside the target zone was designated as out-of-field treatment failure.

Wilcoxon's signed rank test and Wilcoxon's rank sum test (both 2-tailed) were used to assess statistically significant differences in paired continuous variables (all questionnaire outcomes at baseline and 6 months) and unpaired continuous variables (age, PSA, prostate volume, number of positive cores, biopsy ISUP grade, peri-operative treatment variables), respectively. p values <0.05 were taken to indicate statistical significance.

All AEs were recorded using the National Cancer Institute CTCAE version 4.0, graded 1 to 5, with 5 being the most severe.

Study population issues: According to D'Amico risk classification, 12.7% (8/63) of patients were low risk and 87.3% (55/63) were intermediate risk. Gleason scores were 3+3 (or ISUP Grade 1) for 9 out of 63 (14.2%) patients, 3+4 (ISUP Grade 2) for 38 out of 63 patients (60.3%), and 4+3 (ISUP grade 3) for 16 out of 63 patients (25.4%). Median serum PSA was 6 nanograms/ml (IQR 3.2 to 8.4).

Other issues: The safety margin was increased to 10 mm after the first 10 cases included in this analysis. Study also included in Guo (2021) systematic review.

Key efficacy findings

Number of patients analysed: 63

PSA and MRI outcomes

Outcome	
Median (IQR) 6–12-month PSA (n=63)	1.8 (0.96-4.8)
MRI results at 6 months- Clear % (n=55)	85.5 (47/55)
MRI results at 6 months- In-field lesions % (n=55)	7.3 (4/55)
MRI results at 6 months- Out-of-field lesions % (n=55)	3.6 (2/55)
MRI results at 6 months- In- and out-of-field lesions % (n=55)	3.6 (2/55)

Biopsy results

Biopsy outcome at 6-12 months (n=45)	
Significant in-field disease, all patients, % (n=45)	15.6 (7/45)
Significant in-field disease, 5-mm safety margin, % (n=10)	40 (4/10)
Significant in-field disease, 10-mm safety margin, % (n=35)	8.6 (3/35)
Significant out-field disease n (%)*	9.8 (4/41)
All significant disease % (n=45)	24.4 (11/45)
Gleason score 3 + 3 (ISUP Grade 1), >5 mm/50% core involvement	0
Gleason score 3 + 4 (ISUP Grade 2)	15.6 (7/45)
Gleason score 4 + 3 (ISUP Grade 3)	4.4 (2/45)
Gleason 4 + 4 (ISUP Grade 4)	2.2 (1/45)
Gleason 4 + 5 (ISUP Grade 5)	0
High-grade	1 (1/45)

*: Patients who received follow up targeted biopsies were excluded from out-field analysis.

After patients treated with a narrow safety margin and system errors were excluded, in-field disease decreased to 2.6% (1/39) and total disease (in-field and out-field) decreased to 12.8% (34/39).

Quality of life

Questionnaire	Baseline (n=46)	3 months (n=46 for AUA and EPIC scores, n=45 for SF-12 physical, n=44 for SF-12 mental)	6 months (n=40 for SF-12 scores, n=42 for all other scores)	12 months (n=19)	P value for difference between baseline and 6 months
Median AUA score (IQR)	5 (3 to 14)	7 (3 to 10)	5(3 to 10)	4 (2 to 8)	0.25
Median EPIC urinary function summary score (IQR)	92 (78 to 98)	91 (77 to 98)	93 (83 to 98)	94 (92 to 98)	0.41

Median EPIC sexual function summary score (IQR)	66 (47 to 85)	50 (27 to 75)	54 (29 to 72)	48 (15 to 77)	<0.001
Median EPIC bowel function summary score (IQR)	96 (93 to 100)	96 (91 to 100)	96 (91 to 100)	96 (93 to 100)	0.83
Median SF-12 physical component score (IQR)	56 (51 to 57)	55(49 to 57)	55 (49 to 57)	56 (53 to 57)	0.81
Median SF-12 mental component score (IQR)	57 (48 to 58)	57 (52 to 59)	56 (47 to 58)	57 (54 to 59)	0.48

Key safety findings

Rate of adverse events

Complications	% rate of complications (n=63)	Comments
CTCAE grade 1 (Haematuria, dysuria, urgency or frequency complaints, perineal pain)	24 (15/63)	Exact rates of each complication were not reported
CTCAE grade 2 (Urinary incontinence, UTIs, more severe urgency or frequency complaints or epididymitis)	11 (7/63)	1 patient required prolonged (>5 days) catheterisation because of urinary retention 1 patient experienced incontinence at 6 months (one pad per 24h, urinary dribbling) but this resolved at 12 months. Exact rates of other complications were not reported.

Sexual dysfunction

Follow up	Erections sufficient for intercourse %	Impotence %
Baseline	70 (31/44)	-
3 months	55 (24/44)	-

6 months	46 (20/43)	31 (8/26)
12 months	53 (10/19)	23 (3/13)

Study 6 Scheltema (2018b)

Study details

Study type	**Case series**
Country	Australia
Recruitment period	2013 to 2016
Study population and number	n=60 patients with organ-confined prostate cancer
Age and sex	Mean age 68±7.0 years
Patient selection criteria	Patients treated with primary IRE for localised PCa; minimum of 6 months follow up.
Technique	Single-surgeon IRE was done under general anaesthesia, antibiotic prophylaxis, and deep-muscle relaxation. An indwelling catheter was placed before the procedure. Using the Nanoknife® system (AngioDynamics), 4 to 6 needle electrodes were placed with a with a transperineal approach, encircling the tumour lesion.
Follow up	12 months
Conflict of interest/source of funding	Three authors report receiving grants and one author receives consulting fees from AngioDynamics. Funded by the Australian Prostate Cancer Research Centre-NSW and the St. Vincent's Prostate Cancer Centre.

Analysis

Follow-up issues: High loss to follow up; data available for 42% (25/60) of patients at 12 months. Genitourinary function and QoL data were prospectively evaluated using questionnaires at baseline, 3, 6, and 12 months.

Study design issues: Retrospective analysis of single centre data. The EPIC (graded 1 to 100 with 100 representing best QoL, AUA) symptom score (scored 0 to 35 with higher scores indicating increased severity of symptoms, SF-12 physical and mental component summary surveys were used to collect data on QoL and genitourinary function.

Differences in genitourinary function and QoL between segments was tested by the analysis of covariance model. In this model, the dependent variable was the measured value at month 6, the independent variable was the treatment group, and the covariate was the measured baseline value. All data were log-transformed before the analysis. Post-hoc comparison between groups was done with the Tukey's honest significant difference test within the R statistical environment. The level of significance was set at $p<0.05$.

Study population issues: Gleason scores were 6 for 8 out of 60 (13%) patients, 3+4 for 40 out of 63 patients (67%), 4+3 for 10 out of 60 patients (17%) and 4+4 or higher for 2 out of 60 patients (3%). Mean serum PSA was 6±3.3 micrograms/litre

Key efficacy findings

Number of patients analysed: 58

IP overview: Irreversible electroporation for treating prostate cancer

Genitourinary function and QoL – anterior versus posterior

Outcome	Baseline (Anterior: n=18) (Posterior: n=39)	3 months (Anterior n=17) (Posterior n=39)	6 months (Anterior n=17) (Posterior n=35)	12 months (Anterior n=4) (Posterior n=20)	Segment difference Baseline/6 months	Different treatment impact Anterior vs. Posterior
AUA-Anterior	6 (3 to 14)	6 (3 to 11)	4 (3 to 10)	4 (2 to 5)	No (P = 0.55)	No (P = 0.97, E = E= -0.05, CI ±2.5)
AUA-Posterior	6 (3 to 12)	7 (3 to 10)	5 (2 to 11)	4 (2 to 11)	No (P = 0.19)	-
EPIC urinary - Anterior	93 (72 to 98)	89 (69 to 96)	94 (79 to 98)	92 (82 to 97)	No (P = 0.68)	No (P = 0.83, E= -0.71, CI ±6.6)
EPIC urinary - Posterior	89 (81 to 98)	92 (81 to 98)	92 (83 to 98)	94 (85 to 98)	No (P = 0.24)	-
EPIC sexual - Anterior	60 (25 to 82)	52 (29 to 71)	46 (14 to 79)	27 (2 to 79)	Yes (P = 0.03)	No (P = 0.41, E= -4.1, CI ±9.6)
EPIC sexual - Posterior	67 (48 to 81)	47 (31 to 74)	49 (29 to 69)	42 (19 to 76)	Yes (P = 0.008)	-
EPIC bowel - Anterior	96 (92 to 100)	96 (93 to 98)	96 (91 to 99)	93 (87 to 99)	No (P = 0.79)	No (P = 0.80, E= 0.51, CI ±3.9)
EPIC bowel - Posterior	96 (93 to 98)	96 (89 to 100)	96 (89 to 100)	97 (92 to 100)	No (P = 0.70)	-
SF-12 physical - Anterior	55 (44 to 56)	55 (48 to 56)	55 (40 to 57)	57 (43 to 58)	No (P = 0.64)	No (P = 0.74, E= -0.71, CI ±4.1)
SF-12 physical - Posterior	56 (52 to 56)	55 (52 to 57)	55 (52 to 57)	55 (52 to 57)	No (P = 0.35)	-
SF-12 mental - Anterior	56 (39 to 58)	56 (50 to 58)	56 (40 to 60)	53 (48 to 60)	No (P = 0.80)	No (P = 0.64, E= 1.1, CI ±4.4)
SF-12 mental - Posterior	56 (50 to 58)	57 (53 to 59)	56 (48 to 58)	57 (56 to 59)	No (P = 0.45)	

Values reported as median (IQR). E=effect size

Genitourinary function and QoL – apex, base and apex to base

Outcome	Baseline (Apex n=18, Base n=14, Apex-to base n=26)	3 months (Apex n=17, Base n=14, Apex-to base n=26)	6 months (Apex n=17, Base n=13, Apex-to base n=24)	12 months (Apex n=10, Base n=4, Apex-to base n=11)	Segment difference between baseline and 6 months	Difference in treatment impact, apex vs. base	Difference in treatment impact, apex vs. apex-to-base	Difference in treatment impact, base vs. apex-to-base
AUA-Apex	3 (2 to 16)	7 (3 to 10)	4 (2 to 12)	4 (2 to 8)	No (P = 0.86)	No (P =0.79, E=0.43, CI±3.1)	No (P =0.28, E= -1.5, CI±2.7	-
AUA-Base	10 (4 to 12)	10 (4 to 13)	7 (4 to 14)	8 (2 to 23)	No (P = 0.89)	-	-	No (P = 0.41, E= 1.9, CI±3.0
AUA-Apex-to-Base	6 (4 to 14)	6 (3 to 11)	5 (3 to 10)	4 (3 to 5)	No (P = 0.19)	-	-	-
EPIC urinary - Apex	96 (81 to 98)	94 (78 to 99)	96 (77 to 98)	94 (90 to 96)	No (P = 0.88)	No (P = 0.64, E= 2.0, CI ±8.2)	No (P = 0.34, E= 3.4, CI ±7.0)	-
EPIC urinary - Base	87 (78 to 94)	89 (74 to 96)	90 (84 to 97)	85 (70 to 98)	No (P = 0.33)	-	-	No (P = 0.93, E= -1.5, CI±7.8)
EPIC urinary - Apex-to-Base	92 (77 to 98)	89 (72 to 98)	93 (84 to 98)	95 (89 to 98)	No (P = 0.23	-	-	-
EPIC sexual - Apex	67 (55 to 90)	54 (39 to 75)	53 (41 to 76)	48 (26 to 87)	Yes (P = 0.008)	No (P = 0.53, E = -3.7,CI±11.6)	No (P = 0.91, E= 0.60, CI ±10.1)	-
EPIC sexual - Base	62 (49 to 76)	51 (36 to 74)	54 (23 to 73)	50 (8 to 72)	Yes (P =0.046)	-	-	No (P = 0.72, E= -4.3, CI ±11.0)
EPIC sexual - Apex-to-Base	60 (27 to 85)	42 (18 to 73)	41 (21 to 69)	35 (6 to 77)	Yes (P = 0.001)	-	-	-

EPIC bowel - Apex	96 (91 to 98)	96 (94 to 100)	98 (96 to 100)	97 (94 to 100)	P = 0.055)	No (P = 0.08, E= -4.3, CI ±4.7)	No (P = 0.11, E= -3.5, CI ±4.1)	
EPIC bowel - Base	97 (91 to 100)	93 (84 to 100)	93 (85 to 100)	86 (71 to 100)	No (P = 0.44)	-	-	No (P = 0.93, E= -0.87, CI ±4.6)
EPIC bowel - Apex-to-Base	96 (91 to 100)	96 (91 to 99)	96 (89 to 98)	96 (91 to 100)	No (P = 0.44)	-	-	-
SF-12 physical - Apex	56 (53 to 56)	55 (53 to 56)	56 (53 to 57)	55 (54 to 57)	No (P = 0.53)	No (P = 0.26, E= -2.9, CI ±5.0)	No (P = 0.63, E= -1.1, CI ±4.3)	-
SF-12 physical - Base	56 (52 to 58)	56 (47 to 57)	52 (40 to 57)	47 (44 to 56)	No (P = 0.18)	-	-	No (P = 0.73, E= -1.9, CI ±4.8)
SF-12 physical - Apex-to-Base	54 (45 to 57)	55 (46 to 57)	56 (42 to 58)	56 (53 to 58)	No (P = 0.71)	-	-	-
SF-12 mental -- Apex	56 (52 to 58)	7 (54 to 58)	57 (54 to 58)	58 (57 to 59)	No (P = 0.94)	No (P = 0.94,E= -0.23, CI ±5.6)	No (P = 0.77, E= 0.73, CI ±4.9)	-
SF-12 mental - Base	57 (48 to 58)	56 (44 to 58)	56 (41 to 57)	48 (42 to 55)	No (P = 0.66)	-	-	No (P = 0.94, E= -0.96, CI ±5.4)
SF-12 mental - Apex-to-Base	57 (44 to 59)	55/56* (50 to 59)	54 (45 to 59)	56 (49 to 60)	No (P = 0.62)	-	-	-

Data are presented as median (interquartile range). E=effect size.
*value given in study is 556 on a 1-100 scale – presumed error in paper (exact value not known)

Genitourinary function and QoL to bilateral versus unilateral

Unilateral Bilateral	Baseline (n=50) (n=10)	3 months (n=49) (n=10)	6 months (n=47) (n=8)	12 months (n=21) (n=6)	Segment difference baseline/6 months	Different treatment impact Bilateral vs. Unilateral
AUA	-	-	-	-	-	-
Unilateral	6 (3 to 13)	7 (3 to 11)	6 (2 to 11)	4 (2 to 9)	No (P = 0.17)	No (P = 0.75,E= -0.71, CI ±6.6)
Bilateral	11 (4 to 13)	5 (2 to 12)	4 (3 to 14)	5 (4 to 13)	No (P = 0.25)	-
EPIC urinary	-	-	-	-	-	-
Unilateral	92 (80 to 98)	91 (77 to 98)	93 (81 to 98)	94 (92 to 98)	No (P = 0.46)	No (P = 0.084, E= 7.4, CI ±8.3)
Bilateral	84 (76 to 95)	88 (70 to 94)	95 (90 to 99)	88 (79 to 94)	No (P = 0.068)	-
EPIC sexual	-	-	-	-	-	-
Unilateral	62 (45 to 79)	47 (31 to 72)	43 (26 to 69)	38 (15 to 77)	Yes (P < 0.001)	No (P = 0.54,
Bilateral	83 (63 to 90)	41 (21 to 76)	63 (37 to 84)	59 (28 to 77)	No (P = 0.16)	E= 3.8, CI ±12.0)
EPIC bowel	-	-	-	-	-	-
Unilateral	96 (93 to 98)	96 (91 to 100)	96 (91 to 100)	98 (93 to 100)	No (P = 0.67)	No (P = 0.62, E= -1.3, CI ±5.1)
Bilateral	95 (89 to 96)	96 (90 to 98)	93 (86 to 96)	93 (82 to 97)	No (P = 0.31)	-
SF-12 physical	-	-	-	-	-	-
Unilateral	56 (45 to 57)	55 (50 to 57)	56 (51 to 57)	56 (53 to 57)	No (P = 0.63)	No (P = 0.31, E= 2.6, CI ±4.9)
Bilateral	55 (48 to 56)	55 (49 to 57)	54 (49 to 57)	51 (44 to 56)	No (P = 0.40)	-
SF-12 mental	-	-	-	-	-	-
Unilateral	57 (49 to 58)	57 (51 to 58)	56 (48 to 58)	57 (55 to 59)	No (P = 0.46)	No (P = 0.94,

						E= 0.21, CI ±5.5)
Bilateral	58 (43 to 60)	56 (46 to 59)	56 (49 to 60)	58 (49 to 61)	No (P = 0.61)	-

Data are presented as median (interquartile range). E=effect size.

Key safety findings

No safety findings reported.

Study 7 Blazevski (2021)

Study details

Study type	**Case series**
Country	Australia
Recruitment period	2013 to 2018
Study population and number	n=50 patients with apical prostate cancer
Age and sex	Median age 68 years (IQR 63-71)
Patient selection criteria	Patients with apical PCa; 12-month follow up; completion of QoL questionnaires; MRI lesion extended to within <3 mm of the apical capsule/border and so needed the IRE ablation to incorporate the distal 3 mm of the prostate
Technique	IRE was done by a single urologist using an IRE device and 18-gauge electrodes (Nanoknife®; Angiodynamics, Queensbury, NY, USA). All patients were positioned in lithotomy position under general anaesthesia and deep-muscle paralysis. An indwelling catheter was placed to empty the bladder. 4 to 6 electrodes were placed through the perineum through the template grid to surround the PCa lesion. A 10 mm intra-prostatic margin was applied to prostate stroma surrounding the targeted area to allow for MRI volume underestimation.
Follow up	Median 44 months – outcomes reported up to 24 months
Conflict of interest/source of funding	Authors report receiving consultancy and proctor fees to AngioDynamics and other companies. Funding was provided by Australian Prostate Cancer Research Centre-NSW and St. Vincent's Prostate Cancer Centre

Analysis

Follow-up issues: 40 out of 50 (80%) patients had had follow-up biopsy at the time of analysis. The remaining patients had either refused biopsy (against the urologist's recommendation) because of reassuring MRI and PSAs or were awaiting biopsy. All patients consented to have QoL evaluation and questionnaires were completed at baseline, 6 weeks and 3, 6, 12 and 24 months. Serial PSA levels were also measured every 3 months for the first 2 years and multiparametric MRI was done at 6 months.

Study design issues: Small retrospective analysis of prospective cohort registry. QoL and functional outcomes were measured using the EPIC score, including urinary, sexual and bowel domains (all measured 1 to 100 with 100 indicating the greatest QoL.

Follow-up biopsies were reported as follows: (1) negative, (2) in-field recurrence—defined as any PCa found within the intention-to-treat zone, or (3) out-of field—defined as any PCa found outside the intention-to-treat zone. Significant PCa on follow up was defined as Gleason score ≥ 3 + 4. Failure-free survival was defined as progression to whole-gland or systemic treatment or metastasis/death. FFS was reported at 3 years after initial treatment.

Wilcoxon's signed rank test and Wilcoxon's rank sum test (both 2-tailed) were used to assess statistically significant differences in paired continuous variables (all questionnaire outcomes at baseline and 12 months). A Chi-square test for differences between posterior and anterior ablation was performed for urinary incontinence, urinary leakage, and potency post treatment. P values<0.05 were taken to indicate statistical significance.

Study population issues: Median pre-operative PSA was 6.25 (IQR 4.35 to 8.9) nanograms/ml. A total of 43 out of 50 (86%) patients had intermediate-risk, 5 out of 50 (10%) had low-risk and 2 out of 50 (4%) had high-risk disease. A total of 5 out of 50 (10%) had ISUP grade 1 PCa, 37 out of 50 (74%) had ISUP grade 2 PCa, 6 out of 50 (12%) had ISUP grade 3 PCa and 2 out of 50 (4%) had ISUP grade 4 PCa (with higher numbers indicating greater severity).

Other issues: It is possible that patients included in this study may also be included in Blazevski (2020), which includes patients with patients with other locations of prostate cancer in addition to apical PCa.

Key efficacy findings

Number of patients analysed: 50

PSA and MRI outcomes

Outcome	
Median (IQR) PSA at 12 months (n=50)	1.7 nanograms/ml (0.84-3.35)
MRI results at 6 months- Clear % (n=50)	86 (43/50)
MRI results at 6 months- In-field lesions % (n=50)	14 (7/50)
MRI results at 6 months- Out-of-field lesions % (n=50)	0

Biopsy results

Biopsy outcome (n=40)	
Significant in-field disease at 12 months %	2.5 (1/40)
Significant out-field disease at 12 months (%)	20 (8/40)
Low volume Gleason 6 tumour %	32.5 (13/40)
Whole gland free of significant cancer at 12 months %	77.5 (31/40)

Failure-free survival

Of patients that had greater than 3-year follow up; the failure free survival at 3 years was 90% (36/40).

Quality of life

Clinical outcome	Median EPIC Urinary score*	Median EPIC Bowel score*	Median EPIC Sexual score*
Baseline	95	96	65
6 weeks	65	97	46
3 months	96	99	51
6 months	97	100	57
12 months	97	98	59
24 months	99	100	76

*Results taken from graph

There was no statistically significant difference in urinary QoL at baseline and 12 months after treatment (p=0.063) or in bowel QoL(p=0.066).

There was a statistically significant difference in sexual QoL at baseline and 12 months after treatment (p=0.001). Of patients that were potent before IRE, 94% (30/32) remained potent sufficient for sexual intercourse after IRE ablation at 12-month after treatment.

Key safety findings

Complication grade	Listed complications	Incidence %
Clavien-Dindo 1	Dysuria, haematuria, urgency, and postoperative pain)	20 (10/50)
Clavien-Dindo 2	Urinary tract infection, severe urgency/frequency, incontinence	18 (9/50)

Validity and generalisability of the studies

- Most of the studies are case series with relatively short term follow up (6-12 months), and high loss to follow up past this point which severely limits the long-term data.
- Most of the studies included used data from patients in a single centre in Australia; it is possible that that there is some overlap in the patient populations in these studies in addition to the overlaps explicitly indicated in the overview.
- The included studies analysed populations with differing severity of prostate cancer.
- Detection, investigation, and management of prostate cancer now involves an increased use of MRI and the included studies do not reflect this change in practice.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

Related by indication

- Focal therapy using high-intensity focused ultrasound for localised prostate cancer. NICE interventional procedure guidance 424 (2012). Available from http://www.nice.org.uk/guidance/IPG424

- Focal therapy using cryoablation for localised prostate cancer. NICE interventional procedure guidance 423 (2012). Available from http://www.nice.org.uk/guidance/IPG423
- Laparoscopic radical prostatectomy. NICE interventional procedure guidance 193 (2006). Available from http://www.nice.org.uk/guidance/IPG193
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE interventional procedure guidance 174 (2006). Available from http://www.nice.org.uk/guidance/IPG174
- Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedure guidance 145 (2005). Available from http://www.nice.org.uk/guidance/IPG145
- Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedure guidance 132 (2005). Available from http://www.nice.org.uk/guidance/IPG132
- Cryotherapy for recurrent prostate cancer. NICE interventional procedure guidance 119 (2005). Available from http://www.nice.org.uk/guidance/IPG119
- High-intensity focused ultrasound for prostate cancer. NICE interventional procedure guidance 118 (2005). Available from http://www.nice.org.uk/guidance/IPG118

Related by intervention

- Irreversible electroporation for treating liver metastases. NICE interventional procedure guidance 445 (2013). Available from http://www.nice.org.uk/guidance/IPG445
- Irreversible electroporation for treating primary liver cancer. NICE interventional procedure guidance 444 (2013). Available from http://www.nice.org.uk/guidance/IPG444

- Irreversible electroporation for treating renal cancer. NICE interventional procedure guidance 443 (2013). Available from http://www.nice.org.uk/guidance/IPG443
- Irreversible electroporation for treating pancreatic cancer. NICE interventional procedure guidance 442 (2013). Available from http://www.nice.org.uk/guidance/IPG442
- Irreversible electroporation for treating primary lung cancer and metastases in the lung. NICE interventional procedure guidance 441 (2013). Available from http://www.nice.org.uk/guidance/IPG441

NICE guidelines

- Prostate cancer: diagnosis and management. NICE guideline 131 (2019). Available from http://www.nice.org.uk/guidance/NG131

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate. Three professional expert questionnaires for irreversible electroporation for treating prostate cancer were submitted, two of which can be found on the NICE website.

Patient organisation submissions

One patient organisation submission for irreversible electroporation for treating prostate cancer was received and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure. NICE received 101 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 0 completed submissions.

Issues for consideration by IPAC

Ongoing trials and registries:

- Multi-Centre Randomised Clinical Two Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localised Prostate Cancer (NCT01835977); RCT; n=106; study completion date Jan 2025 *[active, not recruiting]*

- Registry of Irreversible Electroporation for the Ablation of Prostate Cancer with Use of Nanoknife Device (NCT02255890); Cohort study; the Netherlands; n=361; study completion date April 2025 *[active, not recruiting]*

- A Prospective, Single-centre, Randomised Controlled Trial Comparing the Functional and Oncological Outcomes of High-frequency Irreversible Electroporation and Laparoscopic Radical Prostatectomy in Men With Localised Prostate Cancer (NCT04278261); RCT; n=216; study completion date September 2026 *[not yet recruiting]*

References

1. Guo RQ, Guo XX, Li YM et al. (2021) Cryoablation, high-intensity focused ultrasound, irreversible electroporation, and vascular-targeted photodynamic therapy for prostate cancer: a systemic review and meta-analysis. International Journal of Clinical Oncology, 26(3): 461–84.
2. Guenther E, Klein N, Zapf S et al. (2019) Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments. PloS One, 14(4): e0215093.
3. Blazevski A, Scheltema MJ, Yuen B et al. (2020) Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort. European Urology Oncology, 3(3): 283–290.
4. Scheltema MJ, Chang JI, Bohm M et al. (2018) Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World Journal of Urology, 36(9): 1383–9.
5. van den Bos W, Scheltema MJ, Siriwardana AR et al. (2018) Focal irreversible electroporation as primary treatment for localised prostate cancer. BJU International, 121(5): 716–24.
6. Scheltema MJ, Chang JI, van den Bos W et al. (2018) Impact on genitourinary function and quality of life following focal irreversible electroporation of different prostate segments. Diagnostic and Interventional Radiology (Ankara, Turkey), 24(5): 268–75.
7. Blazevski A, Amin A, Scheltema MJ et al. (2021) Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World Journal of Urology, 39(4); 1107-14.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	30/03/2022	Issue 2 of 12, February 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	30/03/2022	Issue 2 of 12, February 2022
International HTA database (INAHTA)	30/03/2022	-
MEDLINE (Ovid)	30/03/2022	1946 to March 29, 2022
MEDLINE In-Process (Ovid)	30/03/2022	1946 to March 29, 2022
MEDLINE Epubs ahead of print (Ovid)	30/03/2022	March 29, 2022
EMBASE (Ovid)	30/03/2022	1974 to 2022 March 29

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or mass*)).tw.
4 PIN.tw.
5 or/1-4
6 exp Electroporation/
7 (irrevers* adj4 (electropor* or electro-por* or electropermeab* or electro-permeab*)).tw.
8 IRE.tw.
9 LEDC.tw.
10 Electrochemotherapy/
11 (electrochemo* or electro-chemo* or (electr* adj2 chemo*)).tw.
12 ((bipolar or unipolar) adj4 (pulse? or electrod* or mode?)).tw.
13 Electric Stimulation/
14 Electric Stimulation Therapy/
15 (electric* adj4 (field* or stimul* or pulse* or cell? or membrane* or pore?)).tw.
16 Ablation Techniques/
17 ((tissue* or tumo?r* or non-thermal* or nonthermal*) adj4 ablat*).tw.
18 exp Nanotechnology/
19 (nanotechnolog* or nanopore*).tw.

20 or/6-19
21 5 and 20
22 nanoknife*.tw.
23 Cliniporator*.tw.
24 22 or 23
25 21 or 24
26 animals/ not humans/
27 25 not 26
28 limit 27 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Bates AS, Ayers J, Kostakopoulos N et al. (2021) A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. European Urology Oncology, 4(3): 405–423.	Systematic review n=14 studies	The certainty of the evidence regarding the comparative effectiveness of FT as a primary treatment for localised PCa was low, with significant uncertainties. Until higher-certainty evidence emerges from robust prospective comparative studies measuring clinically meaningful outcomes at long-term time points, FT should ideally be performed within clinical trials or well-designed prospective cohort studies.	IRE outcomes not reported separately from other therapy outcomes.
Baydoun A, Traughber B, Morris N et al. (2017) Outcomes and	Systematic review n=2288 (18 studies)	The outcomes of FT in PCa seem to be similar to those observed with whole	1/18 studies relate to IRE, which is already

toxicities in patients treated with definitive focal therapy for primary prostate cancer: systematic review. Future Oncology (London, England), 13(7): 649–663.		gland therapy and with fewer side effects. Further research, including prospective randomised trials, is warranted to elucidate the potential advantages of focal radiation techniques for treating PCa.	included in the appendix.
Beyer LP, Pregler B, Verloh N et al. (2017) Effect of irreversible electroporation of prostate cancer on microcirculation: Imaging findings in contrast-enhanced T1-weighted 3D MRI. Clinical Hemorheology and Microcirculation, 67(34): 399–405.	n=13 Follow up = 6 months	Ablated prostate was either homogeneously (8/13 [62%]) or heterogeneously (5/13 [38%]) hypo attenuating. Peripheral contrast enhancement manifesting as a hyper attenuating margin was observed during the arterial (60 sec) (3/13 [23%]) and venous (240 sec) (10/13 [77%]) phase. The ablation defect showed a sharp (8/13 [62%]) or blurry (5/13 [38%]) margin.	Study focuses on imaging outcomes.
Collettini F, Enders J, Stephan C et al. (2019) Image-guided Irreversible Electroporation of Localised Prostate Cancer: Functional and Oncologic Outcomes.	n=30 Follow up = median 20 months	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	Larger studies included.

Radiology, 292(1): 250–257.		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.	

Dong S, Wang H, Zhao Y et al. (2018) First Human Trial of High-Frequency Irreversible Electroporation Therapy for Prostate Cancer. Technology in Cancer Research & Treatment, 17: 1533033818789692.	n=40 Follow up = 6 months	A small amount of muscle relaxant was still needed, so there were no visible muscle contractions during the pulse delivery process. Four weeks after treatment, it was found that the ablation margins were distinct in magnetic resonance imaging scans, and the prostate capsule and urethra were retained. Eight patients underwent radical prostatectomy for pathological analysis after treatment, and the results of hematoxylin and eosin staining revealed that theurethra and major vasculature in prostate have been preserved.	Larger studies with longer follow up included
Fallara G, Capogrosso P, Maggio P et al. (2020) Erectile function after focal therapy for localised prostate cancer: a systematic review. International Journal of Impotence Research, 33(4):418-427.	Systematic review n=26 studies	Overall, reported sexual function outcomes after these treatment modalities were generally good, with many studies reporting a complete recovery of EF at 1-year follow up. However, the quality of current evidence is affected both by the lack of well-	All included IRE studies in Table 2 or appendix.

		conducted comparative studies and by a significant heterogeneity in terms of study design, study population, erectile and sexual function assessment modalities.	
Giganti F, Stabile A, Giona S et al. (2019) Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome. Magnetic Resonance Imaging, 58: 143–147.	n=30 Follow up = median 16 months	Six men were undertreated and showed mpMRI recurrence after 6 months. At 1-year, three additional men had recurrence. Overall, four of these 9 men (44%) were retreated. The other five men did not receive any further treatment. Median time to re-treatment was 15 months. Median pre-treatment lesion volume was 0.65 cc, 0.66 cc and 0.43 cc on the different mpMRI sequences (T2-weighted, diffusion-weighted, and dynamic contrast enhanced imaging). Median necrotic volume was 10.77 cc. Median overall residual fibrosis volumes were 0.84 cc and 0.95 cc at 6-month and 1-year mpMRI. Pre-	Larger studies included.

		treatment, necrotic and residual fibrosis volumes were significantly different ($p < 0.001$). Pre-treatment tumour volumes on diffusion-weighted imaging and necrotic volumes were correlated ($r = 0.18$; $p = 0.02$).	
Hopstaken JS, Bomers JGR, Sedelaar MJP et al. (2022) An Updated Systematic Review on Focal Therapy in Localised Prostate Cancer: What Has Changed over the Past 5 Years? European Urology, 81(1): 5–33.	Systematic review n=5827 (72 studies)	Twenty-seven studies reported on high-intensity focused ultrasound (HIFU), nine studies on irreversible electroporation, 11 on cryoablation, eight on focal laser ablation and focal brachytherapy, seven on photodynamic therapy (PDT), two on radiofrequency ablation, and one on prostatic artery embolization. The majority of studies were prospective development stage 2a studies (n = 35). PDT and HIFU, both in stage 3, showed promising results. Overall, HIFU studies reported a median of 95% pad-free patients and a median of 85% patients with no clinically significant cancer (CSC) in the	All eligible IRE studies in Table 2 or appendix.

		treated area. For PDT, no changes in continence were reported and a median of 90% of patients were without CSC. Both treatments were well tolerated.	
Jung EM, Engel M, Wiggermann P et al. (2021) Contrast enhanced ultrasound (CEUS) with parametric imaging after irreversible electroporation (IRE) of the prostate to assess the success of prostate cancer treatment. Clinical Hemorheology and Microcirculation, 77(3): 303–310.	n=50 Follow up = 6 months	While 13 patients showed local recurrence, 37 patients were successfully treated, meaning no local recurrence within six months after ablation. 18 patients showed signs of prostatitis after IRE. Tumorous changes were visually characterized by dynamic early nodular hypervascularization with fast and high wash-in. Correspondingly, nodular red and yellow shades were seen in parametric imaging. All patients with remaining tumor were correctly identified with CEUS and parametric imaging. After IRE there is a relevant decrease in tumor microcirculation in all patients, as seen in more purple shades of the prostate. The	Study focuses on imaging outcomes.

		sensitivity for detecting residual tumor with CEUS compared to MRI was 76%, the specificity was 81%.The corresponding positive predictive value (PPV) was 73% and the negative predictive value (NPV) was 83%.	
Kayano PP, Klotz L (2021) Current evidence for focal therapy and partial gland ablation for organ-confined prostate cancer: systematic review of literature published in the last 2 years. Current Opinion in Urology, 31(1): 49–57.	Systematic review n= 30 studies	Focal therapy and partial gland ablation for organ-confined prostate cancer is an option for patients with intermediate-risk disease because of its low complication profile and preservation of QOL. Trials comparing the outcome of different focal therapy technologies have not been carried out, and the existing evidence does not point to one approach being clearly superior to others. Long-term oncologic outcome is lacking.	All included IRE studies in Table 2 or appendix.
Morozov A, Taratkin M, Barret E et al. (2020) A systematic review of irreversible electroporation in localised prostate cancer treatment.	Systematic review n= 433 (10 studies)	In-field recurrence rate was 0%–39% and out-field 6.4%–24%. In all studies, PSA level decreased: twice lower than baseline after 4 weeks and by 76%	All studies already included in Table 2 or appendix.

Andrologia, 52(10): e13789.		after 2 years. Most of the authors noted sexual and urinary toxicity during the first half year after surgery. However, functional outcomes recovered to baseline after 6 months with mild decrease in sexual function. Complication rates after irreversible electroporation were 0%–1% of Clavien–Dindo III and 5%–20% of Clavien–Dindo I–II. Irreversible electroporation has promise oncological outcomes, rate of post-operative complications and minimal-to-no effects on erectile and urinary function. However, medium and long-term data on cancer-specific and recurrence-free survival are still lacking.	
Murray KS, Ehdaie B, Musser J et al. (2016) Pilot Study to Assess Safety and Clinical Outcomes of Irreversible Electroporation for Partial Gland Ablation in Men with Prostate Cancer.	n=25 Follow up = median 10.9 months	Grade 3 complications occurred in 2 patients including epididymitis (1) and urinary tract infection (1). Fourteen patients experienced grade ≤ 2 complications, mainly transient	Larger studies included.

The Journal of Urology, 196(3): 883–890.		urinary symptoms, hematuria, and urinary tract infections. Of 25 patients, 4 (16%) had cancer in the zone of ablation on routine follow up biopsy at 6 months. Of those with normal urinary function at baseline, 88% and 94% reported normal urinary function at 6 and 12 months after prostate gland ablation, respectively. By 12 months, only 1 patient with normal erectile function at baseline reported new difficulty with potency and only 2 patients (8%) required a pad for urinary incontinence. Prostate gland ablation with irreversible electroporation is feasible and safe in selected men with localised prostate cancer. Intermediate-term urinary and erectile function outcomes appear reasonable. Irreversible electroporation is effective in ablation of tumor-bearing prostate tissue, as a majority of men had	

		no evidence of residual cancer on biopsy 6 months after prostate gland ablation.	
Niessen C, Jung EM, Beyer L et al. (2015) Percutaneous irreversible electroporation (IRE) of prostate cancer: Contrast-enhanced ultrasound (CEUS) findings. Clinical Hemorheology and Microcirculation, 61(2): 135–141.	n=13 Follow up = 6 months	EUS images showed significantly reduced microcirculation of the lesions (mean 0.9 ± 0.6 cm (0.5–1.5 cm) after IRE. Microcirculation was reduced from 2.15 ± 0.56 prior to ablation to 0.65 ± 0.63 ($p < 0.001$) immediately after the ablation and to 0.27 ± 0.44 one day after IRE ($p < 0.001$).	Study focuses on imaging outcomes.
Scheltema MJ, Postema AW, de Bruin DM et al. (2017) Irreversible electroporation for the treatment of localised prostate cancer: a summary of imaging findings and treatment feedback. Diagnostic and Interventional Radiology (Ankara, Turkey), 23(5): 365–370.	n=32 Follow up = 1-12 months	The mean AZV on T2-weighted imaging 4 weeks following IRE was 12.9 cm3 (standard deviation [SD]=7.0), 5.3 times larger than the planned AZV. Linear regression showed a positive correlation ($r=0.76$, $P = 0.002$). For CEUS the mean AZV was 20.7 cm3 (SD=8.7), 8.5 times larger than the planned AZV with a strong positive correlation ($r=0.93$, $P = 0.001$). Prostate volume is reduced over time (mean= -27.5%, SD=11.9%)	Study focuses on imaging outcomes.

		due to ablation zone fibrosis and deformation, illustrated by 3D reconstruction.	
Scheltema MJ, van den Bos W, Siriwardana AR et al. (2017) Feasibility and safety of focal irreversible electroporation as salvage treatment for localised radio-recurrent prostate cancer. BJU International, 120: 51–58.	n=18 Follow up = median 21 months	No high-grade adverse events (CTCAE >2) or recto-urethral fistulae occurred. No statistically significant declines were observed in QoL outcomes (n = 11) on the EPIC bowel domain (P = 0.29), AUA symptom score (P = 0.77), or the SF-12 physical (P =0.17) or SF-12 mental component summary (P = 0.77) questionnaires. At 6 months, patients who had undergone salvage therapy experienced a decline in EPIC sexual domain score (median of 38–24; P = 0.028) and urinary domain (median of 96–92; P = 0.074). Pad-free continence and erections sufficient for intercourse were preserved in 8/11 patients and 2/6 patients at 6 months, respectively. The mpMRI was clear in 11/13 patients, with	Larger studies included.

		two single out-field lesions (true-positive and false-positive, respectively). The median (interquartile range) nadir PSA was 0.39 (0.04–0.43) lg/L. Three and four patients experienced biochemical failure using the Phoenix and Stuttgart definitions of biochemical failure, respectively. Eight out of 10 of the patients were clear of any PCa on follow up biopsy, whereas two patients had significant PCa on follow up biopsy (International Society of Urological Pathology grade 5).	
Valerio M, Stricker PD, Ahmed HU et al. (2014) Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. Prostate Cancer and Prostatic Diseases, 17(4): 343–347.	n=34 Follow up = median 6 months	After a median follow up of 6 months (range 1-24), 12 grade 1 and 10 grade 2 complications occurred. No patient had grade >/= 3 complication. From a functional point of view, 100% (24/24) patients were continent and potency was preserved in 95% (19/20) men potent before treatment. The volume of ablation	More recent studies included.

		was a median 12ml (IQR= 5.6 - 14.5ml) with the median PSA after 6 months of 3.4ng/ml (IQR= 1.9 - 4.8ng/ml). MpMRI showed suspicious residual disease in six patients, of whom four (17%) underwent another form of local treatment.	
Valerio M, Dickinson L, Ali A et al. (2017) Nanoknife Electroporation Ablation Trial: A Prospective Development Study Investigating Focal Irreversible Electroporation for Localised Prostate Cancer. The Journal of Urology, 197(3pt1): 647–654.	n=19 Follow up = 12 months	Of the patients 16 were available for estimating the first outcome as 1 was lost to follow up and 2 had received another form of treatment by study end. All 16 men had pad-free/leak-free continence at 12 months. The proportion of men with erection sufficient for penetration decreased from 12 of 16 (75%) to 11 of 16 (69%). No serious adverse events were recorded. There was a statistically significant improvement in urinary symptoms according to changes in UCLA-EPIC (UCLA Expanded Prostate Cancer Index Composite) and I-PSS (International Prostate Symptom	Larger studies included.

		Score) (p = 0.039 and 0.001, respectively). Erectile function remained stable according to the change in IIEF-15 (15-Item International Index of Erectile Function) (p = 0.572). Median prostate specific antigen significantly decreased to 1.71 ng/ml (p = 0.001). One man refused followup biopsy. No residual disease was found in 11 patients (61.1%). One man (5.6%) harbored clinically insignificant disease and the remaining 6 (33.3%) harbored clinically significant disease.	
van den Bos W, de Bruin DM, van Randen A et al. (2016) MRI and contrast-enhanced ultrasound imaging for evaluation of focal irreversible electroporation treatment: results from a phase I-II study in patients undergoing IRE followed by radical prostatectomy. European	n=16 Follow up = 4 weeks	Evaluation of the imaging demonstrated that with T2-weighted MRI, dynamic contrast enhanced (DCE) MRI, and CEUS, effects of IRE are visible. T2MRI and CEUS closely match the volumes on histopathology (Pearson correlation r= 0.88 resp. 0.80).	Study focuses on imaging outcomes.

Radiology, 26(7): 2252–2260.		However, IRE is not visible with TRUS.	
Walker NA, Norris JM, Shah TT et al. (2018) A comparison of time taken to return to baseline erectile function following focal and whole gland ablative therapies for localised prostate cancer: A systematic review. Urologic Oncology: Seminars and Original Investigations, 36(2): 67–76.	Systematic review n=17 studies	WG cryotherapy was associated with a significant decline in EF at 6 months with minimal improvement at 36 months. Baseline IIEF-15 of patients undergoing focal HIFU fell 30 points at 1 month but returned to baseline by 6 months. The remaining focal therapies demonstrated minimal or no effect on EF, but the men in these studies had small foci of disease. The review is limited by lack of randomised studies and heterogenous outcome measures.	All included IRE studies in Table 2 or appendix.