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 pulses of high-voltage electrical current are passed through to create tiny holes (pores) in the cancer cells. The aim is to kill the cancer cells (irreversible electroporation) 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
Expanded Prostate Cancer Index Composite	EPIC
Erection sufficient for intercourse	ESI
High frequency irreversible electroporation	H-FIRE
High intensity focused ultrasound	HIFU
International Index of Erectile Function	IIEF-5
International Prostate Symptom score	IPSS
Interquartile range	IQR
Irreversible electroporation	IRE
International Society of Urological Pathology	ISUP
Multiparametric MRI	mpMRI
Objective performance criteria	OPC
Prostate imaging reporting and data system	PI-RADS
Prostate-specific antigen	PSA
Quality of life	QoL
Robot-assisted radical prostatectomy	RARP
Randomised controlled trial	RCT
Short form-12 questionnaire	SF-12
Transperineal template-guided prostate mapping biopsy	TTMB
Transurethral resection of the prostate	TURP
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 and updated in April 2023.

Procedure name

- 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. 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 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 IRE 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. Several 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 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 may be 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 score 6, 18 were in patients with Gleason score 7, and 26 were in patients with Gleason scores 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 score 6, 10 in patients with Gleason score 7, 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 greater than 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).

In a case series of 229 patients, 17% (38/229) of patients progressed to radical treatment, with an overall failure-free survival rate of 83% during a median follow up of 60 months. The failure-free survival rate was 79% (15/19) for low-grade disease, 84% (164/195) for intermediate-grade disease and 79% (11/14) for high-grade disease. Kaplan–Meier-estimated failure-free survival rates were 91% at 3 years, 84% at 5 years and 69% at 8 years. Metastasis-free survival was nearly 100% (228/229); prostate cancer-specific and overall survival were 100% (229/229; Scheltema 2022).

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 a single-arm, OPC (target values derived from historical data for comparison) trial of 109 patients with localised prostate cancer who had H-FIRE, prostate cancer was detected in 14% (14/100; 95%CI 7.9% to 22.4%) of the 100 patients with biopsy 6 months after H-FIRE treatment. The rate of clinically significant prostate cancer was 6% (95% CI 2.2% to 12.6%; p<0.001; 1 in the treatment zone and 5 outside the treatment zone). Superiority criteria compared with the historical control of 20% was achieved in the subgroup analysis that only included the 57 patients with a Gleason score of 7 at baseline (3.5% 6-month clinically significant prostate cancer; 95% CI 0.4% to 12.1%; p<0.001; Wang 2022).

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 out-of-field disease at 12-month follow up. With exclusion of the first 32 patients to account for increased treatment margin to 10 mm and improved technique, 85% (63/74) of patients having biopsy were free of clinically significant cancer, 3% (2/74) had significant in-field disease and 12% (9/74) had significant out-of-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 prostate cancer at 12 months, and 1 patient was diagnosed with metastatic disease directly after IRE because of persisting elevated PSA (greater than 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).

In a case series of 70 patients with localised prostate cancer, of the 64 patients who had primary IRE, 88% (35/40) of patients having surveillance biopsy, usually at 12 months, were free from all in-field cancer, 8% (3/40) had significant in-field cancer, and 5% (2/40) had insignificant in-field cancer. Of the 6 patients who had salvage IRE for local recurrence after external beam radiotherapy, 2 patients proceeded with transperineal surveillance biopsies after salvage IRE, and both had benign results and no residual in-field or out-of-field cancer (Yaxley 2022).

In an RCT of 106 patients with localised low-intermediate risk prostate cancer who had focal ablation or extended ablation, of the 101 patients who had transperineal template prostate biopsy at 6 months after IRE, clinically significant prostate cancer (Gleason score of 3 + 4 or more) was reported in 19% (9/48) of patients in the focal ablation group and 13% (7/53) of patients in the extended ablation group. There was no statistically significant difference between the 2 groups. Any grade prostate cancers were found in 56% of patients in the focal ablation group and 43% of patients in the extended ablation group, without statistically significant difference between the 2 groups (de la Rosette 2023).

In the case series of 229 patients, 83% (190/229) of patients had standardised biopsies at 12 months. Residual clinically significant prostate cancer was found in 24% (45/190) of patients; of these 31 were out-of-field and 14 in-field/marginal recurrences. The median (IQR) nadir PSA level (lowest PSA level after treatment) was 1.9 (1.1 to 4.4) nanogram/ml and was not statistically significantly associated with residual clinically significant prostate cancer at biopsy (p=0.21; Scheltema 2022).

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).

In the case series of 70 patients, for the 64 patients who had primary IRE, pre-IRE mpMRI scans showed that PI-RADS 4 was identified in 69% (44/64) of the patients, PI-RADS 5 in 19% (12/64), PI-RADS 3 in 6% (4/64) and PI-RADS 2 or less in 6% (4/64). Post-IRE mpMRI scans (usually at 6 months after IRE) revealed that low-risk PI-RADS 2 was identified in 88% (46/52) of patients, with PI-RADS 3 in 6% (3/52), PI-RADS 4 in 2% (1/52) and PI-RADS 5 in 4% (2/52) of patients. Of the 6 patients who had salvage IRE, 3 patients had surveillance mpMRI scans after salvage IRE and all had low-risk PI-RADS 2 scores (Yaxley 2022).

In the case series of 229 patients, the 6-month MRI was done in 99% (226/229) of patients and showed a complete ablation in 82% (186/226) of patients. Of those with signs of residual disease (n=40), 10 patients had in-field lesions, 10 patients had lesions adjacent to the ablation zone, 17 patients had out-of-field lesions, and 3 patients had both in-field and out-of-field lesions (Scheltema 2022).

Reduction in PSA

In the case series of 123 patients, there was a reduction in median (IQR) PSA levels of 57% to 2.5 nanograms/ml (1.43 to 5.68) 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 (IQR) PSA of 51% (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 (3.3 to 7.3; Scheltema 2018a).

In the single-arm, OPC trial of 109 patients who had H-FIRE, there was a reduction in median (IQR) PSA from 9.0 (6.0 to 12.7) nanograms/ml at the baseline to 1.1 (0.4 to 3.2) nanograms/ml at 6 months after H-FIRE. Biochemical recurrence (PSA level greater than 2.0 nanograms/ml over the nadir) was reported in 5 patients at 6 months (Wang 2022).

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

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

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).

In the single-arm, OPC trial of 109 patients who had H-FIRE, urinary retention was reported in 3% (3/109) of patients at 6 months after H-FIRE (Wang 2022).

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 who were continent at baseline (Scheltema 2018a).

In the single-arm, OPC trial of 109 patients who had H-FIRE, median (IQR) IPSS reduced from 9.0 (4.0 to 15.0) at baseline to 4.5 (2.0 to 7.0) at 6 months after H-FIRE, and the rate of incontinence was 1% (Wang 2022).

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).

In the case series of 70 patients, for the 64 patients having primary IRE, no incontinence developed after primary IRE (0/64), but 1 patient subsequently developed incontinence after a repeat contralateral IRE procedure was done. For the 6 patients having salvage IRE, urinary incontinence developed in 2 patients, although incontinence only happened after both patients subsequently had TURP for bladder outflow obstruction (Yaxley 2022).

In the RCT of 106 patients, the estimated mean difference in IPSS between focal and extended IRE across 24 months was 1.9 (95% CI -0.37 to 4.2, p=0.099; de la Rosette 2023).

Urinary tract infection

In the single-arm, OPC trial of 109 patients who had H-FIRE, UTI was reported in 2% (2/109) of patients at 6 months after H-FIRE (Wang 2022).

Sexual function

In the case series of 429 patients and 471 IRE treatments, there was a mean point 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-month 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 a reduction in 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 case series of 123 patients, median EPIC sexual function summary scores (scored 1 to 100, with 100 indicating greater sexual function) statistically significantly decreased from 65 at baseline to 50 at 12 months (p=0.00001). Of patients who were potent at baseline, 7% were without ESI at 12-month follow up (Blazevski 2020).

In the single-arm, OPC trial of 109 patients who had H-FIRE, median (IQR) IIEF-5 score was 2.0 (1.0 to 18.0) at baseline and 2.0 (0.5 to 12.5) at 6 months after H-FIRE, and the rate of emergent sexual dysfunction was 9% (Wang 2022).

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 the case series of 63 patients, the median (IQR) EPIC sexual function summary scores (scored 1 to 100, with 100 indicating greater sexual function) were 66 (47 to 85), 50 (27 to 75), 54 (29 to 72) and 48 (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 (IQR) were 60 (25 to 82), 52 (29 to 71), 46 (14 to 79) and 27 (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).

In the case series of 70 patients, for sexually active men, erectile function was maintained in 86% (24/28) of patients who had primary IRE and 50% (1/2) of patients who had salvage IRE (Yaxley 2022).

In the RCT of 106 patients, erectile dysfunction was reported in 22% (10/46) of patients in the focal ablation group and 24% (12/51) of patients in the extended ablation group at 3 months. There was no statistically significant difference between the 2 groups. The estimated mean differences in IIEF scores (including IIEF-15 total, IIEF-Q2, erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction) and EPIC scores (including urinary function, bowel habits, sexual function, hormonal function and overall satisfaction) between the 2 groups across 24 months were not statistically significantly different (all p>0.05; de la Rosette 2023).

In the case series of 229 patients, 71% (102/144) of men had erections sufficient for intercourse at baseline and this decreased to 58% (76/131). Baseline age correlated with the risk of developing erectile dysfunction (OR 1.08, 95% CI 1.01 to 1.16, p=0.035). At the 12-month follow up, there was a significant decline in the EPIC sexual domain (p=0.001; Scheltema 2022).

Other adverse events

In the single-arm, OPC trial of 109 patients who had H-FIRE, bladder stones composed of mostly tissue debris (Clavien-Dindo classification grade 3) were reported in less than 1% (1/109) of patients at 6 months after H-FIRE (Wang 2022).

Moderate

In the case series of 429 patients and 471 IRE treatments, 1 patient reported prostatitis, 1 patient reported proctitis, fewer 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 single-arm, OPC trial of 109 patients who had H-FIRE, epididymitis was reported in 5% (5/109) of patients at 6 months after H-FIRE (Wang 2022).

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).

In the case series of 70 patients, a complication of Clavien-Dindo grade greater than 2 was reported in 1 patient who needed dilation of a urethral stricture at 3 months unrelated to IRE of a left mid-anterior horn peripheral zone tumour (Yaxley 2022).

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 the 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).

In the single-arm, OPC trial of 109 patients who had H-FIRE, elevated abnormal white blood cell level in urine was reported in 24% (26/109) of patients and prolonged gross haematuria was reported in 4% (4/109) of patients at 6 months after H-FIRE (Wang 2022).

In the RCT of 106 patients, overall adverse event rates happened in 59% (30/51) of patients in the focal ablation group and 62% (34/55) of patients in the extended ablation group within 3 months after IRE. Of the 30 patients with adverse events in the focal ablation group, grade 1 adverse events were reported in 23 patients, grade 2 in 6 patients and grade 4 in 9 patients. In the 34 patients with adverse events in the extended ablation group, grade 1 adverse events were reported in 27 patients and grade 2 in 7 patients (de la Rosette 2023).

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 14 September 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (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.

List of studies included in the IP overview

This IP overview is based on 7,834 patients (in which 1,219 patients had IRE) from 1 systematic review, 1 RCT, 1 non-randomised comparative study, 1 single-arm, OPC trial and 7 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 2,870 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) and Scheltema (2018a).

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 prostate cancer 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 prostate cancer 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 prostate cancer; no previous androgen suppression treatment for prostate cancer; 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 prostate cancer 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

Sexual dysfunction

Follow up	Value
EPIC sexual score at baseline	65
EPIC sexual score at 12 months	50 (p = 0.00001 compared to baseline)
Patients with no change in potency after 12 months*	76% (40/53)
Patients with erections sufficient for sexual activity after 12 months*	17% (9/53)
Patients without erections sufficient for sexual activity after 12 months*	7% (4/53)

*based on 53 patients who were potent before treatment

Study 4 Scheltema (2018a)

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 prostate cancer (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 prostate cancer (high-volume ISUP 1 or any 2 or 3). For RARP, this was defined as biochemical failure (PSA≥0.2 microgram/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 prostate cancer. 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 prostate cancer 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 prostate cancer; No previous androgen suppression/hormone treatment for prostate cancer; 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 prostate cancer 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 prostate cancer; 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

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,	No (P = 0.11, E= -3.5,	

						CI ±4.7)	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 to 71)
Patient selection criteria	Patients with apical prostate cancer; 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 prostate cancer 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 prostate cancer found within the intention-to-treat zone, or (3) out-of field—defined as any prostate cancer found outside the intention-to-treat zone. Significant prostate cancer 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 prostate cancer, 37 out of 50 (74%) had ISUP grade 2 prostate cancer, 6 out of 50 (12%) had ISUP grade 3 prostate cancer and 2 out of 50 (4%) had ISUP grade 4 prostate cancer (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 prostate cancer.

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)

Study 8 Wang H (2022)

Study details

Study type	Single-arm, objective performance criteria trial (NCT03838432)
Country	China (4 centres)
Recruitment period	2018 to 2019
Study population and number	n=109 Patients with prostate cancer who had H-FIRE
Age and sex	Median 67 years (IQR 62 to 73)
Patient selection criteria	Inclusion criteria: patients with low- or intermediate-risk prostate cancer; aged 40 to 85 years; serum PSA level less than 20 ng/ml; clinical stage of T2c or less; and Gleason score of 7 or less. Exclusion criteria: prior radical prostatectomy, hormonal therapy, or radiotherapy; prostatic calculus greater than 5 mm; history of epilepsy; cardiac pacemaker or any metal implant between L1 and midfemur level; and any other malignant tumour.
Technique	H-FIRE was done using a composite steep-pulse therapeutic apparatus (Remedicine Co) under general anaesthesia with full muscle paralysis. Electrode needles were placed into the target lesion through a 5-mm brachytherapy template grid under the guidance of a biplanar transrectal ultrasound probe. One electrode needle was placed at the centre of each targeted lesion; 3 or 4 were placed 0.5 to 2.0 cm from the centre of each lesion.
Follow up	6 months
Conflict of interest/source of funding	Conflict of interest: 2 authors reported receiving grants from Remedicine Co. No other disclosures were reported. Funding/Support: This work was supported by Remedicine Co, grant 2019YFC0119100 from the National Key Research and Development Program of China, grant 81602220 from the National Natural Science Foundation of China, grant PWRd2020-17 from the Shanghai Pudong New District Health System Medical Talents Training Plan, China, grant PKX2020-S11 from the Fund of Development on Science and Technology of Shanghai Pudong New District, China, and grant 18441910900 from the Shanghai “Action Plan of Technological Innovation.”

Analysis

Follow-up issues: Patients were followed up at 1 week, 1 month, 3 months, and 6 months after H-FIRE ablation. At 6 months, 9 patients withdrew (8 no longer wished to have biopsy and 1 follow up exceeded the time window).

Study design issues: This multicentre, single-group, objective performance criteria, nonrandomised controlled trial evaluated the efficacy and safety of H-FIRE as primary treatment for localised prostate cancer.

The primary end point was 6-month clinically significant prostate cancer, which was defined as any biopsy core with Gleason score of greater than or equal to 7, or Gleason score of 6 plus maximum cancer core length of

greater than 3 mm or an increase from the original cancer burden. Secondary outcomes were calculated in patients who received H-FIRE treatment.

Sample size calculation was based on the following assumptions: (1) the 6-month rate of clinically significant prostate cancer of 20% for historical control with focal therapy and 9% in patients receiving H-FIRE treatment and (2) 80% power and α level of 0.025 (1-sided). The 9% 6-month rate of clinically significant prostate cancer was a conservative estimate based on 7.2% to 10.0% 6-month out-of-field clinically significant prostate cancer and no in-field clinically significant prostate cancer, as previously reported. The calculation yielded 87 participants. Because the clinically significant prostate cancer was diagnosed using an invasive biopsy, a dropout rate of 20% at 6 months was assumed, and the final sample size was set at 110 participants.

Study population issues: A total of 117 patients were enrolled in this study, and 109 patients received H-FIRE ablation. Based on the National Comprehensive Cancer Network risk classification, the risk for biochemical recurrence of locally advanced prostate cancer was low in 27 patients (24.8%) patients and intermediate in 82 patients (75.2%). Median (IQR) serum PSA level was 9.0 (6.0 to 12.7) ng/ml. Median (IQR) number of biopsy cores was 20.0 (19.5 to 23.0). Median (IQR) number of positive biopsy cores was 3 (1 to 4). Gleason score was 4+3=7 in 17patients (15.6%), 3+4=7 in 45 patients (41.3%), and 3+3=6 in the remaining 47 patients (43.1%). Median (IQR) IPSS was 9.0 (4.0 to 15.0) and median (IQR) IIEF-5 score was 2.0 (1.0 to 18.0). The PIRADS was 3 or higher in 85 patients (78.0%; PI-RADS 3: 24 patients [28.2%]; PI-RADS 4: 52 patients [61.2%]; PI-RADS 5: 9 patients [10.6%]).

Other issues: This objective performance criteria trial used a historical control rather than a parallel control group, and there was a lack of data in the historical control group. Also, improvement in preoperative assessment might produce bias that favoured the H-FIRE treatment in the study. Furthermore, the sample size was relatively small.

Key efficacy findings

Number of patients analysed: 109

Efficacy outcomes in patients having H-FIRE

Outcomes	**Number**	**% (95% CI)**
6-month biopsy (n=100)		
Median number of cores	14	NA
Clinically significant prostate cancer	6	6 (2.2 to 12.6)
Any cancer	14	14 (7.9 to 22.4)
Gleason score		
3+3	12	12 (6.4 to 20.0)
4+3	2	2 (0.2 to 7.0)
6-month PSA (n=100)	**Median (IQR)**	**Change from baseline**
PSA, ng/ml	1.08 (0.4 to 3.2)	-6.4 (-7.7 to -5.1)
IPSS	4.50 (2.0 to 7.0)	-4.0 (-6.1 to -1.9)
IIEF-5	2.00 (0.5 to 12.5)	0 (-0.2 to 0.2)

There were 6 clinically significant prostate cancer, including 1 in the treatment zone and 5 outside the treatment zone.

The rate of clinically significant prostate cancer was 6.0% (95% CI, 2.2 to 12.6%). The upper limit of 95% CI was less than 20%, and 1-sided p<0.001. In the worst-scenario sensitivity analysis, in which the clinically significant prostate cancer was assumed in the 6 patients without 6-month biopsy, the 6-month clinically significant prostate cancer rate was 11.0% (95% CI 5.8 to 18.4%). Superiority compared with the 20% historical control was also met in the subgroup analysis that only included the 57 patients with a Gleason score of 7 at the baseline (3.5% 6-month clinically significant prostate cancer; 95% CI, 0.4% to 12.1%; p<0.001). Prostate cancer was detected in 14 patients (14.0%; 95% CI, 7.9% to 22.4%).

Biochemical recurrence occurred in 5 patients (all at 6 months).

Diaper-free rate was 99.1% (108 of 109 patients) at baseline and 98% (98 of 100 patients) at 6 months. Of the 100 patients with 6-month follow up, percentage change in IPSS from baseline to 6 months was 50.0%, and only 9 patients (9%; 95% CI, 4.2 to 16.4%) experienced emergent sexual dysfunction (IIEF-5 >7 at the baseline and ≤7 at 6 months).

Association between ablation ratio and outcomes

Patients with lower ablation ratio (<50%, 50% to 75%, and >75%) had higher rate of 6-month clinically significant prostate cancer (ratio <50%, 4 of 22 [18.2%]; 50% to 75%, 2 of 55 [3.6%]; >75%, 0%; p=0.04), but comparable IPSS and IIEF-5 score. A linear regression analysis showed that ablation ratio was not correlated with the change of either IPSS or IIEF-5 score at 6 months relative to the baseline.

Key safety findings

Safety outcomes in patients having H-FIRE

Complications (n=109)	Number	% (95% CI)
Number of patients	29	26.6 (18.6 to 35.9)
Number of events	41	37.6 (28.5 to 47.4)
Clavien-Dindo grade		
1	33	30.3 (21.8 to 39.8)
2	7	6.4 (2.6 to 12.8)
3	1	0.9 (0 to 5.0)
Type		
Abnormal white bleed cell in urine	26	23.9 (16.2 to 33.0)
Epididymitis	5	4.6 (1.5 to 10.4)
Prolonged gross haematuria	4	3.7 (1.0 to 9.1)
Urinary retention	3	2.8 (0.6 to 7.8)
Urinary tract infection	2	1.8 (0.2 to 6.5)
Bladder stone	1	0.9 (0 to 5.0)

A Clavien-Dindo classification grade 3 complication occurred in 1 patient (0.9%; bladder stone composed of mostly tissue debris). No urethrorectal fistula was reported. Other clinically significant events that were deemed to be not associated with the H-FIRE treatment included acute coronary syndrome (1 [0.9%]), myocardial infarction (2 [1.8%]), gastric cancer (1 [0.9%]), obstructive jaundice (1 [0.9%] caused by hepatic cyst), and proliferative lymphadenopathy (1 [0.9%]).

No intraoperative complications were reported.

Study 9 Yaxley WJ (2022)

Study details

Study type	Case series (retrospective)
Country	Australia (single centre)
Recruitment period	2018 to 2021
Study population and number	n=70 (64 primary IRE and 6 salvage IRE) Patients with localised prostate cancer
Age and sex	Median 72 years (range 51 to 87)
Patient selection criteria	Inclusion criteria: patient with localised prostate cancer based on staging prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) scan were considered for inclusion. Exclusion criteria: patients who had tumours with a maximum diameter of 25 mm or more on mpMRI were considered unsuitable for IRE. Pre-IRE template prostate biopsies were needed to exclude significant volume or Gleason grade cancer outside the IRE treatment zone. Patients were also excluded if they had prior IRE at another centre.
Technique	The IRE procedure was done under general anaesthesia with the patient in lithotomy position and a urethral catheter in situ. In general, surgeons aimed for the distance between IRE needles of 15 mm (10 to 22 mm), a current of 25 Amp (20 to 35 Amp), a voltage of 2,500 volts (1,500 to 3,000 volts) and a needle exposure length of 15 to 20 mm. In the primary IRE setting bilateral tumours were done at surgeon discretion, but single ablations only were done in the salvage setting. Primary IRE was done on 64/70 of whom 4 had bilateral lesions ablated, and salvage IRE for local recurrence after radiotherapy was done in 6 patients.
Follow up	Median 23 months (range 3 to 39)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were investigated with a mpMRI at 6 months after IRE and routine surveillance template transperineal biopsies of the in-field treatment zone and out-of-field prostate tissue at a minimum of 12 months postoperatively. Two patients relocated overseas after IRE and were censored at last follow up.

Study design issues: This retrospective review of prospectively acquired data evaluated histological in-field clearance of prostate cancer at ≥12 months after IRE, and assessed postoperative complications, urinary incontinence and erectile dysfunction.

Significant tumour recurrence on surveillance prostate biopsy was defined as a ≥6 mm core ISUP grade 1 (Gleason 3+3), or ISUP grade 2 (Gleason 3+4) with ≥4 mm tumour length, or any focus of ISUP grade ≥3.

Lesions with a positive core length of <4 mm are associated with tumour volume <0.2 ml on whole mount histopathology. A second definition using any focus length of Gleason score 3+4 (ISUP grade 2) as significant cancer was also evaluated.

Study population issues: Of the 64 patients who had primary IRE, the median PSA was 6.10 micrograms/litre (range 0.77 to 25.00). The median ISUP grade was 2, with 12 patients treated with high risk ISUP grade 4 or 5 malignancy. Most patients had a PI-RADS 4 mpMRI (44/64) at diagnosis, with PI-RADS 5 in 12 patients, PI-RADS 3 in 4 patients and PI-RADS 2 or less in 4 patients. There was no contralateral tumour in 42/64 patients, out-of-field ISUP grade 1 in 17/64, ISUP grade 2 in 4/64 and 1 patient had a 1 mm focus of ISUP grade 3 in the contralateral lobe.

Of the 6 salvage IRE procedures for radiotherapy failure, the baseline median PSA at salvage IRE was 2.20 micrograms/litre (range 0.24 to 8.4). The post-radiotherapy, pre-IRE biopsy results showed ISUP grade less than 4 in 5 patients and ISUP grade 5 in 1 patient. Prior to salvage IRE there was no out-of-field cancer in 4 patients, 1 had a small focus of contralateral lobe ISUP grade 2 and another a small focus of ISUP grade 3.

Other issues: Limitations of the study included the relatively short follow-up and the retrospective review of a prospective database. Complications could be underestimated in retrospective studies.

Key efficacy findings

Number of patients analysed: 70

Of the 70 patients, 64 were discharged on the day of the IRE, or day 1 postoperatively (91.4%). The maximum length of stay was 2 days.

Primary IRE (n=64)

- Surveillance biopsy usually at 12 months:
    - complete ablation of all in-field cancer: 87.5% (35/40)
- mpMRI data usually at 6 months:
    - PI-RADS 2: 88.5% (46/52)
    - PI-RADS 3: 5.8% (3/52)
    - PI-RADS 4: 1.9% (1/52)
    - PI-RADS 5: 3.8% (2/52)
- High-risk cohort (ISUP grades 4&5, n=12):
    - mpMRI data: PI-RADS 2, n=10.
      2 patients declined follow-up mpMRI
    - Biopsy data: n=7
        - In-field recurrence: 0% (0/7)
        - Significant out-of-field recurrence: 14.3% (1/7)
        - Insignificant out-of-field recurrence: 42.9% (3/7)

Patterns of recurrence after primary IRE on follow-up prostate biopsy

Recurrence	Significant cancer	Insignificant cancer
In-field	7.5% (n=3)	5.0% (n=2)

Out-of-field	12.5% (n=5)	30.0% (n=12)

Patterns of recurrence after primary IRE with any volume ISUP ≥2 graded as significant recurrence

Recurrence	Significant cancer	Insignificant cancer
In-field	10.0% (n=4)	2.5% (n=1)
Out-of-field	27.5% (n=11)	15.0% (n=6)

Salvage IRE for radiotherapy failure (n=6)

- mpMRI data (n=3): PI-RADS 2, n=3
  The other 3 patients declined mpMRI follow-up because of low or undetectable PSA levels.
- Transperineal surveillance biopsy: n=2, both patients with benign results and no residual in-field or out-of-field cancer.
- One patient had Gleason score 3+4 in 10% of the TURP chips done 7 months after IRE for bladder outflow obstruction.
- 3 patients refused surveillance biopsy because of undetectable PSA levels.

Key safety findings

Re-admission within 30 days for post-treatment complications: n=0

Primary IRE (n=64):
- Incontinence after primary IRE: n=0
- Incontinence after a repeat contralateral IRE procedure: n=1
- Clavien-Dindo grade >2: n=1 (the patient needed dilation of a urethral stricture at 3 months unrelated to IRE of a left mid-anterior horn peripheral zone tumour)
- Erectile function in sexually active men: 85.7% (24/28)

Salvage IRE (n=6):
- Incontinence after a TURP for bladder outflow obstruction: n=2
- Erectile function: n=1 of the 2 patients who were potent before salvage IRE

Study 10 de la Rosette J (2023)

Study details

Study type	RCT (NCT01835977)
Country	Europe (5 European centres)
Recruitment period	2015 to 2020
Study population and number	n=106 (focal ablation, n=51; extended ablation, n=55) patients with localised low-intermediate risk prostate cancer
Age and sex	Median 64 years
Patient selection criteria	Inclusion criteria: clinical stage T1c to T2b; Gleason sum score 6 or 7 (without tumour volume threshold); PSA <15 ng/ml or PSA >15 ng/ml counselled with caution; life expectancy of >10 years.
Technique	The NanoKnife Systema (AngioDynamics Inc.) was used. The focal ablation group had an ablation of the area of the prostate in which the positive biopsies were presented. The extended ablation group had a zonal ablation. Up to 6 IRE electrode needles were placed into the zone under ultrasound image guidance.
Follow up	Median 30 months (IQR 24 to 48)
Conflict of interest/source of funding	This study was supported by the Clinical Research Office of the Endourological Society. The authors had no conflicts of interest to disclose.

Analysis

Follow-up issues: Patients were followed up at 2 weeks, 1 month, 3 months, 6 months, and then every 6 months, and subsequently every 12 months, for up to 60 months post-IRE. Of the 106 patients, 72 patients were eligible for analysis of IIEF, 60 for EPIC, and 74 for IPSS at 24 months after treatment.

Study design issues: This multicentre, randomised, single-blind, 2-arm intervention study evaluated the effect of focal versus extended IRE on side effects, patient-reported quality of life, and early oncologic control for patients with localised low-intermediate risk prostate cancer. All the treatment-related adverse events were recorded according to the CTCAE (Common Terminology Criteria for Adverse Events). Quality-of-life questionnaires, including IIEF, EPIC, IPSS and VAS pain score, were reported.

Patients were randomised to receive focal or extended IRE ablation with an allocation ratio of 1:1. Randomisation was done by the web-based data management system of the clinical research office of the endourological society and stratified by age (≤60 versus >60 years), Gleason score (6 versus 7), and IIEF score (≤45 versus >45). Patients were blinded to the allocated treatment arm to ensure unbiased reporting of quality-of-life measures.

Study population issues: Patients and disease characteristics including age, PSA, Gleason score, tumour T stage, IIEF, IPSS and operation time were similar between the 2 groups.

Other issues: Authors stated that despite the median follow up was 30 months, many patients were lost to follow up, limiting the long-term follow up. The sample size was relatively small, so it might not be adequately powered to detect small differences between the 2 groups. The long-term oncologic data was lack and the treatment option of the biopsy-positive patients were limited; these results would be reported when the data mature. The template biopsy modality was applied in the repeat biopsy at 6 months post-IRE. Recording of treatment zone was not possible, hence authors were not able to determine the exact rate of recurrence in treated areas.

Key efficacy findings

Number of patients analysed: 106

Repeat biopsy results at 6 months postoperatively

	Focal ablation (n=48)	Extended ablation (n=53)	Extended-focal difference, % (95% CI)	P value
Clinically significant prostate cancer	19% (n=9)	13% (n=7)	-5.5 (-20 to 8.8)	0.4
Any grade prostate cancer	56% (n=27)	43% (n=23)	-13 (-32 to 6.5)	0.2
Gleason score				0.3
3+3	38% (n=18)	30% (n=16)	-7.3 (-26 to 11)	
3+4	15% (n=7)	5.7% (n=3)	-8.9 (-21 to 2.8)	
4+3	2.1% n=1)	7.5% (n=4)	5.5 (-2.7 to 14)	
4+5	2.1% (n=1)	0% (n=0)	-2.1 (-6.1 to 2.0)	

Key safety findings

Number of patients with adverse events reported up to 3 months

3-month follow up	Focal ablation (n=51)	Extended ablation (n=55)	P value
Adverse events	59% (n=30)	62% (n=34)	0.8
Grade			
1	77% (n=23)	79% (n=27)	0.9
2	20% (n=6)	21% (n=7)	
4	3.3% (n=9)	0% (n=0)	

VAS pain scores of patients during follow up

	Focal ablation (n=51) (median, IQR)	Extended ablation (n=55) (median, IQR)	P value
24 hours	0 (0 to 1)	0 (0 to 1)	0.5

2 weeks	0 (0 to 0)	0 (0 to 1)	0.7

Estimated mean differences between focal and extended IRE across 24 months:

- IPSS: 1.9 (95% CI -0.37 to 4.2), p=0.099
- IIEF-15 total: 1.9 (95% CI -2.4 to 6.3), p=0.4
- IIEF-Q2: 0.077 (95% CI -0.31 to 0.46), p=0.7
- IIEF-erectile function: 0.98 (95% CI -1.3 to 3.2), p=0.4
- IIEF-orgasmic function: 0.39 (95% CI -0.31 to 1.1), p=0.3
- IIEF-sexual desire: 0.17 (95% CI -0.45 to 0.78), p=0.6
- IIEF-intercourse satisfaction: 0.55 (95% CI -0.63 to 1.7), p=0.4
- IIEF-overall satisfaction: -0.39 (95% CI -1.2 to 0.43), p=0.4
- EPIC-urinary function: -0.22 (95% CI -1.2 to 0.78), p=0.7
- EPIC-bowel habits: 0.11 (95% CI -0.98 to 1.2), p=0.8
- EPIC-sexual function: 1.4 (95% CI -0.13 to 2.9), p=0.073
- EPIC-hormonal function: -0.31 (95% CI -0.73 to 0.10), p=0.14
- EPIC-overall satisfaction: 0.15 (95% CI -0.43 to 0.73), p=0.6

Erectile dysfunction at 3 months:

- Focal ablation: 21.7% (10/46)
- Extended ablation: 23.5% (12/51)
- p=0.8

Study 11 Scheltema MJ (2022)

Study details

Study type	Case series
Country	Australia (single centre)
Recruitment period	2013 to 2021
Study population and number	n=229 patients with localised prostate cancer
Age and sex	Median 68 years (IQR 64 to 74)
Patient selection criteria	Eligible criteria: patients harboured cT1c-T2b unifocal prostate cancer; there was good co-registration between imaging and biopsy, and prostate cancer contained to 1 region within the prostate.
Technique	IRE electrodes were placed using a transperineal, ultrasound-guided approach, and under general anaesthesia. Three to six electrodes were placed surrounding the tumour lesions (varying per size and location of the lesion), using a 5 to 10 mm treatment margin. A total of 90 electrical pulses were delivered after the patient received a muscle relaxant, prophylactic antibiotics and an indwelling urinary catheter.
Follow up	Median 60 months (IQR 40 to 80)
Conflict of interest/source of funding	Funding: Cancer Institute NSW Grant, Ramsay Foundation, St Vincent's Prostate Cancer Centre, Angio Dynamics. DOI: 3 authors declared conflict of interests and other authors had no interests to declare.

Analysis

Follow-up issues: The standardised follow-up protocol comprised of a 1-week MRI, 6-month mpMRI and 12-month transperineal template mapping biopsies. In the case of treatment success, patients converted to active surveillance with an annual mpMRI and 6-monthly PSA. A total of 264 patients had primary IRE and 14 were lost to follow up, so 229 patients were included in the final analysis.

Study design issues: This study was an extension of a case series (Blazevski 2020). This study reported the median 5-year (and up to 10-year) outcomes of the single-centre prospective biopsy monitored cohort. All patients had focal IRE as primary treatment for localised prostate cancer.

Oncological outcomes included failure-free survival-based, biopsy-based and imaging-based outcomes. Failure-free survival was defined as no need for radical treatment and/or nodal/distant prostate cancer after initial IRE treatment (one re-do treatment of IRE was allowed). For the biopsy-based outcomes a failure was classified as any ISUP ≥2 on follow-up biopsy (definition of clinically significant prostate cancer).

Study population issues: At baseline, median preoperative PSA was 5.9 ng/ml (IQR 4.1 to 8.2); 7% harboured low-risk disease, 86% harboured intermediate-risk disease whilst 7% harboured high-risk disease. Preoperative MRI data was available in 97% of patients.

Key efficacy findings

Number of patients analysed: 229

During the median 60 months of follow-up, 38 patients progressed to radical treatment (17%), with an overall failure-free survival rate of 83%.

Failure-free survival rate:

- Low-grade disease: 79% (n=15/19)
- Intermediate-grade disease: 84% (n=164/195)
- High-grade disease: 79% (n=11/14).

Kaplan-Meier estimated failure-free survival rates were 91% at 3 years, 84% at 5 years and 69% at 8 years. There were no significant differences in the Kaplan-Meier estimated failure-free survival rates per ISUP score (p=0.74). Younger age and the need for a re-do IRE during follow-up were significant predictors for failure over time.

Number of patients having a re-do IRE: n=24 (11 patients had a durable response and 13 patients progressed to needing radical treatment).

Metastasis-free survival was 99.6% (228/229) and prostate cancer-special and overall survival were 100% (229/229).

PSA Nadir: median 1.9 ng/ml (IQR 1.1 to 4.4). This was not statistically significantly associated with residual clinically significant prostate cancer at biopsy (p=0.21).

PSA density at MRI: median 0.04 ng/ml (IQR 0 to 0.08)

mpMRI at 6 months (n=226):

- clear: 82.3% (n=186)
- in-field lesion: 4.4% (n=10)
- adjacent to field (marginal): 4.4% (n=10)
- out of field lesion: 7.5% (n=17)
- in- and out of field lesion: 1.3% (n=3)
- prostate volume before IRE: median 41 ml (IQR 30 to 60)
- prostate volume after IRE: median 33 ml (IQR 22 to 53)

Biopsy results at 12 months (n=190):

- Median number of cores taken: 28 (IQR 24 to 33)
- Median number of positive cores: 1 (IQR 0 to 3)
- Significant in-field disease: 7.4% (n=14)
- Significant out-field disease: 16.3% (n=31)
- Whole-gland free of clinically significant cancer: 76.3% (n=145)

- Insignificant cancer (ISUP score 1): 32.6% (n=62)
- No cancer found on biopsy: 43.7% (n=83)

Urinary continence (n=144): at baseline 98% (3 of 144) of men were pad-free continent and during follow up 99% were continent (1 of 131, the baseline urinary incontinence resolved in 2 men).

Key safety findings

No rectal fistulas or other high-grade adverse events occurred.

Sexual function (n=144): 71% (102/144) of men had erections sufficient for intercourse at baseline and this decreased to 58% (76/131). Baseline age correlated with the risk of developing erectile dysfunction (OR 1.08, 95% CI 1.01 to 1.16, p=0.035). At the 12-month follow-up there was a statistically significant decline on the EPIC sexual domain (p=0.001) remained unchanged.

Validity and generalisability of the studies

- Most studies were carried out in Australia and there was very limited data relevant to the UK context.
- The median follow-up duration ranged from 6 months to 6 years, but most studies had high rates of loss to follow up from 1 year onwards which limits the long-term data.
- Some 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 scanning.
- Nine studies were funded by various organisations, and of these, 2 studies received funding support from industry (Wang 2022; Scheltema 2022). Declarations of interest by 1 or more authors were reported in 5 studies (Blazevski 2022; Scheltema 2018a, 2018b; Blazevski 2021; Wang 2022).

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 did not receive the completed submission.

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. (2018a) 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. (2018b) 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.
8. Wang H, Xue W, Yan W et al. (2022). Extended focal ablation of localized prostate cancer with high-frequency irreversible electroporation: a nonrandomized controlled trial. JAMA Surgery 157(8): 693-700.
9. Yaxley WJ, Gianduzzo T, Kua B et al. (2022). Focal therapy for prostate cancer with irreversible electroporation: oncological and functional results of a single institution study. Investigative and Clinical Urology 63(3): 285-93
10. de la Rosette J, Dominguez-Escrig J, Zhang K et al. (2023) A Multicenter, randomized, single-blind, 2-arm intervention study evaluating the adverse events and quality of life after irreversible electroporation for the ablation of localized low-intermediate risk prostate cancer. The Journal of Urology 209: 347-53.

11. Scheltema MJ, Geboers B, Blazevski A et al. (2022) Median 5-year outcomes of primary focal irreversible electroporation for localized prostate cancer. BJU International, doi:10.1111/bju.15946.

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	14/09/2022	1946 to September 09, 2022
MEDLINE In-Process (Ovid)	14/09/2022	1946 to September 09, 2022
MEDLINE Epubs ahead of print (Ovid)	14/09/2022	September 09, 2022
EMBASE (Ovid)	14/09/2022	1974 to 2022 Sept 12
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/09/2022	Issue 9 of 12, Sept 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/09/2022	Issue 8 of 12, August 2022
International HTA database (INAHTA)	14/09/2022	n/a

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 prostate cancer 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	The outcomes of FT in prostate cancer seem to be similar to those observed with	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.	n=2288 (18 studies)	whole 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 prostate cancer.	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.
Beyer LP, Pregler B, Nießen C, et al. (2017) Percutaneous irreversible electroporation (IRE) of prostate cancer: Contrast-enhanced	Case series n=25 Follow up = 6 months	CEUS showed a significant involution of the prostate gland during the first 3 months and a significant decrease of the ablation zone during the first 6	Studies with larger samples, better design, or longer follow ups are included in

ultrasound (CEUS) findings during follow up. CH. 64(3):501-6		months after IRE of prostate cancer.	the main evidence.
Blazevski A, Geboers B, Scheltema MJ et al. (2022) Salvage irreversible electroporation for radio recurrent prostate cancer – The prospective FIRE trial. BJU International	Single-arm trial n=37 Follow up: median 29 months	The FIRE trial shows that salvage IRE after failed radiation therapy for localized prostate cancer is safe with minimal toxicity, and promising functional and oncological outcomes. Salvage IRE can offer a possible solution for notoriously difficult to manage radio recurrent prostate tumours. Reason, studies with larger samples or longer follow ups included in the key evidence.	Studies with larger samples, better design, or longer follow ups are included in the main evidence.
Collettini F, Enders J, Stephan C et al. (2019) Image-guided Irreversible Electroporation of Localised Prostate Cancer: Functional and Oncologic Outcomes. Radiology, 292(1): 250–257.	n=30 Follow up = median 20 months	After a median follow-up of 20 months, focal irreversible electroporation of localized prostate cancer was associated with low urogenital toxicity and promising oncologic outcomes.	Larger studies included.
Dong S, Wang H, Zhao Y et al. (2018) First Human Trial of High-Frequency Irreversible Electroporation Therapy for Prostate	n=40 Follow up = 6 months	Four weeks after treatment, it was found that the ablation margins were distinct in magnetic resonance imaging scans, and	Larger studies with longer follow up included.

Cancer. Technology in Cancer Research & Treatment, 17: 1533033818789692.		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.	
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-conducted comparative studies and by a significant heterogeneity in terms of study design, study population, erectile and sexual function assessment modalities.	All included IRE studies in Table 2 or appendix.
Giganti F, Stabile A, Giona S et al. (2019) Prostate cancer treated with	n=30 Follow up =	Six men were undertreated and showed mpMRI recurrence after 6	Larger studies included.

irreversible electroporation: MRI-based volumetric analysis and oncological outcome. Magnetic Resonance Imaging, 58: 143–147.	median 16 months	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-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	Over the past 5 years, focal therapy has been studied for eight different energy	All eligible IRE studies in

Systematic Review on Focal Therapy in Localised Prostate Cancer: What Has Changed over the Past 5 Years? European Urology, 81(1): 5–33.	n=5827 (72 studies)	sources, mostly in single-arm stage 2 studies. Although a first randomized controlled trial in focal therapy has been performed, more high-quality evaluations are needed, preferably via multicentre randomised controlled trials with long-term follow-up and predefined assessment of oncological and functional outcomes and health-related quality-of-life measures.	Table 2 or appendix.
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	CEUS and parametric imaging enable a critical analysis of post-ablation defects after IRE for prostate cancer even with a transabdominal approach. Remaining tumour can be detected with the help of pseudo-colours.	Study focuses on imaging outcomes.
Kayano PP, Klotz L (2021) Current evidence for focal therapy and partial gland ablation for	Systematic review n= 30 studies	Focal therapy and partial gland ablation for organ-confined prostate cancer is an option for patients	All included IRE studies in Table 2 or appendix.

organ-confined prostate cancer: systematic review of literature published in the last 2 years. Current Opinion in Urology, 31(1): 49–57.		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.	
López BM, Andrés Boville G, Bernardos GB et al. (2022). Focal therapy of prostate cancer index lesion with irreversible electroporation. a prospective study with a median follow-up of 3 years. Journal of Urology 209; 1-9	Case series n=41 Follow up = median 35 months	Irreversible electroporation can achieve satisfactory 3-year in-field tumour control with excellent quality of life results in selected patients.	Larger studies or studies with longer follow up already included.
Morozov A, Taratkin M, Barret E et al. (2020) A systematic review of irreversible electroporation in localised prostate cancer treatment. Andrologia, 52(10): e13789.	Systematic review n= 433 (10 studies)	Irreversible electroporation has promising 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	All studies already included in Table 2 or appendix.

		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. The Journal of Urology, 196(3): 883–890.	n=25 Follow up = median 10.9 months	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 tumour-bearing prostate tissue, as a majority of men had no evidence of residual cancer on biopsy 6 months after prostate gland ablation.	Larger studies included.
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 role of imaging in conjunction with IRE is of crucial importance to guide clinicians throughout the treatment protocol. CEUS and mpMRI may provide essential treatment feedback by visualising the ablation zone dimensions and volume.	Study focuses on imaging outcomes.
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	Short-term safety, QoL and oncological control data show that focal IRE is a feasible salvage option for localised radio-recurrent prostate cancer. A prospective multicentre study (FIRE trial) has been initiated that will provide further insight into the ability of focal IRE to obtain oncological control of radio-recurrent prostate cancer with acceptable patient morbidity.	Larger studies included.
Ting F, Tran M, Böhm M et al. (2016). Focal irreversible electroporation for prostate cancer: functional outcomes	n=25 Follow up = median 8 months	In selected patients with low-intermediate risk prostate cancer, focal IRE appears to be safe with minimal morbidity. There were no infield recurrences	Larger studies included.

and short-term oncological control. Prostate Cancer and Prostatic Diseases 19(1): 46–52.		and 76% of patients were histologically free of significant cancer at 8 months. Almost all recurrences were adjacent to the treatment zone, and this was addressed by widening the treatment margins.	
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	Focal irreversible electroporation has a low toxicity profile with encouraging genito-urinary functional outcomes. Further prospective development studies are needed to confirm the functional outcomes and to explore the oncological potential.	More recent studies included.
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	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	Larger studies included.

		Expanded Prostate Cancer Index Composite) and I-PSS (International Prostate Symptom 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	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	Study focuses on imaging outcomes.

prostatectomy. European Radiology, 26(7): 2252–2260.		r= 0.88 resp. 0.80). However, IRE is not visible with TRUS.	
van Riel LA, Geboers B, Kabaktepe E et al. (2022). Outcomes of salvage radical prostatectomy after initial irreversible electroporation treatment for recurrent prostate cancer. BJU International (Epub ahead of print)	Case series n=39 Follow up = median 17.7 months	Salvage RP is safe and feasible for patients with recurrent localised prostate cancer following initial IRE treatment. The medium-term oncological and functional outcomes are similar to primary RP. Strict patient selection for focal therapy and standardised follow-up is needed as some patients developed high-grade disease.	Study focuses primarily on radical prostatectomy following IRE rather than IRE as a procedure.
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	All included IRE studies in Table 2 or appendix.

		by lack of randomised studies and heterogenous outcome measures.	