NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for treating prostate cancer

The prostate is a small gland near a man's bladder. 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 through the skin into the tumour and electrical pulses are used to kill the cancer cells.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in May 2016.

Procedure name

- Irreversible electroporation for treating prostate cancer

Specialist societies

- British Society of Interventional Radiology
- British Uro-oncology Group
- British Association of Urological Surgeons.

Description

Indications and current treatment

Prostate cancer is usually diagnosed after a blood test in primary care has shown elevated prostate-specific antigen (PSA) levels. Most prostate cancers are either localised or locally advanced at diagnosis. Localised prostate cancer does not usually cause any symptoms, but some men might have some urinary problems or erectile dysfunction.

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

What the procedure involves

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

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

Literature review

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 29 April 2016: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published

studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 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 where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with prostate cancer.
Intervention/test	Irreversible electroporation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 246 patients from 7 case series (the actual number is lower because there is some patient overlap between the studies)[1–7] .

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on irreversible electroporation for treating prostate cancer

Study 1 Ting F (2016)

Details

Study type	**Case series**
Country	Australia
Recruitment period	2013–14
Study population and number	**n=25** Men with low-intermediate-risk prostate cancer.
Age	Mean 67 years (interquartile range, 60–71)
Patient selection criteria	Men aged ≥40 years with low-intermediate risk (D'Amico criteria) prostate cancer who had not received previous prostate cancer treatment; visible lesion on multi-parametric MRI with no evidence of extra-capsular extension or seminal vesicle invasion; stage ≤T2c; transperineal, trans-rectal ultrasound or MRI-guided biopsies correlating with the visible lesion; Gleason score ≤7 on biopsy. Exclusion criteria: men who are unable to have MRI; evidence of metastatic or nodal disease outside the prostate; previous treatment for prostate cancer; previous radiation therapy to the pelvis; androgen suppression or hormone treatment within the previous 12 months for prostate cancer; Gleason score ≥8 on biopsy.
Technique	The procedure was done as a day procedure, with the patient under general anaesthesia. Between 3 and 6 NanoKnife electrodes (Angiodynamics, USA) were placed, dependent on the volume of tissue to be ablated, with a minimum 5 mm safety margin around the lesion.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 84% (21/25) of men had a follow-up biopsy at 6 months: 1 patient did not have it because of cost, 2 deferred it indefinitely and 1 refused because of side effects. Functional follow-up was completed for 72% (18/25) of patients.

Study design issues: The study population included the initial patients who were treated at a single centre. Functional outcomes were assessed using the validated Expanded Prostate Cancer Index Composite (EPIC) questionnaire, which was completed at baseline, 6 weeks, 3 months and 6 months after the procedure. Oncological follow-up was done using MRI at 6 month follow-up and transperineal template-guided mapping biopsy at 7 month follow-up. Complications were recorded using the Clavien-Dindo classification system.

Study population issues: According to the D'Amico classification system, 2 (8%) patients were low risk and 23 (92%) were intermediate risk. Median PSA at baseline was 6.0 ng/ml (interquartile range 4.3–8.6).

Other issues: The authors noted that the treatment margin was widened from 5 mm to 10 mm after the first 12 patients to reduce the risk of significant adjacent field disease occurrence. One patient had a transurethral resection of the prostate and 1 had a bladder neck incision done at the time of IRE. The preoperative biopsy method was not standardised within the study because patients were often referred from other centres. There is some patient overlap with Valerio M, 2014.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 25

The ablation zone covered the intended lesion in 95% (24/25) of patients (confirmed by MRI at 1 week follow-up); 1 patient had repeat IRE.

Oncological outcomes
84% (21/25) of men had a 7-month follow-up biopsy and the ablated zone was histologically clear of disease in all patients. Overall, 76% (16/21) of men were histologically clear of significant disease (defined as a Gleeson score of 7-10 or a Gleeson score of 6 with a >5mm tumour) and 38% (8/21) of men were histologically clear of any cancer at all. One patient had a significant finding in the field outside the adjacent zone; the lesion was not detected on his 6-month MRI and also was not detected preoperatively.

21% (5/24) of men who had a 6-month follow-up MRI, had suspicious findings in the field adjacent to the ablation zone; 4 of these were significant on biopsy. These 4 patients were all within the first 12 patients to be treated. Eight per cent (2/24) of men had suspicious findings in the field outside the ablation zone; neither was significant on biopsy.

In total, 25% (5/21) of patients had significant disease on follow-up biopsy: 3 remain on active surveillance, 1 is awaiting repeat IRE and 1 had a radical prostatectomy.

At the time of the report, 92% (23/25) of patients remained on active surveillance. No patients died or were switched to systemic treatment.

Functional outcomes (n=18)
<table>
<tr><td>EPIC questionnaire domain</td><td>Baseline (median, IQR)</td><td>6 months (median, IQR)</td><td colspan="2">Difference from baseline at 6 months</td></tr>
<tr><td></td><td></td><td></td><td>median</td><td>p value</td></tr>
<tr><td>AUA urinary symptom score</td><td>8 (3–15)</td><td>5 (3–13)</td><td>−0.5</td><td>0.3</td></tr>
<tr><td>Urinary function score</td><td>90 (72–96)</td><td>94 (83–97)</td><td>0.0</td><td>0.6</td></tr>
<tr><td>Sexual function score</td><td>56 (51–75)</td><td>55 (34–69)</td><td>−0.7</td><td>0.4</td></tr>
<tr><td>Bowel function score</td><td>98 (93–100)</td><td>97 (93–100)</td><td>0.0</td><td>0.9</td></tr>
<tr><td>SF-12 physical component score</td><td>54 (43–56)</td><td>52 (43–56)</td><td>0</td><td>0.8</td></tr>
<tr><td>SF-12 mental component score</td><td>56 (47–58)</td><td>55 (50–60)</td><td>−0.2</td><td>0.2</td></tr>
</table>
Urinary function
Pad-free continence rates were 100, 94, 94 and 100% and leak-free continence rates were 67, 53, 65 and 67% at baseline, 6 weeks, 3 months and 6 months respectively.

Erectile function
The proportion of men with erections sufficient for penetration were 44, 38, 47 and 56% at baseline, 6 weeks, 3 months and 6 months respectively.

Median PSA at 6 month median follow-up=2.2 ng/ml (IQR 1.0–5.0)</td><td>There were no major intraoperative complications.

Postoperative complications
• Urinary retention (Clavien 1)=20% (5/25)
• Intermittent haematuria at 6 weeks=24% (6/25) (all had resolved by 6 months)
• Dysuria=20% (5/25)
• Non-ST elevation myocardial infarction (Clavien 3)=4% (1/25) This was not considered to be a direct effect of IRE. The patient had a bladder neck incision at the time of IRE and antiplatelet medication was stopped 7 days before the procedure. The patient subsequently had an angiogram and drug-eluting stent to his left anterior descending coronary artery.</td></tr>
<tr><td colspan="2">Abbreviations used: AUA, American Urological Association; EPIC, Expanded Prostate Cancer Index Composite; IQR, interquartile range; IRE, irreversible electroporation; PSA, prostate-specific antigen</td></tr>
</table>

Study 2 Valerio M (2014)

Details

Study type	**Case series**
Country	UK and Australia
Recruitment period	2011–13
Study population and number	**n=34** Men with localised prostate cancer.
Age	Mean 65 years
Patient selection criteria	Men with localised prostate cancer. All patients in the cohort had 1 MRI-visible lesion concordant with histological findings showing clinically significant prostate cancer in this area. Any Gleason pattern ≥4 or cancer core length ≥4 mm was considered clinically significant cancer. Eligibility was assessed by multi-parametric MRI and targeted or template biopsy.
Technique	Irreversible electroporation was delivered using the NanoKnife system (Angiodynamics, USA). Men treated in the early part of the study had small volume lesions, and were treated with 2 electrodes into the target area. As experience accumulated, larger volumes were targeted with 4–6 needles. The target volume was defined by multi-parametric MRI and histopathology with a safety margin of 3–5 mm. Urinary catheters were managed differently in the 2 centres. In 1 centre, a urethral or suprapubic catheter was placed at the time of the procedure and removed 3–5 days after treatment. In the other centre, a urethral catheter was inserted for the procedure and removed at the end of the procedure unless the target lesion abutted the urethra.
Follow-up	**Median 6 months**
Conflict of interest/source of funding	One author has received funding for conference attendance from Geoscan Medical; 2 authors receive funding from USHIFU, GSK, AngioDynamics and Advanced Medical Diagnostics for clinical trials; 1 author is a paid consultant to AngioDynamics, Steba Biotech and SonaCare Medical; 1 author has received trial funding support from SonaCare Medical and consultancy fees from SonaCare Medical and Oncura. None of these sources had any input into the article.

Analysis

Follow-up issues: Patients were followed up by clinic visits every 3 months. Of the 34 patients, 24 had a follow-up of at least 6 months.

Study design issues: Two-centre, retrospective analysis. Functional outcomes were reported on the basis of physician-reported measures rather than patient-reported. There was no systematic histological verification of complete ablation in the treatment area. Postoperative multiparametric MRI was used to determine local failure, together with prostate-specific antigen testing. Complications were classified according to the Common Terminology Criteria for Adverse Events (CTCAE).

Study population issues: According to the D'Amico risk classification system, 26% (9/34) of patients were low-risk, 71% (24/34) were intermediate risk and 3% (1/34) were high-risk. Two men (6%) had only transperineal targeted biopsy and 32 (94%) had template prostate mapping with additional targeted biopsy, to assess eligibility. Median PSA at baseline was 6.1 ng/ml (interquartile range 4.3–7.7).

Other issues: There is some patient overlap with Ting F, 2016.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **34** **Functional outcomes** Potency was preserved in 95% (19/20) of men who were potent before treatment. All men who were continent before treatment were still continent afterwards (24/24). **Early disease control** Median PSA at 6 months=3.2 ng/ml (IQR 1.9–4.8). Suspicious residual disease was seen in 17.7% (6/34) of patients (using multiparametric MRI) during follow-up. In 2 of these patients, PSA had dropped significantly from baseline and they remain on surveillance. The other 4 patients had secondary treatment (1 IRE, 2 high intensity focused ultrasound, 1 radical prostatectomy). Only 1 patient had histological verification of treatment failure with transperineal targeted biopsy. No patient died, had metastasis or switched to systemic treatment.	Genito-urinary and rectal toxicity after focal irreversible electroporation: • Urethral stricture=0% (0/34) • Urinary retention=6% (2/34) • Debris or haematuria=18% (6/34) • Dysuria=15% (5/34) • Urinary tract infection=15% (5/34) • Recto-urethral fistula=0% (0/34) Non genito-urinary adverse events: • Self-resolving tachycardia during the procedure=3% (1/34) • Need for prolonged wound dressing at the site of the suprapubic catheter after catheter removal=6% (2/34) All complications were grade 1 or 2 (mild or moderate), and no severe adverse events occurred.
Abbreviations used: IQR, interquartile range; IRE, irreversible electroporation; PSA, prostate specific antigen	

Study 3 Murray KS (2016)

Details

Study type	**Case series**
Country	US
Recruitment period	2011–14
Study population and number	**n=25 (27 for safety outcomes)** Men with prostate cancer.
Age	median 63 years (interquartile range 59.3–67.6)
Patient selection criteria	Men with prostate cancer who were offered but did not accept conventional management options (surveillance, surgery, radiation). Patients treated with salvage treatment were not included in the analysis.
Technique	All procedures were done with the patient under general anaesthesia. All patients received perioperative antibiotics. The number of electrodes was dependent on the target zone of ablation. Cystoscopic examination of the urethra and bladder was done after the procedure.
Follow-up	**Median 10.9 months (interquartile range, 6.7–19.3)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: All patients had a biopsy at 6 months follow-up. Urinary function scores and erectile function scores at baseline, 6 and 12 months were only available for 17 and 15 men respectively.

Study design issues: Patient-reported quality of life was assessed at 6 and 12 months follow-up using the Prostate Quality of Life Survey. Normal urinary function was defined as a total score of ≥17 on the urinary function part of the survey and potency was defined as a total score of ≥22 on the sexual function part of the survey. Any patient subsequently treated for prostate cancer progression within the zone of ablation or on the contralateral prostate lobe was reported as treatment failure. Complications were graded using a standardised reporting system compatible with Clavien-Dindo classification.

Study population issues: All patients had low or intermediate risk disease at baseline, according to the American Urology Association risk classification. An additional 2 patients with less than 6 months' follow-up were included in the safety analysis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **25**

At 6 months' follow-up, 28% (7/25) of men had a template biopsy that was positive for prostate cancer. Primary failure was reported in 16% (4/25) of patients: 2 had unilateral ablation to the base of the prostate and the other 2 had unilateral apical ablation. Three of the 4 men received subsequent definitive surgical treatment.

Functional outcomes after partial prostate gland ablation with irreversible electroporation

	Baseline (n=22)	6 months (n=16)	12 months (n=17)
Urinary function score ≥17	77% (17/22)	81% (13/16)	88% (15/17)
Erectile function score ≥22	59% (13/22)	44% (7/16)	65% (11/17)

Of the 17 patients with normal urinary function at baseline, 2 reported a decrease in score (<17) at 6 months and 1 at 12 months.

At 12 months, 1 patient with normal erectile function at baseline reported new difficulty with potency.

Use of incontinence pads was reported in 1 and 2 men at 6 and 12 months respectively.

Safety

Adverse events reported at 30 days and 90 days after the procedure (n=27, including 2 patients with <6 months' follow-up)

Grade		**30 days**	**90 days**
1	Haematuria	14.8% (4/27)	0% (0/27)
1	Dysuria	3.7% (1/27)	0% (0/27)
1	Haematospermia	3.7% (1/27)	0% (0/27)
2	Urinary retention	22.2% (6/27)	0% (0/27)
2	Urinary tract infection	3.7% (1/27)	0% (0/27)
2	Epididymitis	0% (0/27)	3.7% (1/27)
3	Epididymitis	0% (0/27)	3.7% (1/27)*
3	Urinary tract infection	3.7% (1/27)	0% (0/27)

* Epididymitis in this patient led to abscess formation, which was treated by simple orchiectomy

There were no cases of rectourethral fistula or evidence of rectal injury on MRI.

Study 4 Van den Bos (2015)

Details

Study type	**Case series**
Country	The Netherlands and Greece
Recruitment period	2013–14
Study population and number	**n=16** Men with histopathologically confirmed prostate cancer, scheduled for a radical prostatectomy as their primary treatment.
Age	mean 60 years
Patient selection criteria	Patients who were indicated to undergo a radical prostatectomy and a life expectancy of more than 10 years without prostate calcifications greater than 5 mm. All patients had an electrocardiogram to rule out cardiac rhythm disorders.
Technique	Irreversible electroporation was done using the NanoKnife system (AngioDynamics, USA). General anaesthesia was used and full paralysis was induced before pulsing started. Impulses were synchronised using electrocardiogram triggering. Seven patients had a focal ablation (using ≤3 electrodes) and 9 patients had an extended ablation (using 4–6 electrodes).
Follow-up	**4 weeks**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Patients were followed up for 4 weeks, at which point a radical prostatectomy was done.

Study design issues: The primary aim of the study was to assess safety of the irreversible electroporation ablation procedure. The treatment-related toxicity was graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE). All complications were recorded prospectively by the participating centres. A serious adverse event was defined as any untoward occurrence that required hospital admission or prolongation of hospital stay, resulted in persistent or significant disability or incapacity, was life threatening, or resulted in death. The secondary aim of the study was to determine quality of life, measured by the Expanded Prostate Cancer Index Composite (EPIC) and the IPSS Quality of Life score.

Study population issues: Median PSA at baseline=8 ng/ml (interquartile range 7–13). Ten patients were diagnosed on the basis of systematic 12-core transrectal biopsies and 6 patients had targeted or extended biopsies ranging from 13 to 24 cores.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **16** **Quality of life** ***EPIC questionnaire*** Statistically significant differences were seen in 1 domain in the EPIC questionnaire: quality of life concerning the urinary function decreased (p=0.01) at follow-up. Quality of life concerning sexual function did not significantly decrease during follow-up, but there was a significant rise between 1-week and 4-week follow-up. The quality of life concerning hormonal function and bowel habits did not change significantly after the procedure. ***Mean IPSS quality of life score*** • Baseline=2 (mostly satisfied) • 1-week follow-up=3 (mixed feelings) • 4-week follow-up=2 (mostly satisfied) (p=0.02 for difference between 1 and 4 week follow-up) The erectile function determined by the IIEF-5 showed no significant difference between baseline and follow-up. ***Uroflowmetry results (mean maximal flow)*** • Baseline=17.2 ml/sec • 1-week follow-up=14.1 ml/sec • 4-week follow-up=14.3 ml/sec (p=not significant) The measured residuals after voiding were not statistically different after the procedure. **Median pain scores (VAS)** • Baseline=0 • 4 hours after the procedure=1.5 (p=0.01 compared with baseline) • 24 hours after the procedure=0.5 (p=0.01 compared with baseline) • 1-week follow-up (mean score)=0.4 (p=not significant compared with baseline)	**Adverse events during 4-week follow-up** **CTCAE Grade 1** • Mild haematuria=31.3% (5/16) (resolved spontaneously in all patients within 1–27 days) • Mild haematospermia=12.5% (2/16) (lasting 1 and 30 days respectively) • Painful micturition=12.5% (2/16) • Pelvic pain=6.25% (1/16) • Urgency complaints=12.5% (2/16) • Frequency complaints=12.5% (2/16) • Miscellaneous=25.0% (4/16) (Including a small perineal swelling, inguinal lymphadenopathy, temporarily swollen testis without fever, bilateral shin pain or pain in the lower abdomen without evidence of a urinary tract infection) **CTCAE Grade 2** • Urinary incontinence=18.8% (3/16) • Urinary retention=37.5% (6/16) (an indwelling catheter was placed in 5 patients for a mean duration of 7 days and 1 patient needed self-catheterisation for 6 days. After the indwelling catheter was removed, 1 patient needed self-catheterisation for a further 3 days.) • Urinary tract infection=6.25% (1/16) (treated with oral antibiotics) • Urgency complaints=12.5% (2/16) • Frequency complaints=12.5% (2/16) • Miscellaneous=6.25% (1/16) (diarrhoea including haematochezia lasting 2 days, likely to be caused by haemorrhoids and with no direct relation to the procedure) **CTCAE Grade 3** • Urosepsis=6.25% (1/16) (the patient was admitted to hospital for 6 days and treated with intravenous antibiotics)
Abbreviations used: CTCAE, Common Terminology Criteria for Adverse Events; EPIC, Expanded Prostate Cancer Index Composite; IIEF-5, International Index of Erectile Function questionnaire; VAS, visual analogue scale	

Study 5 Murray K (2015) - conference abstract for safety outcomes only

Details

Study type	**Case series**
Country	US
Recruitment period	2011–14
Study population and number	**n=30** Men with localised prostate cancer.
Age	Mean 63 years
Patient selection criteria	Patients were selected based in MRI assessment and confirmed biopsy of the tumours for low or intermediate risk disease.
Technique	Irreversible electroporation was delivered with transperineal needle insertion under transrectal ultrasound guidance using 3–6 probes.
Follow-up	**Median 11.6 months**
Conflict of interest/source of funding	Study was funded by the Sidney Kimmel Center for Prostate and Urological Cancers.

Analysis

Follow-up issues: 28 patients had at least 6 months' follow-up.

Study design issues: Complications were reported based on the Clavien-Dando classification.

Study population issues: Median PSA at baseline was 4.5 $ngml^{-1}$. Four patients had received prior radiation therapy. There is likely to be considerable patient overlap with Murray KS, 2016.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **30** Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	Complications within 90 days=18% (n=5) • Acute urinary retention (grade 1), n=3 • Epididymitis (grade 3), n=1 • Urethral stricture (grade 3), n=1

Study 6 Tomihama RT (2015) – conference abstract for safety outcomes only

Details

Study type	**Case series**
Country	Germany
Recruitment period	2011–4
Study population and number	**n=103** Patients with prostate adenocarcinoma (stage T1aN0M0–T4NXM1c)
Age	Not reported
Patient selection criteria	Not reported
Technique	Whole gland ablation (n=23) or partial gland ablation (n=80) was done. The treatment field also included urethra (n=93), neurovascular bundle (n=82), bladder (n=24), rectum (n=2), urethral sphincter (n=12), seminal vesicles (n=27) and small bowel (n=1).
Follow-up	**3 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: A total of 130 patients were treated during the study period but the analysis only used data from patients with at least 3 months' follow-up.

Study design issues: Retrospective analysis.

Study population issues: Of the 130 patients treated in total, 25 had recurrences after other treatments (5 transurethral resections of the prostate, 8 irreversible electroporation, 4 radiation, 3 high-intensity focused ultrasound, 3 prostatectomies alone, 2 prostatectomies and radiation).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **103** Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	• Recto-urethral fistula=1.0% (1/103) • Transient dysuria=2.9% (3/103) • Transient incontinence=11.7% (12/103) • Transient urgency=3.9% (4/103) • Dysejaculation=4.9% (5/103) • Postoperative infection (cystitis, epididymo-orchitis, or other infection)=2.9% (3/103) • Temporary reduction in potency (<9 months)=9.7% (10/103) • Complete reduction in potency (>3 years)=1.9% (2/103)

Study 7 Niessen C (2015)

Details

Study type	**Case series**
Country	Germany
Recruitment period	Not reported
Study population and number	**n=13** Patients with histologically confirmed prostate cancer.
Age	Median 61.4 years
Patient selection criteria	Patient selection was based on the following criteria: clinical stage T1 to T2, N0, M0, no previous radical treatment for prostate cancer (radical prostatectomy, external beam radiotherapy, or brachytherapy) and a Gleason score of ≤6. Patients treated with neoadjuvant hormone therapy were excluded from the study.
Technique	The NanoKnife system (Angiodynamics, USA) was used. General anaesthesia with deep neuromuscular blockade was used. Irreversible electroporation impulses were synchronised using electrocardiogram triggering.
Follow-up	**24 hours**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: The aim of the study was to evaluate the use of contrast-enhanced ultrasound after irreversible electroporation to assess the ablation status in terms of microvascularisation. Contrast-enhanced ultrasound images were retrospectively and independently evaluated by 2 experienced radiologists to assess the extent of microvascularisation of the lesion or the ablation defect.

Study population issues: Mean tumour size=0.9 cm (range 0.5–1.5)

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **13** **Evaluation values of microcirculation of prostate cancer lesions** (5-point scale: 5=pronounced hypervascularisation, 4=clear vascularisation, 3=moderate vascularisation, comparable to surrounding tissue, 2=low vascularisation, 1=only partial vascularisation and low in comparison with surrounding tissue, 0=no vascularisation)	No safety outcomes were reported.

	Baseline	Immediately after IRE	24 hours after IRE
Mean	2.15	0.65	0.27
Standard deviation	0.56	0.63	0.44
Minimum	1	0	0
Maximum	3	2	1

Abbreviations used: IRE, irreversible electroporation

Efficacy

Oncological outcomes

In a case series of 25 patients treated by irreversible electroporation for prostate cancer, the ablated zone was histologically clear of disease in all of the men who had a 7-month follow-up biopsy (84% [21/25] of patients)[1]. Overall, 76% (16/21) of men were histologically clear of significant disease and 38% (8/21) of men were histologically clear of any cancer at all. One patient had a significant finding in the field outside the adjacent zone; the lesion had not been detected preoperatively or on his 6-month MRI. Of the 5 patients with significant disease on follow-up biopsy, 3 remain on active surveillance, 1 is awaiting repeat irreversible electroporation and 1 had a radical prostatectomy.

In a case series of 34 patients, suspicious residual disease was seen on multiparametric MRI in 18% (6/34) of patients during follow-up [2]. In 2 of these patients, prostate-specific antigen (PSA) levels dropped significantly from baseline, and they remain on surveillance. The other 4 patients had secondary treatment (1 irreversible electroporation, 2 high intensity focused ultrasound, 1 radical prostatectomy). Only 1 patient had histological verification of treatment failure with transperineal targeted biopsy.

In a second case series of 25 patients, 28% (7/25) of men had a template biopsy that was positive for prostate cancer at 6-month follow-up[3]. Primary failure was reported in 16% (4/25) of patients: 3 patients subsequently had surgery.

Functional outcomes

In the first case series of 25 patients, there were no statistically significant changes in urinary symptom score, urinary function score, sexual function score, bowel function score, SF-12 physical component score or SF-12 mental component score at 6-month follow-up (n=18)[1]. Pad-free continence rates were 100%, 94%, 94% and 100% and leak-free continence rates were 67%, 53%, 65% and 67% at baseline, 6-week, 3-month and 6-month follow-up respectively. The proportion of men with erections sufficient for penetration were 44%, 38%, 47% and 56% at baseline, 6-week, 3-month and 6-month follow-up respectively.

In the case series of 34 patients, potency was preserved in 95% (19/20) of men who were potent before treatment. All men who were continent before treatment were still continent afterwards (24/24).

In the second case series of 25 patients, 77% (17/22), 81% (13/16) and 88% (15/17) of patients had normal urinary function at baseline, 6-month and 12-month follow-up respectively[3]. Of the 17 patients with normal urinary function at baseline, 2 reported a decrease in score to below normal at 6-month and 1 at 12-month follow-up. At 12-month follow-up, 1 patient with normal erectile function

at baseline reported new difficulty with potency. Use of incontinence pads was reported in 1 and 2 men at 6-month and 12-month follow-up respectively.

In a case series of 16 patients, statistically significant differences were seen in 1 domain in the Expanded Prostate Cancer Index Composite (EPIC) questionnaire: quality of life concerning urinary function decreased (p=0.01) at 1-week and 4-week follow-up[4]. Quality of life concerning sexual function, hormonal function and bowel habits did not significantly decrease during follow-up.

Safety

Urinary retention

Urinary retention was reported in 6% (2/34), 10% (3/30), 20% (5/25), 22% (6/27), and 38% (6/16) of patients in 5 case series of 34, 30, 25, 27 and 16 patients respectively [2,5,1,3,4].

Haematuria

Intermittent haematuria was reported in 24% (6/25) of patients in the case series of 25 patients (all had resolved by 6 months)[1]. Debris or haematuria was reported in 18% (6/34) of patients in the case series of 34 patients[2]. Haematuria was reported in 15% (4/27) of patients at 30-day follow-up in the case series of 27 patients (all had resolved by 90 days)[3]. Mild haematuria was reported in 31% (5/16) of patients in the case series of 16 patients (resolved spontaneously in all patients within 1–27 days)[4].

Dysuria

Dysuria was reported in 3% (3/103), 4% (1/27), 15% (5/34), and 20% (5/25) of patients in the case series of 103, 27, 34, and 25 patients respectively[6,3,2,1].

Painful micturition during 4-week follow-up was reported in 13% (2/16) of patients in the case series of 16 patients[4].

Infection

Urinary tract infection was reported in 6% (1/16), 7% (2/27), and 15% (5/34) of patients in the case series of 16, 27, and 34 patients respectively[4,3,2].

Postoperative infection (cystitis, epididymo-orchitis, or other infection) was reported in 3% (3/103) of patients in a case series of 103 patients[6].

Urosepsis was reported in 1 patient in the case series of 16 patients[4]. The patient was admitted to hospital for 6 days and treated with intravenous antibiotics.

Epididymitis

Epididymitis was reported in 7% (2/27) of patients in the case series of 27 patients. In 1 of the patients, epididymitis led to abscess formation, which was treated by simple orchiectomy[3]. Epididymitis (grade 3) was reported in 1 patient in the case series of 30 patients[5].

Urgency and frequency

Urgency and frequency (Common Terminology Criteria for Adverse Events [CTCAE] grade 2) were each reported in 13% (2/16) of patients in the case series of 16 patients[4].

Transient urgency was reported in 4% (4/103) of patients in the case series of 103 patients[6].

Incontinence

Transient incontinence was reported in 12% (12/103) of patients in the case series of 103 patients[6].

Dysejaculation

Dysejaculation was reported in 5% (5/103) of patients in the case series of 103 patients[6].

Urethral stricture

Urethral stricture (grade 3) was reported in 1 patient in the case series of 30 patients[5].

Recto-urethral fistula

Recto-urethral fistula was reported in 1 patient in the case series of 103 patients[6].

Impotence

A temporary reduction in potency (<9 months) was reported in 10% (10/103) of patients and complete reduction in potency (>3 years) in 2% (2/103) of patients in a case series of 103 patients[6].

Other

Self-resolving tachycardia during the procedure was reported in 1 patient in the case series of 34 patients[2].

Validity and generalisability of the studies

- All the studies are small case series with relatively short-term follow-up. There is no comparative or long-term data.

- There is some patient overlap between the studies.
- One study includes patients from the UK[2].
- Two conference abstracts have been included in accordance with the interventional procedures programme manual, which states that data on safety may be considered by the committee regardless of their source and publication status[5,6]. It is difficult to assess the quality of these studies and the validity of the assessment measures used.
- There is some heterogeneity in patient populations; 3 studies only included patients with low- to intermediate-risk prostate cancer[1,3,5] and 2 studies only specified that the patients had localised prostate cancer[2,5].
- The studies are likely to include the first patients to be treated by the procedure and outcomes may improve with increasing experience. One study reported that the treatment margin was widened because of the occurrence of adjacent field disease in some of the initial patients to be treated[1].

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. Appendix B gives details of the recommendations made in each piece of guidance listed.

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 clinical guideline 175 (2014). Available from http://www.nice.org.uk/guidance/CG175

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist 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 Specialist Advisers, 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, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for Irreversible electroporation for treating prostate cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent xxx questionnaires to xxx NHS trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted if there is no patient commentary

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Section to be inserted if patient commentators raised no new issues

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Section to be inserted if patient commentators raised new issues

The patient commentators raised the following issues about the safety/efficacy of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

- Multi-Center Randomized Clinical Two Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localized Prostate Cancer (NCT01835977); RCT; The Netherlands; estimated enrolment 200; estimated study completion date June 2019.
- Irreversible Electroporation(IRE) For Unresectable Prostatic Neoplasms: Phase I and Phase II Clinical Trial (NCT02430649); single group assignment; China; estimated enrolment 30; estimated study completion date January 2020.
- A Prospective Development Study Evaluating Focal Therapy Using Irreversible Electroporation (NanoKnife) in Men With Localised Prostate Cancer (NCT01726894); single group assignment; UK; estimated enrolment 20; estimated primary completion date August 2015.
- Registry of Irreversible Electroporation for the Ablation of Prostate Cancer With Use of NanoKnife Device; A Multi-Center, International Registry to

Evaluate the Treatment of Prostate Cancer in Terms of Recurrence, Functional Outcomes and Safety (NCT02255890); cohort study; the Netherlands; estimated enrolment 2000; estimated study completion date December 2024.

References

1. Ting F, Tran M, Böhm M et al. (2015) Focal irreversible electroporation for prostate cancer: functional outcomes and short-term oncological control. Prostate cancer and Prostatic Diseases 19: 46–52
2. 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: 343–47
3. 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 DOI: 10.1016/j.juro.2016.02.2986
4. Van den Bos W, De Bruin DM, Veelo DP et al. (2015) Quality of life and safety outcomes following irreversible electroporation treatment for prostate cancer: results from a phase I-Ii study. Cancer Science and Therapy 7: 312–21
5. Murray K, Musser J, Mashni J et al. (2015) Irreversible electroporation (IRE) as a localized treatment for prostate cancer: A report on safety and outcomes. Journal of Urology 193: e964
6. Tomihama RT, Günther E, Kim D et al. (2015) Irreversible electroporation treatment for prostate adenocarcinomas: A safety outcome study. Journal of Vascular and Interventional Radiology 26: S121-S122
7. Niessen C, Jung EM, Beyer L et al. (2015) Percutaneous irreversible electroporation (IRE) of prostate cancer: Contrast-enhanced ultrasound (CEUS) findings. Clinical Hemorheology & Microcirculation 61: 135-141

Appendix A: Additional papers on irreversible electroporation for treating prostate cancer

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Neal RE, Millar JL, Kavnoudias H et al. (2014) In vivo characterization and numerical simulation of prostate properties for non-thermal irreversible electroporation ablation. The Prostate 74: 458–68	n=2	Histology showed regions of tissue necrosis surrounding the electrodes.	Larger studies are included.
van den Bos W, Jurhill RR, de Bruin M et al. (2016) Histopathological outcomes after irreversible electroporation in prostate cancer; Results of an ablate-and-resect study. Journal of Urology 196: 1–8	n=16	Histopathological assessment of the prostate four weeks after IRE ablation showed sharp-demarcated fibrotic and necrotic tissue within the ablation zone. No viable tissue was observed within the IRE ablation zone.	Results from the same study are included (Van den Bos, 2015)
van den Bos W, de Bruin DM, Jurhill RR et al. (2016) The correlation between the electrode configuration and histopathology of irreversible electroporation ablations in prostate cancer patients. World Journal of Urology 34: 657-664	n=16	IRE in prostate cancer results in completely ablated, sharply demarcated lesions with a histological ablation zone beyond the electrode configuration. No skip lesions were observed within the electrode configuration.	Results from the same study are included (Van den Bos, 2015)
van den Bos W, de Bruin DM, van Randen A et al. (2015) MRI and contrast-enhanced ultrasound imaging for evaluation of focal irreversible electroporation treatment: results from a phase I-II study in patients undergoing IRE followed by radical prostatectomy. European Radiology doi: 10.1007/s00330-015-4042-3	n=16	Multiparametric MRI (mp MRI) and contrast-enhanced ultrasound are appropriate imaging modalities for assessing IRE effects. mpMRI and contrast-enhanced ultrasound are the most feasible imaging modalities to visualise the IRE ablation zone. The imaging is concordant with results of histopathological examination after IRE. Grey-scale ultrasound is insufficient for assessing IRE ablations.	Paper focuses on appropriate imaging techniques.

Appendix B: Related NICE guidance for irreversible electroporation for treating prostate cancer

Guidance	Recommendations
Interventional procedures	**Focal therapy using high-intensity focused ultrasound for localised prostate cancer. NICE interventional procedure guidance 424 (2012)** 1.1 Current evidence on focal therapy using high-intensity focused ultrasound (HIFU) for localised prostate cancer raises no major safety concerns. However, evidence on efficacy is limited in quantity and there is a concern that prostate cancer is commonly multifocal. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake focal therapy using HIFU for localised prostate cancer should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and the risks (specifically the risk of sexual dysfunction), and provide them with clear written information. In addition, the use of NICE's information for patients (Understanding NICE guidance) is recommended. 1.3 Patient selection and treatment should be carried out by a multidisciplinary urological cancer team. 1.4 NICE encourages further research into focal therapy using HIFU for localised prostate cancer. This should take the form of controlled studies comparing the procedure against other forms of management. Studies should clearly define patient selection criteria and should report outcomes including local recurrence in the long term. 1.5 Clinicians should collect data on all patients undergoing focal HIFU (including details of case selection, methods of follow-up and outcomes) for local audit and for submission to national and/or international registers when these become available. The European

Registry for Cryosurgical Ablation of the Prostate (EuCAP) register is being developed to receive data on focal therapy using HIFU for localised prostate cancer. When this facility is available clinicians should submit data on all patients undergoing focal therapy using HIFU for localised prostate cancer to that register.

Focal therapy using cryoablation for localised prostate cancer. NICE interventional procedure guidance 423 (2012).

1.1 Current evidence on focal therapy using cryoablation for localised prostate cancer raises no major safety concerns. However, evidence on efficacy is limited in quantity and there is a concern that prostate cancer is commonly multifocal. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to undertake focal therapy using cryoablation for localised prostate cancer should take the following actions.

- Inform the clinical governance leads in their Trusts.
- Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and the risks (specifically the risk of sexual dysfunction), and provide them with clear written information. In addition, the use of NICE's information for patients (Understanding NICE guidance) is recommended.

1.3 Patient selection and treatment should be carried out by a multidisciplinary urological cancer team.

1.4 NICE encourages further research into focal cryoablation for localised prostate cancer. This should take the form of controlled studies comparing the procedure against other forms of management. Studies should clearly define patient selection criteria and should report outcomes including local recurrence in the long term.

1.5 Clinicians should collect data on all patients undergoing focal cryoablation (including details of case selection, methods of follow-up and outcomes) for local audit. Clinicians should enter details about all patients undergoing focal therapy using cryoablation for localised

	prostate cancer onto the European Registry for Cryosurgical Ablation of the Prostate (EuCAP) register and review clinical outcomes locally. **Laparoscopic radical prostatectomy. NICE interventional procedure guidance 193 (2006).** 1.1 Current evidence on the safety and efficacy of laparoscopic radical prostatectomy appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should ensure that men understand the benefits and risks of all the alternative treatment options. In addition, use of the Institute's information for patients is recommended. 1.3 Clinicians undertaking laparoscopic radical prostatectomy require special training. The British Association of Urological Surgeons has produced training standards. **High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE interventional procedure guidance 174 (2006).** 1.1 Current evidence on the safety and efficacy of high dose rate (HDR) brachytherapy in combination with external-beam radiotherapy for localised prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 A multidisciplinary team should be involved in the planning and use of this procedure. **Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedure guidance 145 (2005).** 1.1 Current evidence on the safety and efficacy of cryotherapy, measured by reduction of prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure as a primary treatment in patients with prostate cancer provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 The effects of cryotherapy as a primary treatment for prostate cancer on quality of life and long-term survival remain uncertain.

	Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options. They should provide them with clear written information and, in addition, use of the Institute's information for the public is recommended. 1.3 Further research and audit should address quality of life, clinical outcomes and long-term survival. **Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedure guidance 132 (2005).** 1.1 Current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy for localised prostate cancer appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Most of the evidence on the efficacy of low dose rate brachytherapy for localised prostate cancer relates to the reduction of prostate-specific antigen (PSA) levels and to biopsy findings. The effects on quality of life and long-term survival remain uncertain. Clinicians should ensure that patients understand these uncertainties and the alternative treatment options. Use of the Institute's information for the public is recommended. 1.3 A multidisciplinary team should be involved in the planning and use of this procedure. The Institute has issued a cancer service guideline on improving outcomes in urological cancers. 1.4 Further research and audit should address quality of life, clinical outcomes and long-term survival. **Cryotherapy for recurrent prostate cancer. NICE interventional procedure guidance 119 (2005).** 1.1 Current evidence on the safety and efficacy of cryotherapy, as measured by a reduction of prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure in patients with recurrent prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The effects of cryotherapy for recurrent prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should

	therefore ensure that patients understand the uncertainties and the alternative treatment options. Use of the Institute's information for the public is recommended. 1.3 Further research and audit should address quality of life, clinical outcomes and long-term survival. **High-intensity focused ultrasound for prostate cancer. NICE interventional procedure guidance 118 (2005).** 1.1 Current evidence on the safety and efficacy of high-intensity focused ultrasound (HIFU), as measured by reduction in prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure for the treatment of prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The effects of HIFU for prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options. Use of the Institute's information for the public is recommended. 1.3 Interpretation of the data was difficult because it was not clear from the literature when the procedure was used for primary or for salvage treatment. Further research and audit should address clinical outcomes, long-term survival and indications for treatment (differentiating between the use of the procedure for primary and for salvage treatment). **Irreversible electroporation for treating liver metastases. NICE interventional procedure guidance 445 (2013).** 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating liver metastases is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival. **Irreversible electroporation for treating primary liver cancer. NICE interventional procedure guidance 444 (2013).** 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating primary liver cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in

	the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival. **Irreversible electroporation for treating renal cancer. NICE interventional procedure guidance 443 (2013).** 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating renal cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival. **Irreversible electroporation for treating pancreatic cancer. NICE interventional procedure guidance 442 (2013).** 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival. **Irreversible electroporation for treating primary lung cancer and metastases in the lung. NICE interventional procedure guidance 441 (2013).** 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating primary lung cancer and metastases in the lung is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival.

NICE guidelines	**Prostate cancer: diagnosis and management. NICE clinical guideline 175 (2014).** 1.3 Localised and locally advanced prostate cancer 1.3.1 Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. **[2008, amended 2014]** 1.3.2 Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. **[2008, amended 2014]** 1.3.3 Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function. **[2008, amended 2014]** 1.3.4 Offer men experiencing troublesome urinary symptoms before treatment a urological assessment. **[2008]** 1.3.5 Given the range of treatment modalities and their serious side effects, men with prostate cancer who are candidates for radical treatment should have the opportunity to discuss their treatment options with a specialist surgical oncologist and a specialist clinical oncologist. **[2008]** 1.3.6 Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer. **[new 2014]** **Low-risk localised prostate cancer** **Active surveillance** 1.3.7 Offer active surveillance (in line with recommendation 1.3.8) as an option to men with low-risk localised prostate cancer for whom radical prostatectomy or radical radiotherapy is suitable. **[new 2014]** 1.3.8 Consider using the protocol in table 2 for men who have chosen active surveillance. **[new 2014]**

Table 2 Protocol for active surveillance

Timing	Tests [1]
At enrolment in active surveillance	Multiparametric MRI if not previously performed
Year 1 of active surveillance	Every 3–4 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 6–12 months: DRE[4] At 12 months: prostate rebiopsy
Years 2–4 of active surveillance	Every 3–6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 6–12 months: DRE[4]
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 12 months: DRE[4]

[1] If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy.

[2] May be carried out in primary care if there are agreed shared-care protocols and recall systems.

[3] May include PSA doubling time and velocity.

[4] Should be performed by a healthcare professional with expertise and confidence in performing DRE.

1.3.9 The decision to proceed from an active surveillance regimen to radical treatment should be made in the light of the individual man's

	personal preferences, comorbidities and life expectancy. **[2008]** **Radical treatment** 1.3.10 Offer radical treatment to men with localised prostate cancer who have chosen an active surveillance regimen and who have evidence of disease progression. **[2008, amended 2014]** **Intermediate- and high-risk localised prostate cancer** **Active surveillance** 1.3.11 Consider active surveillance (in line with recommendation 1.3.8) for men with intermediate-risk localised prostate cancer who do not wish to have immediate radical prostatectomy or radical radiotherapy. **[new 2014]** 1.3.12 Do not offer active surveillance to men with high-risk localised prostate cancer. **[2014]** **Radical treatment** 1.3.13 Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer. **[2008]** 1.3.14 Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control. **[2008]** 1.3.15 Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. **[new 2014]** 1.3.16 Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are cost effective by basing them in centres that are expected to perform at least 150 robot-assisted laparoscopic radical prostatectomies per year. **[new 2014]** 1.3.17 Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. **[2008]** 1.3.18 For men with localised prostate cancer receiving radical external

	beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage**. [2008]** 1.3.19 Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. **[new 2014]** 1.3.20 Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy. **[new 2014]** 1.3.21 Consider continuing androgen deprivation therapy for up to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. **[new 2014]** 1.3.22 Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. **[new 2014]** 1.3.23 Do not offer brachytherapy alone to men with high-risk localised prostate cancer. **[2008]** 1.3.24 Do not offer high-intensity focused ultrasound and cryotherapy to men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions. **[2008]** **Watchful waiting** 1.3.25 A member of the urological cancer MDT should review men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (that is, rapidly rising PSA level or bone pain). **[2008]** **Locally advanced prostate cancer** 1.3.26 Clinical oncologists should consider pelvic radiotherapy in men with locally advanced prostate cancer who have a higher than 15% risk

	of pelvic lymph node involvement and who are to receive neoadjuvant hormonal therapy and radical radiotherapy. **[2008]** 1.3.27 Do not offer immediate post-operative radiotherapy after radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. **[2008]** 1.3.28 Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. **[2008]** 1.3.29 Do not offer high-intensity focused ultrasound and cryotherapy to men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions. **[2008]** 1.3.30 Do not offer bisphosphonates for the prevention of bone metastases in men with prostate cancer. **[2008]** **Managing adverse effects of radical treatment** **Sexual dysfunction** 1.3.31 Ensure that men have early and ongoing access to specialist erectile dysfunction services. **[2008, amended 2014]** 1.3.32 Offer men with prostate cancer who experience loss of erectile function phosphodiesterase type 5 (PDE5) inhibitors to improve their chance of spontaneous erections. **[2008]** 1.3.33 If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer men vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative. **[2008]** **Urinary incontinence** 1.3.34 Ensure that men with troublesome urinary symptoms after treatment have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include coping strategies, along with pelvic floor muscle re-education, bladder

	retraining and pharmacotherapy. **[2008]** 1.3.35 Refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter. **[2008]** 1.3.36 Do not offer injection of bulking agents into the distal urinary sphincter to treat stress incontinence. **[2008]** **Radiation-induced enteropathy** 1.3.37 Ensure that men with signs or symptoms of radiation-induced enteropathy are offered care from a team of professionals with expertise in radiation-induced enteropathy (who may include oncologists, gastroenterologists, bowel surgeons, dietitians and specialist nurses). **[new 2014]** 1.3.38 The nature and treatment of radiation-induced enteropathy should be included in the training programmes for oncologists and gastroenterologists. **[2014]** 1.3.39 Carry out full investigations, including flexible sigmoidoscopy, in men who have symptoms of radiation-induced enteropathy to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. Use caution when performing anterior wall rectal biopsy after brachytherapy because of the risk of fistulation. **[2014]** **Follow-up** 1.3.40 Discuss the purpose, duration, frequency and location of follow-up with each man with localised prostate cancer, and if he wishes, his partner or carers. **[2008]** 1.3.41 Clearly advise men with prostate cancer about potential longer-term adverse effects of treatment and when and how to report them. **[2008]** 1.3.42 Men with prostate cancer who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care in accordance with protocols agreed by the local

	urological cancer MDT and the relevant primary care organisation(s). Their PSA should be measured at least once a year. **[2008]** 1.3.43 Check PSA levels for all men with prostate cancer who are having radical treatment at the earliest 6 weeks following treatment, at least every 6 months for the first 2 years and then at least once a year thereafter. **[2008]** 1.3.44 Do not routinely offer DRE to men with localised prostate cancer while the PSA remains at baseline levels. **[2008]** 1.3.45 After at least 2 years, offer follow-up outside hospital (for example, in primary care) by telephone or secure electronic communications to men with a stable PSA who have had no significant treatment complications, unless they are taking part in a clinical trial that requires formal clinic-based follow-up. Direct access to the urological cancer MDT should be offered and explained. **[2008]**

Appendix C: Literature search for irreversible electroporation for treating prostate cancer

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	29/04/2016	Issue 4 of 12, April 2016
HTA database (Cochrane)	29/04/2016	Issue 1 of 4, January 2016
Cochrane Central Register of Controlled Trials (Cochrane)	29/04/2016	Issue 3 of 12, March 2016
MEDLINE (Ovid)	29/04/2016	1946 to April Week 3 2016
MEDLINE In-Process (Ovid)	29/04/2016	April 27, 2016
EMBASE (Ovid)	29/04/2016	1974 to 2016 Week 17
PubMed	29/04/2016	n/a
BLIC (British Library)	29/04/2016	n/a

Trial sources searched on 29 April 2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 29 April 2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

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

1 Electroporation/

2 Electric Stimulation/

3 exp Nanotechnology/

4 nanoknife.tw.

5 (irrevers* adj4 (electropor* or electro-por* or electropermeab* or electro-permeab*)).tw.

6 (electric* adj4 (field* or stimul* or pulse* or cell? or membrane* or pore?)).tw.

7	Electric Stimulation Therapy/
8	IRE.tw.
9	LEDC.tw.
10	Electrochemotherapy/
11	electrochemo*.tw.
12	Ablation Techniques/
13	((tissue* or tumor* or tumour*) adj4 ablat*).tw.
14	(bipolar adj4 (puls? or electrod* or mode?)).tw.
15	or/1-14
16	Prostatic Neoplasms/
17	(Prostat* adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcoma* or Metastasis*)).tw.
18	16 or 17
19	15 and 18
20	animal/ not human/
21	19 not 20