NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of focal therapy using high-intensity focused ultrasound for localised prostate cancer

Symptoms of localised prostate cancer may include difficulties in passing urine, although many people do not have symptoms at the time of diagnosis. This procedure uses high-intensity focused ultrasound to heat up and destroy only the areas of the prostate with cancer (focal therapy). The aim is to destroy the cancer while reducing damage to healthy prostate tissue. This can reduce the risk of side effects (such as loss of bladder control and sexual function) that can happen when the whole prostate gland is treated.

Contents

Abbreviations

Word or phrase	Abbreviation
Androgen deprivation therapy	ADT
Cambridge Prognostic Group	CPG
Confidence interval	CI
Expanded Prostate Cancer Index Composite	EPIC
External beam radiotherapy	EBRT
Failure-free survival	FFS
Functional Assessment of Cancer Therapy – Prostate	FACT-P
Hazard ratio	HR
HIFU Evaluation and Assessment of Treatment	HEAT
High-intensity focused ultrasound	HIFU
International Continence Society male short form	ICSmaleSF
International Index of Erectile Function	IIEF
International prostate symptom score	IPSS
Odds ratio	OR
Overall survival	OS
Preferred Reporting Items for Systematic Reviews and Meta-Analyses	PRISMA
Prostate-specific antigen	PSA
Quality of life	QoL
Randomised controlled trial	RCT
Transurethral resection of the prostate	TURP
Urinary tract infection	UTI

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 June 2022.

Procedure name

- Focal therapy using high-intensity focused ultrasound for localised 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 causes the prostate to enlarge, resulting in symptoms such as difficulty in urinating and frequent urination. Localised prostate cancer is confined to the prostate and has not spread to nearby tissues or to other parts of the body.

Decisions on treatment are based on imaging, tumour staging, risk assessment, and prostate-specific antigen (PSA) levels. For some people, localised prostate cancer grows slowly or not at all, and treatment may not be necessary. In such cases, watchful waiting or active surveillance strategies may be appropriate. If treatment is needed, several options are available. These include radical treatments (such as radical prostatectomy, external beam radiotherapy [EBRT], and radical brachytherapy), focal treatments (such as focal high-intensity focused ultrasound [HIFU], focal cryoablation, irreversible electroporation, focal laser ablation, and focal brachytherapy), and adjunctive treatments (such as chemotherapy and androgen deprivation therapy [ADT]).

What the procedure involves

Imaging and biopsy mapping are used to confirm that the tumour is suitable for focal therapy and to show its precise location. With the person under spinal or general anaesthesia, the bladder is catheterised using a urethral or supra-pubic catheter and the HIFU probe is inserted transrectally. Ultrasound imaging guidance is used to position the probe and to monitor the procedure. Pulses of HIFU are directed at the targeted part of the prostate, inducing tumour necrosis by a thermal effect, and causing cavitation (which can be visualised by ultrasound to assess the adequacy of treatment) until satisfactory ablation of the

target area is judged to have occurred. This procedure differs from standard whole-gland HIFU in that only some of the prostate is treated. Transurethral resection of the prostate (TURP) may be done at the same time as focal HIFU to reduce urinary symptoms.

After treatment, follow up consists of repeated PSA measurements and biopsies to detect recurrence.

Outcome measures

Prostate cancer risk stratification

Risk stratification for prostate cancer is typically based on 3 factors: PSA levels, tumour staging (T-stage), and the Gleason score. There may be 3 risk levels (low, intermediate, and high, as per the D'Amico classification), or 5 levels (as per the Cambridge Prognostic Group [CPG]).

Gleason score

The Gleason scoring system is an internationally recognised grading system, based on examination of the architectural differentiation of prostate tissue. When the prostate is biopsied, 10 to 12 cores are taken from different parts of the gland (5 or 6 per side). The 2 most common tumour patterns are analysed and graded from 1 to 5:

- Grade 1: small, uniform glands with minimal nuclear changes.
- Grade 2: medium-sized acinii, separated by stromal tissue but more closely arranged.
- Grade 3: marked variation in glandular size and organization and infiltration of stromal and neighbouring tissues.
- Grade 4: marked atypical cytology with extensive infiltration.
- Grade 5: sheets of undifferentiated cells.

The Gleason score is the sum of these 2 grades. For example, if the grade given to the most common growth pattern is 4 and the grade given to the second most common growth pattern is 4, the total Gleason score is 8 (4 + 4). A Gleason score of 2 is the most well differentiated tumour, and 10 is the most poorly differentiated. Lower scores are associated with a better prognosis than higher scores.

- Low-grade tumour: Gleason score ≤6.
- Intermediate-grade tumour: Gleason score 7.
- High-grade tumour: Gleason score 8 to 10.

Tumour staging

Taken from the Tumour Node Metastasis classification, the T-stage refers to the size of the tumour and whether it invades surrounding structures:

- T0 No evidence of primary tumour
- T1 Clinically inapparent tumour that is not palpable
- T1a Tumour incidental histological finding in 5% or less of tissue resected
- T1b Tumour incidental histological finding in more than 5% of tissue resected
- T1c Tumour identified by needle biopsy (for example, because of elevated PSA)
- T2 Tumour that is palpable and confined within the prostate
- T2a Tumour involves half of one lobe or less
- T2b Tumour involves more than half of one lobe, but not both lobes
- T2c Tumour involves both lobes
- T3 Tumour extends through the prostatic capsule
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumour invades seminal vesicle(s)
- T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

Risk classification

The D'Amico and CPG classifications combine PSA levels, Gleason score, and T-stage to estimate risk:

- Low risk (similar to CPG 1):
    - T-stage of T1 to T2a, and
    - Gleason score no higher than 6, and
    - PSA level less than 10 ng/ml
- Intermediate risk (similar to CPG 2 and 3):
    - T-stage of T2b, or
    - Gleason score of 7, or
    - PSA level between 10 and 20 ng/ml
- High risk (similar to CPG 4 and 5):
    - T-stage of T2c, or
    - Gleason score between 8 and 10, or
    - PSA level higher than 20 ng/ml

Functional and QoL outcomes

IPSS

The International prostate symptom score (IPSS) is an 8-item instrument to measure urinary symptoms (7-items) and overall quality of life (QoL; 1-item). Symptoms include incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Symptoms are scored from 1 to 5 and the QoL item is scored from 1 to 6. Higher scores indicate worse symptoms/QoL.

EPIC

The Expanded Prostate Cancer Index Composite (EPIC) is a 32-item instrument that assesses functional outcomes in people with prostate cancer. The questionnaire includes items covering urinary function, bowel habits, sexual function, hormonal function, and treatment satisfaction.

ICSmaleSF

The International Continence Society male short form (ICSmaleSF) is an 11-item instrument that assesses voiding and incontinence. Higher scores indicate worse voiding and incontinence.

IIEF

The International Index of Erectile Function (IIEF) questionnaire is a 15-item instrument that assesses erectile function, orgasm, sexual desire, intercourse satisfaction, and overall satisfaction. Lower scores indicate worse function.

FACT-P

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire is a 39-item instrument that assesses QoL across physical well-being, social/family well-being, emotional well-being, functional well-being, and a prostate cancer subscale.

Complications grading

Clavien–Dindo system

The Clavien–Dindo system is widely used in urological surgery for grading adverse events which occur because of surgical procedures. The system ranges from:

- Grade I

        - Any deviation from the normal postoperative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (for example antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside.
- Grade II
    - Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition.
- Grade III
    - Complications requiring surgical, endoscopic or radiological intervention.
        - Grade IIIa - intervention not under general anaesthetic
        - Grade IIIb - intervention under general anaesthetic
- Grade IV
    - Life-threatening complications: this includes central nervous system complications (for example brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks.
        - Grade IVa - single-organ dysfunction (including dialysis)
        - Grade IVb - multi-organ dysfunction
- Grade V
    - Death of the person

Efficacy summary

Note: there was substantial overlap in the studies included in the systematic reviews, refer to List of studies included in the IP overview for more information.

Oncological outcomes

Cancer control outcomes

Overall survival

In an analysis of a prospective registry of 1,379 people, overall survival (OS) at 7 years was 97% (95% confidence interval [CI] 96% to 99%; Reddy 2022).

A propensity score weighted analysis compared 530 people who had focal therapy (including 419 who had focal HIFU) to 830 people who had radical therapy (including EBRT and prostatectomy; van Son 2021). The following outcomes were reported:

- Two-way analysis (focal compared with radical therapy):
    - People treated with focal therapy had statistically significantly higher OS at 6 years than people treated with radical therapy (97.5% compared with 93.4%, p=0.02; Kaplan–Meier analysis).
    - There were no statistically significant differences between the groups in overall mortality (p>0.05; regression analysis).
- Three-way analysis (focal therapy compared with radical prostatectomy compared with radical EBRT):
    - Overall mortality was statistically significantly less likely in the focal therapy group than the EBRT group (hazard ratio [HR] 0.29, 95% CI 0.11 to 0.76, p=0.008; regression analysis).
    - There was no statistically significant difference in overall mortality between the focal therapy and radical prostatectomy groups.

In a retrospective case series of 1,032 people, OS at 96 months was 96.6% (Stabile 2019).

Failure-free survival

In the analysis of a prospective registry of 1,379 people, failure-free survival (FFS) at 7 years was 69% (95% CI 64% to 74%; Reddy 2022). Failure was defined as evidence of cancer requiring whole-gland salvage treatment or 3rd focal treatment (2 were permitted in the protocol), systemic treatment, development of prostate cancer metastases, or prostate cancer-specific death. By D'Amico risk class, FFS at 7 years was:

- Low risk cancers 88% (95% CI 77% to 99%)
- Intermediate risk cancers 68% (95% CI 62% to 75%)
- High risk cancers 65% (95% CI 56% to 74%).

The propensity score weighted analysis compared 530 people who had focal therapy (including 419 who had focal HIFU) to 830 people who had radical therapy (including EBRT and prostatectomy; van Son 2021). FFS was a composite endpoint of need for local salvage treatment, development of metastatic disease, use of systemic treatment (ADT or chemotherapy) or progression to a watchful waiting strategy. The following outcomes were reported:

- Two-way analysis (focal compared with radical therapy):
    - There was no statistically significant difference in FFS at 6 years between focal and radical therapy groups (p=0.10; Kaplan–Meier analysis).
    - There was no statistically significant difference between the groups in treatment failure (p>0.05; regression analysis).
- Three-way analysis (focal therapy compared with radical prostatectomy compared with radical EBRT):

- Treatment failure was statistically significantly more likely in both focal therapy and radical prostatectomy groups compared to EBRT (HR 2.24 [95% CI 1.4 to 3.64] and HR 2.41 [95% CI 1.44 to 4.05]; both p<0.001; regression analysis).

In the retrospective case series of 1,032 people, biopsy FFS at 96 months was 54.0%. Biopsy FFS was defined as the presence of clinically significant prostate cancer at post-treatment biopsy (Stabile 2019).

Recurrence

In a systematic review of 20 studies, 9 studies reported that clinically significant infield recurrence was detected in 5% to 22% of people over median follow up ranging from 6 to 56 months. Seven studies reported that any prostate cancer (clinically significant or not) in the HIFU field was detected in 10% to 37% of people over median follow up ranging from 12 to 56 months. Furthermore, 7 studies reported that clinically significant out-of-field progression was detected in 2% to 29% of people over median follow up ranging from 6 to 33 months. Six studies reported that any prostate cancer (clinically significant or not) out of the HIFU field was detected in 8% to 35% of people over median follow up ranging from 12 to 56 months (Bakavicius 2022).

A retrospective cohort study compared 152 people who had focal HIFU to 54 people who had whole-gland HIFU. At 12 months follow up, outcomes were available for 59 partial-gland people and 27 whole-gland people. There was no statistically significant difference in the proportion of people in each group who had any positive biopsy (partial-gland 27.1% compared with whole-gland 29.6%, p=0.713; Byun 2022).

Metastasis

In a systematic review of 3 studies on focal HIFU as a salvage treatment, postoperative metastasis rates ranged from 5% to 12.5% over a median follow up ranging from 16.3 to 35 months (Khoo 2020).

In the analysis of a prospective registry of 1,379 people, metastasis-free survival at 7 years was 100% (95% CI 99% to 100%; Reddy 2022).

PSA outcomes

In the systematic review of 20 studies, 10 studies reported that the median PSA reduction was 53% to 84%. Six studies reported that the median time to reach PSA nadir ranged from 3 to 12 months after surgery (Bakavicius 2022).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, biochemical disease-free survival (BDFS) was defined as a rise of 2 ng/mL or

more above the PSA nadir level (Khoo 2020). In the 3 studies, BDFS ranged from 0% to 67% over follow up ranging from 16.3 to 35 months.

Retreatments

In the systematic review of 20 studies, 13 studies reported details of retreatments. These included (Bakavicius 2022):

- Further focal HIFU:
    - In-field recurrence: 5% to 11% of people had a second focal HIFU (2 studies).
    - Out-of-field progression: 2% to 13% of people had a second focal HIFU (4 studies).
    - Not specified disease location: 4% to 19% of people had a second focal HIFU (7 studies).
- Other retreatments:
    - Salvage focal cryotherapy: 1% of people (1 study).
    - Salvage whole-gland HIFU: 0.4% to 10% of people (3 studies).
    - Salvage radical prostatectomy: 1% to 22% of people (10 studies).
    - Salvage EBRT with or without ADT: 0.9% to 8% of people (9 studies).
    - ADT only: 0.2% to 6% of people (6 studies).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 1 study reported that 8% of people converted to second-line therapy (Khoo 2020).

In the analysis of a prospective registry of 1,379 people, salvage whole-gland or systemic treatment-free survival at 7 years was 75% (95% CI 71% to 80%; Reddy 2022).

In the retrospective case series of 1,032 people, retreatment-free survival was 45.8% and radical treatment-free survival was 80.8% at 96 months after surgery. Radical treatment-free survival was defined as radical prostatectomy, EBRT and other whole-gland therapies (Stabile 2019). Throughout the follow-up period, 271 people were retreated (26.3%). Retreatments included:

- Focal HIFU, n=193
- Focal cryotherapy, n=12
- EBRT, n= 9
- Radical prostatectomy, n=30
- Whole-gland HIFU, n=4
- ADT, n=20
- Other, n=3.

Quality of life

In the systematic review of 20 studies, 2 studies reported no deterioration in QoL on the FACT-P questionnaire (Bakavicius 2022).

Safety summary

Complications

In the systematic review of 20 studies, 12 studies reported that overall, 13% to 41% of people who had focal HIFU experienced some type of complication over median follow up ranging from 6 to 56 months. Most complications (85% to 100%) presented up to 3 months after the procedure (3 studies) and complications were mostly minor (80% to 100%; Clavien–Dindo grade I to II) and did not require any surgical intervention (9 studies; Bakavicius 2022).

In the analysis of a prospective registry of 1,379 people, there were a total of 83 (6.0%) complications. The rate of complications with Clavien–Dindo score >2 was 0.5% (7/1,379; Reddy 2022).

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, there were statistically significantly fewer complications in the focal HIFU group (37.5% compared with 66.7%, p=0.023; Byun 2022).

Urinary system complications

Urinary retention

In the systematic review of 20 studies, 8 studies reported acute urinary retention in 7% to 27% of people (Bakavicius 2022).

In a systematic review of 9 studies, 5 studies were included in a meta-analysis of urinary retention (He 2020). The pooled urinary retention rate for focal HIFU was 9% with no heterogeneity (I^2=0%). There was no statistically significant difference in incidence of urinary retention with focal HIFU compared with whole-gland HIFU (9% compared with 11%; p=0.945; whole-gland HIFU meta-analysis based on 5 studies).

In the analysis of a prospective registry of 1,379 people, 10 people reported urinary retention (0.7%; Reddy 2022).

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, similar proportions of people had urinary retention in both groups (10.5% compared with 18.5%; Byun 2022).

Urethral sloughing

In the systematic review of 20 studies, 4 studies reported urethral sloughing in 7% to 43% of people (Bakavicius 2022).

Urinary tract infection

In the systematic review of 20 studies, 8 studies reported urinary tract infection (UTI) in 5% to 18% of people (Bakavicius 2022).

In the systematic review of 9 studies, 4 studies were included in a meta-analysis of UTI (He 2020). The pooled UTI rate for focal HIFU was 11% with moderate heterogeneity (I^2=67%). There was a statistically significantly higher incidence of UTI with focal HIFU compared with whole-gland HIFU (11% compared with 7%; p=0.001; whole-gland HIFU meta-analysis based on 4 studies).

In the analysis of a prospective registry of 1,379 people, 52 people reported UTIs (3.8%; Reddy 2022).

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, similar proportions of people had UTIs in both groups (2.0% compared with 1.9%; Byun 2022).

Epididymitis

In the systematic review of 20 studies, 8 studies reported acute infective epididymitis in 2% to 8% of people (Bakavicius 2022).

In the analysis of a prospective registry of 1,379 people, 11 people reported epididymitis (0.8%; Reddy 2022).

Fistula

In the systematic review of 20 studies, 2 studies reported fistula in 0.3% to 3% of people (Bakavicius 2022).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 2 studies reported rectourethral fistulae in 2% to 3.6% of people (Khoo 2020).

In the analysis of a prospective registry of 1,379 people, 2 people reported rectourethral fistulae (0.1%; Reddy 2022).

Urinary obstruction

In the systematic review of 9 studies, 5 studies were included in a meta-analysis of urinary obstruction (He 2020). The pooled urinary obstruction rate for focal HIFU was 2% with no heterogeneity (I^2=0%). There was a statistically significantly lower incidence of urinary obstruction with focal HIFU compared with

whole-gland HIFU (2% compared with 15%; p<0.001; whole-gland HIFU meta-analysis based on 12 studies).

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, a statistically significantly lower proportion of people had bladder outlet obstruction and required endoscopic surgery in the focal HIFU group (15.8% compared with 35.2%, p=0.005; Byun 2022).

Stricture

In the systematic review of 20 studies, 3 studies reported Iatrogenic urethral stricture disease in 2% to 4% of people (Bakavicius 2022).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 1 study reported bladder neck stenosis in 8% of people (Khoo 2020).

Bladder stones

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, similar proportions of people had bladder stones in both groups (0.7% compared with 3.7%; Byun 2022).

Other complications

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 2 studies reported pubic bone osteitis in 0.7% to 4.2% of people (Khoo 2020).

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, similar proportions of people had bleeding in both groups (5.2% compared with 5.6%; Byun 2022).

Functional outcomes

Urinary continence

In the systematic review of 20 studies, incontinence was defined as the use of any pad in 9 studies or more than 1 pad per day in 2 studies. The following continence rates were reported for focal HIFU (Bakavicius 2022):

- 3 months: 86% to 98% reported to be totally continent (3 studies).
- 6 months: 90% to 98% reported to be totally continent (6 studies).
- 12 months: 93% to 97% reported to be totally continent (6 studies).

In studies that used scales to assess continence, the following results were reported:

- IPSS remained unchanged during the first 6 months after surgery (3 studies).

- EPIC urinary domain: the incontinence score showed initial deterioration, although 6 months after the procedure, the score had returned to baseline (1 study) and remained high at 2 years (97% continent) and 3 years (98% continent) afterwards (1 study).

In the systematic review of 9 studies, 5 studies were included in a meta-analysis of urinary incontinence (He 2020). The pooled incontinence rate was 2% with no heterogeneity (I^2=0%). There was a statistically significantly lower incidence of incontinence with focal HIFU compared with whole-gland HIFU (2% compared with 10%; p<0.001; whole-gland HIFU meta-analysis based on 13 studies).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 2 studies reported pad-free rates of approximately 87% (Khoo 2020). Leak-free rates ranged from 64% to 67.6%.

In an analysis of a prospective registry of 420 people, people were stratified into 2 cohorts – cohort 1 had 1 focal HIFU treatment; cohort 2 had 2 focal HIFU treatments (Lovegrove 2020):

- Cohort 1:
    - There was a statistically significant decrease (implying better function) in mean IPSS from baseline to 1 to 2 years after the first focal HIFU (mean change -0.03, p=0.02).
    - There was no statistically significant change in mean IPSS from baseline to 2 to 3 years after the first focal HIFU, or from 1 to 2 years to 2 to 3 years after (both p>0.05).
    - There were no statistically significant changes in the proportion of people who were pad-free and leak-free continent after the first focal HIFU.
- Cohort 2 (2 HIFUs):
    - There was a statistically significant decrease (implying better function) in mean IPSS from baseline to before the second focal HIFU (mean change -1.3, p=0.02).
    - There were statistically significant increases (implying worse function) in mean IPSS from before the second focal HIFU to 1 to 2 years after the second focal HIFU (mean change 1.4, p=0.03), and from before the second focal HIFU to 2 to 3 years after the second focal HIFU (mean change 1.2, p=0.003).
    - There were no other statistically significant changes in IPSS observed.
    - There were no statistically significant changes in the proportion of people who were pad-free and leak-free continent after the first focal HIFU.

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, the partial-gland ablation group

recovered continence statistically significantly faster than the whole-gland ablation group (p=0.047; Byun 2022).

Erectile function

In the systematic review of 20 studies, erectile dysfunction was defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual intercourse (Bakavicius 2022). The following erectile function rates were reported after focal HIFU:

- 6 months postoperatively: 69% to 80% had retained sufficient erections for sexual intercourse (2 studies), and these rates remained stable (5 studies) or improved slightly (1 study) within the next 2 years.

In studies that used scales to assess erectile function, the following results were reported:

- 15-question IIEF questionnaire: initially decreased by 23 points in 1 study, with a gradual recovery during the early postoperative phase. 6 months after the procedure, the total score was still inferior by 17 points compared with baseline. In another study, 88% of people had normal erectile function at 12 months.
- 5 question IIEF: 1 study reported no deterioration in erectile function, while 2 other studies reported that 52% to 70% of people retained the same preoperative values on the IIEF-5 after the procedure. One study reported erectile dysfunction rates after a second focal HIFU, where retreatment was associated with a 7% increased erectile dysfunction rate.

In the systematic review of 9 studies, 6 studies were included in a meta-analysis of erectile dysfunction (He 2020). The pooled erectile dysfunction rate was 21% with moderate heterogeneity (I^2=62%). There was a statistically significantly lower incidence of erectile dysfunction with focal HIFU compared with whole-gland HIFU (21% compared with 44%; p<0.001; whole-gland HIFU meta-analysis based on 8 studies).

In the systematic review of 3 studies on focal HIFU as a salvage treatment, 2 studies reported declines in IIEF5 scores. Tests of statistical significance were not reported (Khoo 2020).

In the analysis of a prospective registry of 420 people, people were stratified into 2 cohorts – cohort 1 had 1 focal HIFU treatment; cohort 2 had 2 focal HIFU treatments (Lovegrove 2020):

- Cohort 1 (1 HIFU):
    - There was a statistically significant decrease (implying worse function) in erectile function score from baseline to 1 to 2 years after the first focal HIFU (mean change -0.4, p=0.02).
    - There was no statistically significant change in the proportion of people reporting erectile dysfunction (a score of 0 or 1 on question 2 of the IIEF) after the first focal HIFU.

- Cohort 2 (2 HIFUs):
    - There were statistically significant decreases (implying worse function) in erectile function score from baseline to 1 to 2 years and 2 to 3 years after the second focal HIFU (mean change -0.8, p=0.005, and -1.1, p=0.008, respectively).
    - There was no statistically significant change in the proportion of people reporting erectile dysfunction (a score of 0 or 1 on question 2 of the IIEF) after the first or second focal HIFU.

In the retrospective cohort study of 152 people who had focal HIFU compared with 54 people who had whole-gland HIFU, there was no statistically significant difference in the recovery of erectile function between the groups (p=0.317; Byun 2022).

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 occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: reduced volume of semen, dry orgasm, and perianal tear.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to focal therapy using HIFU for localised prostate cancer. The following databases were searched, covering the period from their start to 26 April 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	People with localised prostate cancer.
Intervention/test	Focal therapy with HIFU.
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 5,000 people from 3 systematic reviews, 2 registry analyses, 1 propensity score weighted study, 1 retrospective case series, and 1 retrospective cohort study. There was significant overlap between the studies. Each of the studies included in the He (2020) meta-analysis were included in the Bakavicius (2022) systematic review. Several of the studies used data from a UK-based registry (The HIFU Evaluation and Assessment of Treatment [HEAT] registry). There may have been further overlap between people in the HEAT registry and people included in Stabile (2019) as the publications have similar authorship.

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 focal therapy using HIFU for localised prostate cancer

Study 1 Bakavicius A (2022)

Study details

Study type	Systematic review
Country	Not reported for individual studies
Recruitment period	Studies published from 2010 to 2020
Study population and number	n=20 studies, 4,209 people in total (fewer reported for outcomes) People with treatment-naïve localised prostate cancer who had focal HIFU as primary treatment
Age and sex	Not reported for individual studies; 100% male
Patient selection criteria	Inclusion criteria: • Population: people with treatment-naïve localised prostate cancer. • Intervention: focal HIFU as primary treatment. • Outcomes: technical aspects of focal HIFU therapy, oncologic and functional outcomes, complications, and management of disease recurrence. • Study design: meta-analyses, randomised controlled trials (RCTs), prospective development studies, prospective and retrospective case series with more than 50 people. Exclusion criteria: Review articles, case reports, congress abstracts, studies reporting whole-gland ablation or procedures performed in a salvage setting.
Technique	All people had transrectal focal HIFU using 1 of 3 devices: Sonablate 500 (SonaCare Medical LLC; 8 studies and 2786 people), Ablatherm Fusion (EDAP TMS; 8 studies and 778 people), and Focal One (EDAP TMS; 6 studies and 679 people). Four studies used a 6 mm safety margin from the apex of the prostate to preserve sphincter functionality and maintain continence, 1 used 3 mm and 1 used 10 mm. TURP was done in 6 of 20 studies, typically 6 to 12 months preoperatively. ADT was done in 2 studies.
Follow up	Ranged from 3 to 73 months
Conflict of interest/source of funding	Conflict of interest: The authors declared no conflict of interest. Source of funding: One author reports a grant from the European Urological Scholarship Programme.

Analysis

Study design issues: This systematic review summarises the available evidence on focal HIFU for prostate cancer. The systematic review was conducted according to the Cochrane handbook and reported according to

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Only the MEDLINE database was searched, possibly leading to the identification of fewer studies. Twenty studies were included in the final analysis, including 1 RCT (that reported no functional or oncological outcomes), 10 prospective development studies, and 9 retrospective case series. No bias assessment was conducted. Outcomes included:

- Technical aspects of focal HIFU therapy, oncologic and functional outcomes, complications, and management of disease recurrence.

Study population issues: All studies used focal HIFU in a primary treatment setting – studies reporting on salvage therapy were excluded. Most studies included people in low and intermediate prostate cancer risk groups (based on modified D'Amico classification system).

Key efficacy findings

Oncological outcomes

Number of people analysed: 16 studies, n=3,440

PSA nadir

- Median time to reach PSA nadir ranged from 3 to 12 months postoperatively (6 studies)
- Median PSA reduction was 53% to 84% (10 studies)

Infield recurrence

- Clinically significant infield recurrence was detected in 5% to 22% of people (9 studies)
- Any prostate cancer in the HIFU field was detected in 10% to 37% of people (7 studies)

Out-of-field progression

- Clinically significant out-of-field progression was detected in 2% to 29% of people (7 studies)
- Any prostate cancer out of the HIFU field was detected in 8% to 35% of people (6 studies)

Summary of oncological outcomes reported

Author, years	Study design	People, N	Follow up, months	Infield recurrence, %		Out-of-field progression, %	
				Any	Clinically significant	Any	Clinically significant
Ahmed HU et al. (2015) Eur Urol. 68:927-36	Prospective development study	56	12	34.6	15.4	7.7	3.8
Dickinson L et al. (2017) Urol Oncol. 35:30.e9-30.e15	Prospective development study	118	12	36.9	18.9	–	–
Feijoo ER et al. (2016) Eur Urol. 69:214-20.	Prospective development study	67	12	16.4a	–	10.4a	–
Guillaumier S et al. (2018) Eur Urol. 74:422-9	Prospective development study	625	56	18.0	–	12.2	–
Rischmann P et al. (2017) Eur Urol. 71:267-73	Prospective development study	111	30	13.9	5.0	20.8	6.9
van Velthoven R et al. (2016) Prostate Cancer Prostatic Dis. 19:79-83.	Prospective development study	50	35	6.0b	–	10.0b	–
Ganzer R et al. (2018) J Urol. 199:983-9.	Prospective development study	51	17	26.5	8.2	34.7	2.0

Author, years	Study design	People, N	Follow up, months	Infield recurrence, %		Out-of-field progression, %	
				Any	Clinically significant	Any	Clinically significant
Mortezavi A et al. (2019) J Urol. 202:717-24.	Prospective development study	75	6	–	20.6	–	29.4
Albisinni S et al. (2017) J Endourol. 31:14-9	Retrospective cases series	55	36	12.7b	9.1b	21.8b	–
Tourinho-Barbosa RR et al. (2020) J Urol. 203:320-30	Retrospective cases series	190	37	30.0	–	16.8	–
Stabile A et al. (2019) BJU Int. 24:431-440	Retrospective cases series	1032	36		31.5		
Johnston MJ et al. (2019) Urology 133:175-81	Retrospective cases series	107	30		28.0		
Bass R et al. (2019) J Urol. 201:113-9	Retrospective cases series	150	24	–	12.7	–	12.0
Annoot A et al. (2019) World J Urol. 37:261-8.	Retrospective cases series	55	33	–	21.8	–	5.5

Author, years	Study design	People, N	Follow up, months	Infield recurrence, %		Out-of-field progression, %	
				Any	Clinically significant	Any	Clinically significant
Huber PM et al. (2020) J Urol. 203:734-42.	Retrospective cases series	598	–		35.1c		
Abreu AL et al. (2020) J Urol. 204:741-7.	Retrospective cases series	100	18	10.0	8.0	23.0	10.0

In some studies control biopsies were performed not routinely per-protocol and (a) based on scheduled clinical visits without postoperative mpMRI, (b) on PSA kinetics only, as well as (c) triggered only when a suspicious lesion on postoperative mpMRI was detected or PSA rising was observed.

Quality of life

Number of people analysed: 2 studies, n=131

- There was no deterioration in QoL on the FACT-P questionnaire (2 studies).

Retreatment

Number of people analysed: 13 studies, n=2,657

- Further focal HIFU:
  - Infield recurrence: 5% to 11% of people had a second focal HIFU (2 studies).
  - Out-of-field progression: 2% to 13% of people had a second focal HIFU (4 studies).
  - Not specified disease location: 4% to 19% of people had a second focal HIFU (7 studies).
- Other retreatments:
  - Salvage focal cryotherapy: 1% of people (1 study).
  - Salvage whole-gland HIFU: 0.4% to 10% of people (3 studies).
  - Salvage radical prostatectomy: 1% to 22% of people (10 studies).
  - Salvage EBRT with or without ADT: 0.9% to 8% of people (9 studies).
  - ADT only: 0.2% to 6% of people (6 studies).

Key safety findings

Complications

Number of people analysed: 13 studies, n=1,870

- Overall, 13% to 41% of people who had focal HIFU experienced some type of complication (12 studies).

- The most common treatment-related adverse events included:
  - Acute urinary retention (7% to 27% of people) (8 studies)
  - Urethral sloughing (7% to 43%) (4 studies)
  - UTI (5% to 18%) (8 studies)
  - Acute infective epididymitis (2% to 8%) (2 studies)
  - Fistula (0.3% to 3%) (2 studies)
  - Iatrogenic urethral stricture disease (2% to 4%) (3 studies)
- Most complications (85% to 100%) presented up to 3 months after the procedure (3 studies).
- Complications were mostly minor (80% to 100%; Clavien–Dindo grade I-II) and did not require any surgical intervention (9 studies).
- Ablation volume and inclusion of the urethra were identified as the main predictors for postoperative complications.

Functional outcomes

Number of people analysed: 13 studies, n=2,057

Urinary continence

- Incontinence was defined as the use of any pad in 9 studies or more than 1 pad per day in 2 studies.
  - 3 months postoperatively: 86% to 98% reported to be totally continent (3 studies).
  - 6 months postoperatively: 90% to 98% reported to be totally continent (6 studies).
  - 12 months postoperatively: 93% to 97% reported to be totally continent (6 studies).
- IPSS: IPSS remained unchanged during the first 6 months postoperatively (3 studies).
- ICSmaleSF: No changes in ICSmaleSF score were detected for 85% of people 3 months after the procedure (1 study), although the same improvement from baseline was observed 12 months after focal therapy in another study.
- EPIC urinary domain: the incontinence score showed initial deterioration, although 6 months after the procedure, the score had returned to baseline (1 study) and remained high at 2 (97% continent) and 3 years (98% continent) afterwards (1 study).

Erectile function

- Erectile dysfunction was defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual intercourse.
  - 6 months postoperatively: 69% to 80% had retained sufficient erections for sexual intercourse (2 studies), and these rates remained stable (5 studies) or improved slightly (1 study) within the next 2 years.
- IIEF:
  - 15-question IIEF questionnaire initially decreased by 23 points in 1 study, with a gradual recovery during the early postoperative phase, 6 months after the procedure, the total score was still inferior by 17 points compared with baseline. In another study, 88% of people had normal erectile function at 12 months.
  - 5 question IIEF: 1 study reported no deterioration in erectile function, while 2 other studies reported that 52% to 70% of people retained the same preoperative values on the IIEF-5 after the procedure. One study reported erectile dysfunction rates after a second focal HIFU, where retreatment was associated with a 7% increased erectile dysfunction rate.

Study 2 He Y (2020)

Study details

Study type	Systematic review and meta-analysis (of complications)
Country	Belgium (1 study), Canada (1 study), France (3 studies), Germany (1 study), Switzerland (1 study), UK (2 studies)
Recruitment period	Study publication dates range from 2016 to 2019
Study population and number	Partial-gland ablation evidence: n=9 studies, 1,698 people People with prostate cancer who had whole-gland or partial-gland HIFU as primary treatment.
Age and sex	Means ranged from 45 to 81; 100% male
Patient selection criteria	Inclusion criteria: • Population: people with prostate cancer • Intervention: HIFU in primary therapy (whole-gland or partial-gland) • Outcomes: oncological and functional outcomes • Study design: RCTs, case series, prospective studies, retrospective series Exclusion criteria: Recurrent prostate cancer, HIFU as salvage therapy, reviews, conference or poster presentation, editorial commentaries, overlapping cohorts, or fewer than 50 people included.
Technique	Hemiablation was the most common technique used by the included studies.
Follow up	Ranged from 12 to 39 months
Conflict of interest/source of funding	Conflict of interest: The authors declared that they have no conflict of interest. Source of funding: The authors report the receipt of several grants from academic and public sources.

Analysis

Study design issues: This systematic review and meta-analysis summarises the outcomes of primary treatment with partial-gland and whole-gland HIFU for prostate cancer. Meta-analyses were only conducted on complications; efficacy outcomes are less comprehensively described than in Bakavicius (2022) and are not described in this overview. The methods of the meta-analysis are not well described.

Incidence of complications after HIFU were compared between partial-gland and whole-gland. $p<0.05$ was considered statistically significant.

Other issues: Forest plots generated by the meta-analysis appear to be in the wrong format. The plots describe the pooled rate of complications but are formatted as risk difference between experimental and control arms.

Key efficacy findings

Meta-analyses were only conducted on complications; efficacy outcomes are less comprehensively described than in Bakavicius (2022) and are not described in this overview.

Key safety findings

Complications and functional outcomes

Urinary incontinence

Number of people analysed: 5 studies, n=469

- The pooled incontinence rate for focal HIFU was 2% with no heterogeneity (I^2=0%).
- There was a statistically significantly lower incidence of incontinence with focal HIFU versus whole-gland HIFU (2% vs. 10%; p<0.001; whole-gland HIFU meta-analysis based on 13 studies).

Erectile dysfunction

Number of people analysed: 6 studies, n=536

- The pooled erectile dysfunction rate for focal HIFU was 21% with moderate heterogeneity (I^2=62%).
- There was a statistically significantly lower incidence of erectile dysfunction with focal HIFU versus whole-gland HIFU (21% vs. 44%; p<0.001; whole-gland HIFU meta-analysis based on 8 studies).

Urinary retention

Number of people analysed: 5 studies, 429 people

- The pooled urinary retention rate for focal HIFU was 9% with no heterogeneity (I^2=0%).
- There was no statistically significant difference in incidence of urinary retention with focal HIFU versus whole-gland HIFU (9% vs. 11%; p=0.945; whole-gland HIFU meta-analysis based on 5 studies).

Urinary obstruction

Number of people analysed: 5 studies, n=386

- The pooled urinary obstruction rate for focal HIFU was 2% with no heterogeneity (I^2=0%).
- There was a statistically significantly lower incidence of urinary obstruction with focal HIFU versus whole-gland HIFU (2% vs. 15%; p<0.001; whole-gland HIFU meta-analysis based on 12 studies).

Urinary infection

Number of people analysed: 4 studies, n=279

- The pooled urinary infection rate for focal HIFU was 11% with moderate heterogeneity (I^2=67%).
- There was a statistically significantly higher incidence of urinary infection with focal HIFU versus whole-gland HIFU (11% vs. 7%; p=0.001; whole-gland HIFU meta-analysis based on 4 studies).

Study 3 Khoo CC (2020)

Study details

Study type	Systematic review
Country	Not reported for individual studies.
Recruitment period	Study publication dates ranged from 2012 to 2017
Study population and number	n=3 studies, 237 people People with radiorecurrent prostate cancer who had focal HIFU salvage therapy
Age and sex	Means ranged from 68.8 to 70.5; 100% male
Patient selection criteria	Inclusion criteria: • Population: people with radiorecurrent prostate cancer • Intervention: salvage focal HIFU (other focal interventions were included, but not relevant to this overview) • Outcomes: BDFS, rates of metastases, second-line therapies, and adverse events • Study design: randomised and non-randomised comparative and non-comparative studies. Exclusion criteria: whole-gland ablation, review articles, unpublished studies, case reports, letters, bulletins, comments, conference abstracts, small series (n<10), duplicates, and studies with follow-up articles.
Technique	Treatment strategies varied, and included quadrant-, hemi- and index lesion ablation (with residual cancer left untreated).
Follow up	Ranged from 16.3 to 35 months.
Conflict of interest/source of funding	Conflict of interest: The authors declare various grants, some of which were from manufacturers of HIFU devices. Source of funding: The authors declared that no funding was received.

Analysis

Study design issues: This systematic review summarises the evidence on the use of focal HIFU as a salvage therapy in people with radiorecurrent prostate cancer. Reporting of the review followed the PRISMA statement. A quality assessment was conducted using the Methodological Index for Non-Randomized Studies instrument. Using this instrument, the 3 studies identified for HIFU scored 12, 12, and 13 out of 16, respectively. Outcomes included:

- BDFS, rates of metastases, second-line therapies, and adverse events.

Key efficacy findings

Number of people analysed: 3 studies, n=237

- BDFS: BDFS at the end of follow up or 3 years ranged from 0% to 67%. One study split people by whether they had achieved a PSA nadir of <0.5 ng/mL; those that did had higher BDFS rates.
- Metastasis rates ranged from 5 to 12.5%.
- Conversion to second-line therapy was only reported in 1 study and was 8%.

Summary of efficacy findings of focal HIFU

Author	n	Mean age (years)	Median pre-salvage PSA (ng/mL)	Median follow up (months)	Biochemical disease-free survival	Metastasis	Conversion to second-line salvage therapies
Ahmed HU et al. (2012) Cancer 118:4148-55	39	70.5	4.6	17	PSA nadir <0.5 ng/mL: 1 year: 86% 2 years: 75% 3 years: 63% PSA nadir ≥0.5 ng/mL: 1 year: 55% 2 years: 24% 3 years: 0%	5%	n.a.
Baco E et al. (2014) BJU 114:532-40	48	68.8	na	16.3	End of follow-up: 67%	12.5%	n.a.
Kanthabalan A et al. (2017) BJU Int 120:246-56.	150	69.8	5.5	35	3 years: 48%	6%	8.0% (sRP: 3, EBRT of spinal metastatic disease: 1, irreversible electroporation: 1, sCT: 1, chemotherapy: 4, other drug treatments: 2)

Key safety findings

Complications

Number of people analysed: 3 studies, n=237

Reported complications included:

- Rectourethral fistula (2% to 3.6%; 2 studies)
- Bladder neck stenosis (8.0%; 1 study)
- Pubic bone osteitis (0.7% to 4.2%; 2 studies)

Functional outcomes

Number of people analysed: 2 studies, n=189

- Incontinence rates:
    - One study reported a pad-free, leak-free continence rate of 64% and the pad-free rate was 87% at last follow up.
    - The other study reported a pad-free rate of 87.5% at 2 years and 67.6% of people drip-free continent at baseline remained drip-free.
- Erectile dysfunction:
    - One study reported worsening IIEF5 scores from a pre-procedure median of 18 to 13 at 6 months.
    - The other study reported a minor decline in median IIEF5 scores from 15 to 13.

Study 4 Reddy D (2022)

Study details

Study type	Prospective, multicentre registry analysis – the HEAT registry
Country	UK
Recruitment period	2005 to 2020
Study population and number	n=1,379 People with non-metastatic prostate cancer who were treated using focal HIFU
Age and sex	Median 66; 100% male
Patient selection criteria	People with Gleason score of 6 to 9 prostate cancer and radiological stage up to T3bN0M0 were offered focal therapy.
Technique	Focal HIFU using the Sonablate (500 and 3G) device (Sonacare Inc., Charlotte, NC, USA). Quadrant was the most used ablative pattern (62%), with hemiablation (35%), and hockey-stick ablation (3%) less common. Up to 2 focal HIFU treatments were permitted (differences in functional outcome between 1 and 2 treatments are provided in Lovegrove 2020; study 5).
Follow up	Overall: median 32 months (interquartile range [IQR] 17 to 58 months) For people with more than 5-year follow up: median 82 months (IQR 72 to 94 months)
Conflict of interest/source of funding	Conflict of interest: Authors report various industry and governmental grants. Source of funding: The HEAT registry is funded by Sonacare, the manufacturer of a HIFU device.

Analysis

Follow-up issues: The median follow up was 32 months in all people. In 325 people with more than 5 years of follow up, the median follow up was 82 months.

Study design issues: This study was an analysis of the HEAT registry and reported cancer control outcomes. Functional outcomes are reported in Lovegrove (2020; study 5). People suitable for focal HIFU were prospectively and consecutively entered into the registry. Recommended follow up included 3 to 6 monthly PSA follow up in the 1st year and 6-monthly thereafter, with MRI at 6 to 12 months. Outcomes included:

- Primary: FFS, with failure defined as evidence of cancer requiring whole-gland salvage treatment or 3rd focal therapy treatment, systemic treatment, development of prostate cancer metastases, or prostate cancer-specific death.
- Secondary: any retreatment-free survival, salvage whole-gland and systemic treatment-free survival, ADT-free survival, metastasis-free and prostate cancer-specific survival, OS, and adverse events and complications.

The Kaplan–Meier method was used to calculate survival outcomes.

Study population issues: Most people were D'Amico risk level intermediate (65%), followed by high (28%). Pretreatment T-stage was most commonly T2 (74%), and Gleason score was most commonly 3 + 4 = 7 (62%). A total of 13 people (0.9%) had neoadjuvant or cytoreductive ADT.

Key efficacy findings

Cancer control outcomes

Number of people analysed: 1,379

- FFS at 7 years was 69% (95% CI 64% to 74%).
    - By D'Amico risk class, FFS at 7 years was:
        - Low risk cancers 88% (95% CI 77% to 99%)
        - Intermediate risk cancers 68% (95% CI 62% to 75%)
        - High risk cancers 65% (95% CI 56% to 74%)
- Salvage whole-gland or systemic treatment-free survival at 7 years was 75% (95% CI 71% to 80%).
    - 132 people had salvage local whole-gland or systemic treatment.
    - 53 people transitioned to salvage radical prostatectomy and 39 had salvage radiotherapy or brachytherapy.
- Metastasis-free and prostate cancer-specific survival at 7 years were 100% (95% CI 99% to 100%).
- There were 20 deaths in the study period; the OS at 7 years was 97% (95% CI 96% to 99%).

Cancer control outcomes

Kaplan–Meier estimate, % (95% CI)	1-year	2-year	3-year	4-year	5-year	6-year	7-year
Failure-free survival	100 (100 to 100)	96 (95 to 98)	93 (91 to 95)	88 (85 to 90)	82 (79 to 86)	75 (71 to 79)	69 (64 to 74)
By D'Amico risk class							
Low	100 (100 to 100)	99 (96 to 100)	99 (96 to 100)	94 (88 to 100)	91 (84 to 100)	91 (84 to 100)	88 (77 to 99)
Intermediate	100 (100 to 100)	97 (96 to 98)	93 (91 to 95)	88 (85 to 91)	83 (79 to 87)	75 (70 to 81)	68 (62 to 75)
High	100 (99 to 100)	95 (93 to 97)	91 (88 to 94)	85 (81 to 90)	79 (73 to 85)	69 (62 to 78)	65 (56 to 74)
Salvage or systemic treatment-free survival	100 (100 to 100)	97 (96 to 98)	93 (91 to 95)	89 (86 to 91)	85 (83 to 88)	80 (77 to 84)	75 (71 to 80)
By D'Amico risk class							
Low	100 (100 to 100)	99 (96 to 100)	99 (96 to 100)	99 (96 to 100)	99 (96 to 100)	99 (96 to 100)	95 (87 to 100)
Intermediate	100 (100 to 100)	97 (96 to 99)	94 (91 to 96)	89 (86 to 92)	84 (80 to 88)	79 (74 to 84)	73 (67 to 80)
High	100 (99 to 100)	95 (93 to 98)	91 (87 to 94)	86 (82 to 91)	84 (79 to 89)	78 (71 to 85)	73 (65 to 82)

Key safety findings

Complications

Number of people analysed: 1,379

- There were a total of 83/1379 (6.0%) postoperative complications.
- The rate of complications with Clavien–Dindo score >2 was 0.5% (7/1,379).
- Most common complications were:
  - UTIs, n=52 (3.8%)
  - Epididymitis, n=11 (0.8%)
  - Urinary retention, n=10 (0.7%)
  - Rectourethral fistulae, n=2 (0.1%)
  - Incomplete focal treatment due to movement, n=1

Study 5 Lovegrove CE (2020)

Study details

Study type	Prospective, multicentre registry analysis – the HEAT registry
Country	UK
Recruitment period	2005 to 2016
Study population and number	n=420 People with non-metastatic prostate cancer who were treated using 1 (cohort 1; n=355) or 2 (cohort 2; n=65) focal HIFU treatments
Age and sex	66.4 (cohort 1)/65.6 (cohort 2); 100% male
Patient selection criteria	Inclusion criteria: Gleason 7 or high-volume Gleason 6 disease with maximum cancer core length of more than 4 mm, stage T1c radiological T3aN0M0 disease, and PSA level of 20 ng/mL or less. However, some people with disease characteristics outside of these criteria chose to have focal HIFU. Exclusion criteria: previous use of whole-gland therapy.
Technique	As per Reddy (2022; study 4). A second focal HIFU procedure was permitted in the protocol as part of the focal therapy intervention for residual or recurrent disease detected during follow up.
Follow up	Cohort 1: median 64.9 months (IQR 41.9 to 78.9 months) Cohort 2: median 72.5 months (IQR 65.8 to 91.0 months)
Conflict of interest/source of funding	Conflict of interest: One author reports consultancy fees for Sonacare, the manufacturer of a HIFU device. Source of funding: Not reported, though Reddy (2022) notes that the HEAT registry is funded by Sonacare.

Analysis

Follow-up issues: A total of 821 people were entered into the HEAT registry during the recruitment period. A total of 420 people returned questionnaires and were included in this analysis: 355 people had 1 focal HIFU (cohort 1) and 65 people had 2 focal HIFUs (cohort 2).

Study design issues: This study was an analysis of the HEAT registry that reported functional outcomes and presented a comparison of outcomes between people who had 1 focal HIFU with people who had 2. Outcomes included:

- Urinary continence, as measured by the IPSS and EPIC questionnaires.
- Erectile function, as measured by the IIEF-5 questionnaire.

Data were collected at baseline, 1 to 2 years, and 2 to 3 years. Various tests were used to evaluate statistical significance. $p<0.05$ was considered statistically significant. No adjustment for multiple comparisons was made.

Study population issues: Cohorts 1 and 2 were comparable at baseline, except that cohort 2 had a higher proportion of people with T2 disease.

Key safety findings

Functional outcomes

Urinary outcomes

Number of people analysed: 355 (cohort 1), 65 (cohort 2)

- Cohort 1 (1 HIFU):
  - There was a statistically significant decrease (implying better function) in mean IPSS from baseline to 1 to 2 years after the first focal HIFU (mean change -0.03, p=0.02).
  - There was no statistically significant change in mean IPSS from baseline to 2 to 3 years after the first focal HIFU, or from 1 to 2 years to 2 to 3 years after (both p>0.05).
  - There were no statistically significant changes in the proportion of people who were pad-free and leak-free continent after the first focal HIFU.
- Cohort 2 (2 HIFUs):
  - There was a statistically significant decrease (implying better function) in mean IPSS from baseline to before the second focal HIFU (mean change -1.3, p=0.02).
  - There were statistically significant increases (implying worse function) in mean IPSS from before the second focal HIFU to 1 to 2 years after the second focal HIFU (mean change 1.4, p=0.03), and from before the second focal HIFU to 2 to 3 years after the second focal HIFU (mean change 1.2, p=0.003).
  - There were no other statistically significant changes in IPSS observed.
  - There were no statistically significant changes in the proportion of people who were pad-free and leak-free continent after the first focal HIFU.

Urinary outcomes

IPSS	Cohort 1		Cohort 2	
	Group mean (SD)		Group mean (SD)	
Baseline	9.47 (5.9)		9.5 (6.6)	
1 to 2 years after 1st HIFU	9.44 (6.3)		7.9 (5.5)	
2 to 3 years after 1st HIFU	9.6 (6.2)		8.2 (4.8)	
Before 2nd HIFU			8.2 (5.4)	
1 to 2 years after 2nd HIFU			9.6 (5.8)	
2 to 3 years after 2nd HIFU			9.5 (5.5)	
	Change in mean	p-value	Change in mean	p-value
Baseline vs. 1 to 2 years after 1 HIFU	-0.03	0.02		

IPSS	Cohort 1		Cohort 2	
Baseline vs. 2 to 3 years after 1 HIFU	0.1	0.8		
1 to 2 years after 1 HIFU vs. 2 to 3 years after 1 HIFU	0.2	0.2		
Baseline vs. before 2nd HIFU			-1.3	0.02
Baseline vs. 1 to 2 years after 2nd HIFU			0.1	0.36
Baseline vs. 2 to 3 years after 2nd HIFU			0.0	0.37
Before 2nd HIFU vs. 1 to 2 years after 2nd HIFU			1.4	0.03
Before 2nd HIFU vs. 2 to 3 years after 2nd HIFU			1.2	0.003
1 to 2 years after 2nd HIFU vs. 2 to 3 years after 2nd HIFU			-0.1	0.06
Pad-free continent proportions	%	p-value vs. baseline	%	p-value vs. baseline/ before 2nd HIFU
Baseline	98.6	-	100	-
1 to 2 years after 1st HIFU	94.8	0.07	100	>0.05
2 to 3 years after 1st HIFU	95.3	0.2	100	>0.05
Before 2nd HIFU			100	>0.05
1 to 2 years after 2nd HIFU			98.2	>0.05
2 to 3 years after 2nd HIFU			97.4	>0.05
Leak-free continent proportions	%	p-value vs. baseline	%	p-value vs. baseline/ before 2nd HIFU
Baseline	77.9	-	72.1	-
1 to 2 years after 1st HIFU	72.8	0.06	66.7	>0.05
2 to 3 years after 1st HIFU	73.5	0.5	80.6	>0.05
Before 2nd HIFU			72.9	>0.05
1 to 2 years after 2nd HIFU			71.4	>0.05
2 to 3 years after 2nd HIFU			78.9	>0.05

Erectile function outcomes

Number of people analysed: 355 (cohort 1), 65 (cohort 2)

- Cohort 1 (1 HIFU):
    - There was a statistically significant decrease (implying worse function) in EF score from baseline to 1 to 2 years after the first focal HIFU (mean change -0.4, p=0.02).

  - There was no statistically significant change in the proportion of people reporting erectile dysfunction (a score of 0 or 1 on question 2 of the IIEF) after the first focal HIFU.

- Cohort 2 (2 HIFUs):
  - There were statistically significant decreases (implying worse function) in EF score from baseline to 1 to 2 years and 2 to 3 years after the second focal HIFU (mean change -0.8, p=0.005, and -1.1, p=0.008, respectively).
  - There was no statistically significant change in the proportion of people reporting erectile dysfunction (a score of 0 or 1 on question 2 of the IIEF) after the first or second focal HIFU.

Erectile function outcomes

EF score	Cohort 1		Cohort 2	
	Group mean (SD)		Group mean (SD)	
Baseline	3.9 (1.3)		4.1 (1.3)	
1 to 2 years after 1st HIFU	3.5 (1.6)		3.3 (1.5)	
2 to 3 years after 1st HIFU	3.8 (1.5)		3.6 (1.3)	
Before 2nd HIFU			3.5 (1.4)	
1 to 2 years after 2nd HIFU			3.3 (1.7)	
2 to 3 years after 2nd HIFU			3.0 (1.4)	
	Change in mean	p-value	Change in mean	p-value
Baseline vs. 1 to 2 years after 1 HIFU	-0.4	0.02		
Baseline vs. 2 to 3 years after 1 HIFU	-0.2	0.6		
1 to 2 years after 1 HIFU vs. 2 to 3 years after 1 HIFU	0.3	0.2		
Baseline vs. before 2nd HIFU			-0.6	0.2
Baseline vs. 1 to 2 years after 2nd HIFU			-0.8	0.005
Baseline vs. 2 to 3 years after 2nd HIFU			-1.1	0.008
Before 2nd HIFU vs. 1 to 2 years after 2nd HIFU			-0.2	0.6
Before 2nd HIFU vs. 2 to 3 years after 2nd HIFU			-0.5	0.1
1 to 2 years after 2nd HIFU vs. 2 to 3 years after 2nd HIFU			-0.3	0.6
Erectile dysfunction proportions	%	p-value vs. baseline	%	p-value vs. baseline/ before 2nd HIFU
Baseline	9.9	-	5.9	-
1 to 2 years after 1st HIFU	20.8	0.08	19.5	>0.05
2 to 3 years after 1st HIFU	18.3	NR	3.7	>0.05
Before 2nd HIFU			12.8	>0.05
1 to 2 years after 2nd HIFU			30.6	>0.05
2 to 3 years after 2nd HIFU			19.0	>0.05

Study 6 van Son MJ (2021)

Study details

Study type	Propensity score weighted analysis – focal HIFU data from the HEAT registry
Country	UK (radiotherapy, prostatectomy, focal HIFU, focal cryotherapy data) and the Netherlands (brachytherapy data)
Recruitment period	2005 to 2018 (focal therapy data); 2007 to 2018 (radical therapy data)

Study population and number	• People who had focal therapy for localised prostate cancer: 530
	  ○ Focal HIFU: 419 (79.1%)
	  ○ Focal cryotherapy: 81 (15.3%)
	  ○ Focal HDR-brachytherapy: 30 (5.7%)
	• People who had radical therapy for localised prostate cancer: 830
	  ○ External-beam radiotherapy: 440 (53.0%)
	  ○ Laparoscopic radical prostatectomy: 390 (47.0%)

Age and sex	Not reported; 100% male
Patient selection criteria	Inclusion criteria: PSA less than 20 ng/mL, ≤Gleason 4+3=7 and T-stage T2c or lower (National Comprehensive Cancer Network low to intermediaterisk) Exclusion criteria: history of previous prostate cancer treatment.
Technique	Focal HIFU (Sonablate, Sonacare) was offered to people with peripheral or posterior tumours or those anteriorly based in which the anterior-posterior height was 3.5 cm or less.
Follow up	Focal therapy group: median 62 months (IQR 42 to 83 months)
Conflict of interest/source of funding	Conflict of interest: Authors report various grants and fees, some of which are from Sonacare, the manufacturer of a HIFU device. Source of funding: Not reported.

Analysis

Study design issues: This propensity score matched analysis compared the outcomes of focal versus radical therapy. People were identified from 5 different registries. The radical radiotherapy registry was retrospective; the others were prospective. Missing data were imputed with single imputation. Identified people were assigned a propensity score based on age, PSA, Gleason score, maximum cancer core length, T-stage, and year of treatment. People were then weighted to correct for imbalances between treatment groups, with more weights applied to people with equal probabilities of assignment to either treatment group. The purpose of this weighting is to reduce the effect of non-random assignment to treatments in observational research. That is, people in the focal therapy group and the radical therapy group may differ in baseline characteristics other than assignment to treatment. These differences may influence the estimate of treatment effect in each group. Outcomes included:

- Primary: FFS, a composite endpoint of (1) need for local salvage treatment, (2) development of metastatic disease, (3) use of systemic treatment (ADT or chemotherapy) or (4) progression to a watchful waiting strategy.
- Secondary: OS.

Two-way analyses (focal therapy versus radical therapy) and three-way analyses (focal therapy versus radiotherapy versus prostatectomy) were performed. For all three-way analyses, p<0.017 was considered statistically significant (Bonferroni correction). For all two-way comparisons, p<0.05 was considered statistically significant. The Kaplan–Meier method was used to analyse survival over time.

Key efficacy findings

Number of people analysed: Focal therapy, n=530 (of which focal HIFU, n=419); radical therapy, n=830

- Two-way analysis:
  - There was no statistically significant difference in FFS at 6 years between focal and radical therapy groups (p=0.10).
  - People treated with focal therapy had a statistically significantly higher OS at 6 years than people treated with radical therapy (97.5% vs. 93.4%, p=0.02).
  - There were no statistically significant differences between the groups in treatment failure or overall mortality (both p>0.05).
- Three-way analysis:
  - There was a statistically significant difference in FFS at 6 years between the 3 groups (p<0.001).
    - Treatment failure was statistically significantly more likely in both LRP and focal therapy groups compared to EBRT (both p<0.001).
  - Overall mortality was statistically significantly less likely in the focal therapy group than the EBRT group (HR 0.29, 95% CI 0.11 to 0.76, p=0.008).
  - There was no statistically significant difference in overall mortality between the focal therapy and radical prostatectomy groups.

Failure and survival outcomes after focal and radical therapy

Two-way analysis	**Focal therapy, % (95% CI)**	**Radical therapy, % (95% CI)**	**p-value**
FFS at 6 years	72.8 (66.8 to 79.8)	80.3 (73.9 to 87.3)	0.10
OS at 6 years	97.5 (94.0 to 99.9)	93.4 (90.1 to 95.2)	0.02
	HR (95% CI)	**SE**	**p-value**
Treatment failure, focal vs. radical	1.29 (0.96–1.75)	0.15	0.10
Overall mortality, focal vs. radical	0.49 (0.22–1.09)	0.41	0.08

Three-way analysis	**Focal therapy**	**EBRT**	**LRP**	**p-value**
FFS at 6 years	74.4 (68.4 to 81.5)	87.4 (79.9 to 93.9)	73.9 (68 to 80.9)	<0.001
OS at 6 years	97.5 (94.9 to 100)	92.3 (83.5 to 95.8)	95.3 (88.9 to 98.3)	0.05
	HR (95% CI)		**SE**	**p-value**

Treatment failure			
LRP vs. EBRT	2.41 (1.44 to 4.05)	0.26	0.0005
FT vs. EBRT	2.24 (1.4 to 3.64)	0.25	0.0002
FT vs. LRP	0.93 (0.65 to 1.33)	0.18	0.69
Overall mortality			
LRP vs. EBRT	0.54 (0.23 to 1.29)	0.44	0.17
FT vs. EBRT	0.29 (0.11 to 0.76)	0.48	0.008
FT vs. LRP	0.54 (0.19 to 1.52)	0.53	0.24

Study 7 Stabile A (2019)

Study details

Study type	Two-centre, retrospective case series
Country	UK
Recruitment period	2005 to 2017
Study population and number	n=1032 People with low or intermediate risk prostate cancer who received focal HIFU
Age and sex	Median 65; 100% male
Patient selection criteria	Inclusion criteria: consecutive people who had focal HIFU for low or intermediate risk prostate cancer.
Technique	Transrectal focal HIFU (Sonablate 500; Sonacare Inc). Focal ablation was most common (70.7%) with hemiablation less common (29.3%).
Follow up	Median 36 months (IQR 14 to 64 months)
Conflict of interest/source of funding	Conflict of interest: The authors report various grants and fees, including from Sonacare, the manufacturer of a focal HIFU device. Source of funding: Not reported.

Analysis

Study design issues: This two-centre, retrospective case series presented the outcomes of focal HIFU in a large cohort. Consecutive people were enrolled to a prospective registry; the data were then analysed retrospectively. During follow up, PSA was assessed every 3 to 4 months and an MRI was offered at 6 or 12 months. Later MRIs were offered between 1 and 3 years, with additional scans based on PSA levels. Follow up biopsies were offered to a subset of people who were involved in other studies or where there was a concern. Outcomes included:

- Oncological outcomes including:
    - OS
    - Retreatment-free survival
    - Radical treatment-free survival, defined as radical prostatectomy, external-beam radiotherapy and other whole-gland therapies
    - Biopsy FFS, defined as the presence of clinically significant prostate cancer at post-treatment biopsy.

Kaplan–Meier curves were plotted to assess survival. Multivariable regression was used to assess the predictors of 5-year retreatment. All tests were 2-sided with $p<0.05$ considered statistically significant.

Study population issues: Most people had Gleason score of 3 + 4 (63%) and T2 stage (78%).

Key efficacy findings

Oncological outcomes

Number of people analysed: 1,032

- At 96 months, OS was 96.6%, biopsy FFS was 54.0%, retreatment-free survival was 45.8%, and radical treatment-free survival was 80.8%.
    - Predictors of 5-year retreatment included:
        - Year of surgery, odds ratio (OR) 0.77 (95% CI 0.67 to 0.89, p<0.001), suggesting a learning curve
        - PSA, OR 1.07 (95% CI 1.01 to 1.12, p=0.015)
        - T2 or T3 stage prostate cancer (compared to T1), OR 3.75 (95% CI 1.63 to 9.82, p=0.003) and OR 5.0 (95% CI 1.9 to 14.9, p=0.002), respectively.

Oncological outcomes

Follow up (months)	Outcome (%)			
	Overall survival	Biopsy FFS	Retreatment-free survival	Radical treatment-free survival
12	99.3	93.5	97.5	99.8
24	99.1	83.8	85.0	97.6
60	97.3	63.6	58.9	90.6
96	96.6	54.0	45.8	80.8

Retreatments

Number of people analysed: 1,032

- Throughout the follow up period, 271 people were retreated (26.3%).
- Retreatments included:
    - Focal HIFU, n=193
    - Focal cryotherapy, n=12
    - EBRT, n= 9
    - Radical prostatectomy, n=30
    - Whole-gland HIFU, n=4
    - ADT, n=20
    - Other, n=3

Key safety findings

Safety findings were not reported.

Study 8 Byun S-S (2022)

Study details

Study type	Single-centre, retrospective cohort study
Country	South Korea
Recruitment period	2018 to 2020
Study population and number	n=206 (152 partial-gland HIFU and 54 whole-gland HIFU) People who had partial- or whole-gland HIFU for localised prostate cancer
Age and sex	Median 68; 100% male
Patient selection criteria	Inclusion criteria: all people who had HIFU for localised prostate cancer during the study period.
Technique	HIFU was performed using the Focal One device (Edaps TMS, France). Whole-gland ablation was defined as ablation of all the prostate; partial-gland ablation was defined as hemiablation and subtotal ablation. Transurethral prostatectomy (TURP) was performed before HIFU in all people.
Follow up	Median 12 months (IQR 7 to 17 months)
Conflict of interest/source of funding	Conflict of interest: The authors declare that they have no conflicts of interest. Source of funding: This work was supported by institutional grant from university research fund.

Analysis

Follow up issues: Incontinence and erectile function were assessed at every follow up visit. Prostatic biopsy was recommended at the 12-month follow up. At 12 months follow up, biopsy results were available for 27 whole-gland and 59 partial-gland ablation people. The reasons for loss to follow up are not reported.

Study design issues: This retrospective cohort study compared the outcomes of partial-gland and whole-gland ablation for treating localised prostate cancer. People were identified retrospectively from a prospectively maintained registry. Outcomes included:

- Primary outcomes were not defined.
- Other listed outcomes:
    - Urinary continence, using the EPIC-CP, with incontinence was defined based on pad usage.
    - Erectile function, using the IIEF-5, with normal erectile function was defined as an IIEF-5 score of 22 or more.
    - Cancer control, assessed through biopsy.

Kaplan–Meier analyses were performed to assess survival. All statistical tests were 2-sided, and $p<0.05$ was considered statistically significant. There was no adjustment for multiple comparisons.

Study population issues: There were several statistically significant differences in baseline characteristics between the whole-gland and partial-gland ablation groups, including:

- Age: Partial-gland ablation people were younger (p=0.033)
- Risk and severity: Partial-gland ablation people had lower D'Amico risk classification (p=0.015), Gleason score (p=0.023), and T-stage (p=0.032)

- Tumour characteristics: Partial-gland ablation people had fewer positive cores (p<0.001) and a small median maximal tumour length (p=0.01)

Key efficacy findings

Oncological outcomes

Number of people analysed: 59 (partial-gland ablation), 27 (whole-gland ablation)

- There were no statistically significant differences in positive biopsies between the whole-gland and partial-gland ablation groups.

Oncological outcomes summary

Outcomes at 12 months after HIFU	Whole-gland ablation (n=27)	Partial-gland ablation (n=59)	p-value
Any positive biopsy	8 (29.6%)	16 (27.1%)	0.713
Infield positive	8 (29.6%)	2 (3.4%)	
Outfield positive	0	10 (16.9%)	
Both positive	0	4 (6.8%)	
Clinically significant cancer positive biopsy	5 (18.5%)	9 (15.3%)	NR
Infield positive	5 (18.5%)	2 (3.4%)	
Outfield positive	0	5 (8.5%)	
Both positive	0	2 (3.4%)	

Key safety findings

Complications

Number of people analysed: 152 (partial-gland ablation), 54 (whole-gland ablation)

- The postoperative complication rate was statistically significantly higher in the whole-gland ablation group compared to the partial-gland ablation group (66.7% vs. 37.5%, p=0.023).

	Whole-gland ablation (n=54)	Partial-gland ablation (n=152)	p-value
Complications by grade	46 (66.7%)	57 (37.5%)	0.023
None	18 (33.3%)	95 (62.5%)	
Grade I	13 (24.1%)	23 (15.1%)	
Grade II	0 (0%)	0 (0%)	
Grade III	23 (42.6%)	34 (22.4%)	
Grade IV	0 (0%)	0 (0%)	
Type of complications			0.476
Urinary retention	10 (18.5%)	16 (10.5%)	
Bladder outlet obstruction	19 (35.2%)	24 (15.8%)	
Of who required endoscopic surgery	19 (35.2%)	24 (15.8%)	0.005
Urinary tract infection	1 (1.9%)	3 (2.0%)	
Bleeding	3 (5.6%)	8 (5.2%)	
Bladder stone	2 (3.7%)	1 (0.7%)	
Incontinence (any pad usage)	6 (11.1%)	12 (7.9%)	
Incontinence (pad ≥ 2/day)	2 (3.7%)	4 (2.6%)	0.661

Functional outcomes

Number of people analysed: 152 (partial-gland ablation), 54 (whole-gland ablation)

- In Kaplan–Meier analysis, the partial-gland ablation group recovered continence statistically significantly faster than the whole-gland ablation group (p=0.047).
- There was no statistically significant difference in the recovery of erectile function between the groups (p=0.317).

Validity and generalisability of the studies

- Focal HIFU was typically used as primary treatment for localised prostate cancer, though 1 systematic review (Khoo 2020) found 3 studies that used focal HIFU in a salvage setting.
- There was a total of approximately 5,000 people included in the key evidence studies. More were included in the studies listed in appendix.
- The focal HIFU treatment protocol was similar between studies. There were differences in the ablative patterns used.
- A large amount of the data came from the UK-based HEAT registry (Reddy [2022], Lovegrove [2020], and van Son [2021]). This registry prospectively collected consecutive people who had focal HIFU. One further study (Stabile [2019]) was a retrospective analysis of a large cohort of consecutive UK people. It is therefore likely that the outcomes found by these studies are generalisable to UK clinical practice.
- There was limited comparative evidence in the literature. There are several ongoing RCTs (refer to Issues for consideration by IPAC), but none have yet published oncological or functional outcomes. A feasibility RCT (Hamdy, 2018) is listed in the appendix and found that randomisation of men to an RCT comparing partial ablation with radical treatments of the prostate is feasible.
    - Comparative safety evidence came from a meta-analysis of complications (He, 2020).
    - Comparative efficacy evidence came from a propensity score weighted analysis of focal therapy (mostly focal HIFU) versus radical therapy (van Son, 2021). This is a quasi-experimental study design that aims to mimic the unbiased treatment assignment of randomisation by giving more weight to those people with baseline characteristics that mean they could be assigned to either treatment group. However, it cannot account for unknown covariates.
    - A further comparative study of partial-gland versus whole-gland HIFU was also included (Byun, 2022). The findings of this study were limited by the retrospective design, high attrition, and statistically significant differences in baseline characteristics of the groups.
- The longest median follow up reported was 82 months. This was recorded in a subset of people in the HEAT registry who had more than 5 years of follow up (Reddy, 2022).

Existing assessments of this procedure

In 2022, the German S3 Evidence-Based Guidelines on Focal Therapy in Localized Prostate Cancer: The First Evidence-Based Guidelines on Focal Therapy were published (Borkowetz, 2022). A systematic review was performed to identify relevant literature. Recommendations were then made via consensus of an expert committee. The following recommendation relevant to focal HIFU was made:

- 6.44: The available data are insufficient to assess the oncological effectiveness and safety of focal HIFU. Evidence-based statement, level of evidence: 4, 95% consensus.

In 2018, the European Association of Urology published Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position (van der Poel, 2018). This position statement provides overall recommendations on focal therapy. These recommendations include:

- Focal therapy can ablate cancer cells, but currently, imaging methods cannot reliably identify all high risk cancer clones within the prostate.
- The literature suggests that the oncological effectiveness of focal therapy remains unproven due to the lack of reliable comparative data against standard-of-care including active surveillance. We recommend awaiting prospective comparative trial data before implementing focal therapy in routine clinical practice.
- Focal therapy studies targeting smaller regions of the prostate have reported reduced toxicity compared with whole-gland treatment options, but robust comparative studies with toxicity end points are still lacking.
- Given the considerable uncertainties regarding the optimal follow up of men treated with focal therapy, people should only be treated within the context of a clinical trial using predefined criteria.
- Better understanding of the toxicity of secondary treatments and retreatments after focal therapy is needed, and its assessment should be part of prospective investigations.

Related NICE guidance

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

Interventional procedures

- Irreversible electroporation for treating prostate cancer. Interventional procedures guidance 572 (2016); *research*
- Focal therapy using cryoablation for localised prostate cancer. Interventional procedures guidance 423 (2012); *special arrangements*

- Laparoscopic radical prostatectomy. Interventional procedures guidance 193 (2006); standard arrangements
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. Interventional procedures guidance 174 (2006); standard arrangements
- Cryotherapy as a primary treatment for prostate cancer. Interventional procedures guidance 145 (2005); standard arrangements
- Low dose rate brachytherapy for localised prostate cancer. Interventional procedures guidance 132 (2005); standard arrangements
- Cryotherapy for recurrent prostate cancer. Interventional procedures guidance 119 (2005); standard arrangements
- High-intensity focused ultrasound for prostate cancer. Interventional procedures guidance IPG118 (2005); standard arrangements

Technology appraisals

- Padeliporfin for untreated localised prostate cancer. Technology appraisal guidance 546 (2018)
- Enzalutamide for hormone-relapsed non-metastatic prostate cancer. Technology appraisal guidance 580 (2019)

NICE guidelines

- Prostate cancer: diagnosis and management. NICE guideline 131. Published date: 09 May 2019

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.

Seven professional expert questionnaires for focal therapy using high-intensity focused ultrasound for localised prostate cancer were submitted and can be found on the NICE website.

Patient organisation submissions

NICE received 2 submissions from patient organisations about focal therapy using high-intensity focused ultrasound for localised prostate cancer.

Patient commentators' opinions

NICE received 307 questionnaires from patients who had the procedure (or their carers).

Patients' 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 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Several RCTs are ongoing:

- Focal Prostate Ablation Versus Radical Prostatectomy (FARP; NCT03668652). Randomised controlled trial, open label. Est. enrolment: 200 people; est. completion: September 2024.
- Phase 3, Multicenter, Randomized Study, Evaluating the Efficacy and Tolerability of Focused HIFU (High Intensity Focused Ultrasound) Therapy Compared to Active Surveillance in Patients With Significant Low Risk Prostate Cancer (HIFUSA; NCT03531099). Randomised controlled trial, open label. Est. enrolment: 146 people; est. completion: October 2026.
- A randomised controlled trial of Partial prostate Ablation versus Radical prosTatectomy (PART) in intermediate risk unilateral clinically localised prostate cancer (https://fundingawards.nihr.ac.uk/award/12/35/54). Planned in 2 parts – a feasibility study (Hamdy, 2018 in the appendix) and then an RCT (status unknown; https://part.octru.ox.ac.uk/). Est. enrolment: 800 people; est. completion: unknown.
- Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer (IP4-CHRONOS; NCT04049747). Randomised controlled trial of radical therapy vs. focal therapy (including HIFU). Est. enrolment: 2450 people; est. completion: May 2027.

- Additional Treatments to the Local Tumour for Metastatic Prostate Cancer: Assessment of Novel Treatment Algorithms (IP2-ATLANTA) Randomised controlled trial (including HIFU). Est. enrolment: 918 people; est. completion: March 2024.

References

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2. He Y, Tan P, He M et al. (2020) The primary treatment of prostate cancer with high-intensity focused ultrasound: A systematic review and meta-analysis. Medicine 99(41):e22610.
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4. Reddy D, Peters M, Shah TT et al. (2022) Cancer Control Outcomes Following Focal Therapy Using High-intensity Focused Ultrasound in 1379 Men with Nonmetastatic Prostate Cancer: A Multi-institute 15-year Experience. European urology 81(4):407-13.
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6. van Son MJ, Peters M, Reddy D et al. (2021) Conventional radical versus focal treatment for localised prostate cancer: a propensity score weighted comparison of 6-year tumour control. Prostate cancer and prostatic diseases 24(4):1120-8.
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8. Byun S-S, Jin N, and Lee H. (2022) High Intensity Focused Ultrasound Ablation for Prostate Cancer: Whole Versus Partial Gland Ablation. Clinical Genitourinary Cancer 20(1):e39-e44.
9. Borkowetz A, Blana A, Bohmer D et al. (2022) German S3 Evidence-Based Guidelines on Focal Therapy in Localized Prostate Cancer: The First Evidence-Based Guidelines on Focal Therapy. Urologia Internationalis.
10. van der Poel HG, van den Bergh RCN, Briers E et al. (2018) Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018 European Urology 74(1):84-91

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	26/04/2022	1946 to April 25, 2022
MEDLINE In-Process (Ovid)	26/04/2022	1946 to April 25, 2022
MEDLINE Epubs ahead of print (Ovid)	26/04/2022	April 25, 2022
EMBASE (Ovid)	26/04/2022	1974 to 2022 April 25
EMBASE Conference (Ovid)	26/04/2022	1974 to 2022 April 25
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/04/2022	Issue 4 of 12, April 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/04/2022	Issue 4 of 12, April 2022
International HTA database (INAHTA)	26/04/2022	-

Trial sources searched

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

Websites searched

- 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)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1 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 High-Intensity Focused Ultrasound Ablation/ or Ablation Techniques/

7	(HIFU or HIFU-F or HIFUA or MRgHIFU or MR-HIFU or MRgFUS).tw.
8	(high* adj2 (inten* or frequen*) adj2 ultras*).tw.
9	(high* adj2 inten* adj2 foc* adj2 (therap* or treatment* or ultras*)).tw.
10	((hemi* adj4 ablat*) or (hemi-gland* adj4 ablat*) or hemi-ablat* or hemiablat*).tw.
11	((therm* adj2 ablat*) or thermoablat*).tw.
12	(foc* ablat* or ultras* ablat*).tw.
13	or/6-12
14	5 and 13
15	sonablate*.tw.
16	Ablatherm*.tw.
17	(Focal One* or FocalOne*).tw.
18	Tulsa-pro*.tw.
19	or/15-18
20	5 and 19
21	14 or 20
22	Animals/ not Humans/
23	21 not 22
24	limit 23 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. Studies with fewer than 50 people were excluded from this appendix.

Additional papers identified

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Abreu AL, Peretsman S, Iwata A et al. (2020) High Intensity Focused Ultrasound Hemigland Ablation for Prostate Cancer: Initial Outcomes of a United States Series. The Journal of urology 204(4):741-7	Case series n=100 FU=20 months	Short-term results of focal high intensity focused ultrasound indicate safety, excellent potency and continence preservation, and adequate short-term prostate cancer control. Radical treatment was avoided in 91% of men at 2 years. Men with bilateral prostate cancer at diagnosis have increased risk for Grade Group 2 or greater recurrence.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Abufaraj M, Siyam, A, Ali M et al. (2021) Functional outcomes after local salvage therapies for radiation-recurrent prostate cancer patients: a systematic review. Cancers 13(2):244.	Systematic review n=2 studies using focal HIFU	Local salvage therapies for radiation recurrent prostate cancer affect continence, lower urinary tract symptoms and sexual functions. The use of local salvage therapies may be warranted in the setting of local disease control, but each individual decision must be made with the informed patient in a shared decision working process.	Most studies included did not use focal HIFU.
Ahmed HU, Dickinson L, Charman S et al. (2015) Focal ablation targeted to the index lesion in multifocal localised prostate cancer: a prospective development study. European urology 68(6):927-936.	Prospective case series n=56 FU=12 months	Index lesion ablation had low rates of genitourinary side effects and acceptable short-term absence of clinically significant cancer. Comparative effectiveness trials are required to assess cancer control outcomes against radical therapy.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Albisinni S, Melot C, Aoun F et al. (2018) Focal Treatment for Unilateral Prostate Cancer Using High-Intensity Focal Ultrasound: A Comprehensive Study of Pooled Data. Journal of endourology 32(9):797-804	Pooled analysis n=366 FU=26 months	This pooled analysis of the results of focal HIFU treatment of prostate cancer shows promising oncologic and functional outcomes. Well-selected people may be candidates for such a conservative partial treatment of the gland. Well-designed trials are awaited to compare HIFU focal treatment with current standard of care	More recent systematic reviews included.
Albisinni S, Aoun F, Bellucci S et al. (2017) Comparing High-Intensity Focal Ultrasound Hemiablation to Robotic Radical Prostatectomy in the Management of Unilateral Prostate Cancer: A Matched-Pair Analysis. Journal of endourology 31(1):14-9	Matched-pair analysis n=55 FU=36 months	HIFU hemiablation was comparable to robot-assisted laparoscopic prostatectomy in controlling localised unilateral prostate cancer, with no significant differences in the need for salvage therapies. HIFU was also associated to significantly better functional outcomes.	Larger matched-pair analysis included. Included in the Bakavicius, 2022 systematic review.
Annoot A, Olivier J, Valtille P et al. (2019) Extra-target low-risk prostate cancer: implications for focal high-intensity focused ultrasound of clinically significant prostate cancer. World journal of urology 37(2):261-8	Retrospective cohort n=55 FU=33 months	Presence or not of an extra-target non-clinically significant cancer in the untreated part of the gland had no impact on radical treatment free survival. Radical treatment free survival was 80% at 3 years which support the concept of focal/partial treatment as a treatment option of prostate cancer.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Aoun F, Limani K, Peltier A et al. (2015) High Intensity Focused Ultrasound versus Brachytherapy for the Treatment of Localized Prostate Cancer: A Matched-Pair Analysis. Advances in urology 2015:350324	Matched-pair analysis n=70 FU=83 months	HIFU and brachytherapy are safe with no significant difference in cancer specific survival on long term oncologic follow-up. Nonetheless, a randomised controlled trial is needed to confirm these results	Larger matched-pair analysis included.
Avila M, Patel L, Lopez S et al. (2018) Patient-reported outcomes after treatment for clinically localized prostate cancer: A systematic review and meta-analysis. Cancer treatment reviews 66:23-44	Systematic review and meta-analysis	No remarkable differences in patient-reported outcomes appeared between modalities within each treatment. Nowadays, available evidence supports brachytherapy as possible alternative to radical prostatectomy for people seeking an attempted curative treatment limiting the risk for urinary incontinence and sexual dysfunction.	Not all included HIFU studies used focal HIFU.
Bacchetta F, Martins M, Regusci S et al. (2020) The utility of intraoperative contrast-enhanced ultrasound in detecting residual disease after focal HIFU for localized prostate cancer. Urologic Oncology: Seminars and Original Investigations 38 (11):846	Registry analysis n=66 FU=14 months	Contrast-enhanced ultrasound has a higher added value compared to early mpMRI in ruling out clinically significant cancer after focal HIFU. It should be evaluated whether the use of Contrast-enhanced ultrasound intraoperatively enhances the efficacy of focal HIFU.	Studies with more people or longer follow up included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Bakavicius A, Sanchez-Salas R, Muttin F et al. (2019) Comprehensive Evaluation of Focal Therapy Complications in Prostate Cancer: A Standardized Methodology. Journal of endourology 33(7): 509-15	Case series n=336 FU=11 months	Focal HIFU and focal cryosurgical ablation of the prostate provide a tolerable toxicity, with primarily minor complications presenting in the early postoperative period.	Studies with more people or longer follow up included.
Bass R, Fleshner N, Finelli A et al. (2019) Oncologic and Functional Outcomes of Partial Gland Ablation with High Intensity Focused Ultrasound for Localized Prostate Cancer. The Journal of urology 201(1): 113-9	Case series n=150 FU=24.3 months	Partial gland ablation with high intensity focused ultrasound therapy was safe and it had a minimal impact on functional outcomes. Local recurrence and/or failure occurred in 42% of people at high risk for recurrence. Medially located tumours were associated with a higher failure rate. Serious complications were rare. Whole gland treatment was avoided in 81% of people.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

Article	Number of people/ 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):405-23	Systematic review n=1 study	The certainty of the evidence regarding the comparative effectiveness of focal therapy 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, focal therapy should ideally be performed within clinical trials or well-designed prospective cohort studies.	More recent systematic reviews included.
Baydoun A, Traughber B, Morris N et al. (2017) Outcomes and toxicities in patients treated with definitive focal therapy for primary prostate cancer: Systematic review. Future Oncology 13(7):649-63	Systematic review n=2 studies	Focal therapy has fewer adverse side effects and is more easily tolerated than conventional, whole-gland prostate cancer treatments.	More recent systematic reviews included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Borges RC, Tourinho-Barbosa, RR, Glina S et al. (2021) Impact of Focal Versus Whole Gland Ablation for Prostate Cancer on Sexual Function and Urinary Continence. The Journal of urology 205(1):129-36	Cohort study n=117 FU=55 months	Focal ablation instead of whole gland therapy is the most important factor related to better sexual and urinary continence recovery after high intensity focused ultrasound and cryotherapy for prostate cancer.	Comparative studies with more people or longer follow up included. High proportion of people treated with cryotherapy in focal therapy group.
Claros OR, Tourinho-Barbosa RR, Carneiro A et al. (2019) HIFU focal therapy for prostate cancer using intraoperatory contrast enhanced ultrasound. Archivos espanoles de urologia 72(8):825-30	Case series n=59 FU=18 months	Our study shows that the use of Sonovue after HIFU focal therapy was safe. People present a significant proportion of failure after HIFU focal therapy but with good functional outcomes and without incidence of severe complications	Studies with more people or longer follow up included.
Dellabella M, Branchi A, Di Rosa M et al. (2021) Oncological and functional outcome after partial prostate HIFU ablation with Focal-One R: a prospective single-center study. Prostate cancer and prostatic diseases 24 (4):1189-97	Case series n=189 FU=29 months	Index lesion HIFU ablation demonstrated satisfactory early oncological outcome but anteriorly located tumours had inadequate ablation. Urinary function was well preserved. Sexual function slightly decreased during follow-up.	Studies with more people or longer follow up included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Dickinson L, Ahmed HU, Hindley RG et al. (2017) Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urologic oncology 35(1):30e9-30e15	Case series n=118 FU=716 days	Early and late MRI performed better than PSA measurements in the detection of residual tumour after focal therapy	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Donis Canet F, Sanchez Gallego, MD, Arias Funez F et al. (2017) Cryotherapy versus high-intensity focused ultrasound for treating prostate cancer: Oncological and functional results. Actas urologicas espanolas	Systematic review	Both techniques have comparable functional results, although the somewhat poorer oncological results for HIFU reflect a steeper learning curve, which could lead to its use in centres with high volumes of people.	More recent systematic reviews included.
Fainberg JS, Al Awamlh BAH, DeRosa AP et al. (2021) A systematic review of outcomes after thermal and nonthermal partial prostate ablation. Prostate International 9(4):169-75	Systematic review n=4 studies	Although oncologic outcomes vary between treatment modalities, systematic review of existing data demonstrates that partial gland ablation is a safe treatment option for people with localised prostate cancer.	More comprehensive systematic reviews included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Fallara G, Capogrosso P, Maggio P et al. (2020) Erectile function after focal therapy for localized prostate cancer: a systematic review. International Journal of Impotence Research	Systematic review n=8 studies	Overall, reported sexual function outcomes after these treatment modalities were generally good, with many studies reporting a complete recovery of erectile function 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.	More recent systematic reviews included.
Faure 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 localized prostate cancer: A systematic review. Urologic oncology 36(2):67-76	Systematic review n=3 studies	Most studies assessing the outcomes of focal therapy on sexual function were not of high quality, used heterogenous outcomes, and had relatively short follow up, highlighting the need for more robustly designed studies using validated patient reported outcome measures for comparison. However, focal therapy in general resulted in less effect on erectile function than whole gland ablation.	More recent systematic reviews included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Feijoo ERC, Sivaraman A, Barret E et al. (2016) Focal High-intensity Focused Ultrasound Targeted Hemiablation for Unilateral Prostate Cancer: A Prospective Evaluation of Oncologic and Functional Outcomes. European urology 69(2):214-20	Before-and-after study n=71 FU=12 months	Focal HIFU hemiablation appears to achieve acceptable oncologic outcomes with low morbidity and minimal functional changes. Longer follow-up will establish future considerations.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Ganzer R, Hadaschik B, Pahernik S et al. (2018) Prospective Multicenter Phase II Study on Focal Therapy (Hemiablation) of the Prostate with High Intensity Focused Ultrasound. The Journal of urology 199(4):983-9	Before-and-after study n=54 FU=17.4 months	Focal therapy hemiablation is safe with little alteration of functional outcome. The oncologic outcome is acceptable on short-term follow-up.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Garcia-Barreras S, Sanchez-Salas R, Sivaraman A et al. (2018) Comparative Analysis of Partial Gland Ablation and Radical Prostatectomy to Treat Low and Intermediate Risk Prostate Cancer: Oncologic and Functional Outcomes. The Journal of urology 199(1):140-6	Propensity score matching analysis n=188 FU=38.44 months	In select people with organ confined prostate cancer partial gland ablation offered good oncologic control with fewer adverse effects that required additional treatments. Potency and continence appeared to be better preserved after partial gland ablation.	Larger propensity score analysis included (van Son, 2021).

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Golan R, Bernstein AN, McClure TD et al. (2017) Partial Gland Treatment of Prostate Cancer Using High-Intensity Focused Ultrasound in the Primary and Salvage Settings: A Systematic Review. The Journal of urology 198(5):1000-9	Systematic review n=13 studies	Early evidence suggests that partial gland ablation is a safe treatment option for men with localized disease. Longer term data are needed to evaluate oncologic efficacy and functional outcomes, and will aid in identifying the optimal candidates for therapy	More recent systematic reviews included.
Guillaumier S, Peters M, Arya M et al. (2018) A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. European Urology 74 (4):422-9	Registry analysis n=625 FU=56 months	Focal therapy for select people with clinically significant nonmetastatic prostate cancer is effective in the medium term and has a low probability of side effects.	Cohort captured in Reddy, 2022.
Guo R-Q, Guo X-X, Li Y-M 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.	Systemic review and meta-analysis n=11	This meta-analysis shows that cryoablation, HIFU, irreversible electroporation, and vascular-targeted photodynamic therapy are promising therapies for prostate cancer people with similar clinical outcomes. However, further larger, well-designed randomised controlled trials are required to confirm this assertion.	Mix of focal and whole-gland HIFU studies.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Hamdy FC, Elliott D, le Conte S et al. (2018) Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health technology assessment (Winchester, England) 22(52):1-96	Feasibility RCT n=80	Randomisation of men to a RCT comparing partial ablation with radical treatments of the prostate is feasible. A full RCT comparing clinical effectiveness, cost-effectiveness and quality-of-life outcomes between radical treatments and partial ablation is now warranted	Feasibility study.
Hanada I, Shoji S, Takeda K et al. (2021) Significant Impact of the Anterior Transition Zone Portion Treatment on Urinary Function After Focal Therapy with High-Intensity Focused Ultrasound for Prostate Cancer. Journal of endourology 35(7):951-60	Before-and-after study n=90	There was a greater risk of urinary dysfunction with treatment in the anterior transition zone portion than in the other portion at 1 month after focal therapy with HIFU.	Studies with more people or longer follow up included.

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Hong SK and Lee H. (2022) Outcomes of partial gland ablation using high intensity focused ultrasound for prostate cancer. Urologic Oncology: Seminars and Original Investigations.	Case series n=163 FU=17 months	Partial gland ablation with HIFU was safe and showed good preservation of functional outcomes as well as satisfactory oncological control. The remnant disease was observed in the 24.5% of people who underwent follow-up biopsy in the present study. Thus, further prospective study is needed to evaluate oncological and functional outcomes of partial gland ablation with HIFU more accurately	Studies with more people or longer follow up included.
Hopstaken JS, Bomers JGR, Sedelaar MJP et al. (2022) An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? European Urology 81(1):5-33	Systematic review n=27 studies	Over the past 5 yr, focal therapy has been studied for eight different energy 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 multicenter randomized controlled trials with long-term follow-up and predefined assessment of oncological and functional outcomes and health-related quality-of-life measures.	Shorter time range of included studies (5 years) than Bakavicius, 2022.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Huber PM, Afzal N, Arya M et al. (2020) An Exploratory Study of Dose Escalation vs Standard Focal High-Intensity Focused Ultrasound for Treating Nonmetastatic Prostate Cancer. Journal of Endourology 34(6):641-6	Matched pair analysis n=162	This exploratory study shows that dose escalation focal HIFU may achieve higher rates of disease control compared with standard focal HIFU. Further prospective comparative studies are needed.	Larger matched analysis included (van Son, 2021)
Huber PM, Afzal N, Arya M et al. (2020) PSA Criteria to Diagnose Failure of Cancer Control following Focal Therapy for Non-metastatic Prostate Cancer Using High Intensity Focused Ultrasound. The Journal of urology.	Retrospective analysis n=598	Following focal HIFU, nadir+1.0ng/ml at 12 months and nadir+1.5ng/ml at 24 to 36 months might be used to triage those men requiring MRI and biopsy. These need prospective validation.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Huber PM, Afzal N, Arya M et al. (2020) Focal HIFU therapy for anterior compared to posterior prostate cancer lesions. World journal of urology	Case series n=598	Treating anterior prostate cancer lesions with focal HIFU may be less effective compared to posterior tumours.	Studies with more people or longer follow up included.

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Ingrosso G, Becherini C, Lancia A et al. (2020) Nonsurgical Salvage Local Therapies for Radiorecurrent Prostate Cancer: A Systematic Review and Meta-analysis. European urology oncology 3(2):183-97	Systematic review and meta-analysis	Nonsurgical therapeutic options, especially brachytherapy, showed good outcomes in terms of biochemical control and tolerability in the local recurrence setting.	Mixture of focal and whole-gland HIFU studies included.
Johnston MJ, Emara A, Noureldin M et al. (2019) Focal High-intensity Focussed Ultrasound Partial Gland Ablation for the Treatment of Localised Prostate Cancer: A Report of Medium-term Outcomes From a Single-center in the United Kingdom. Urology 133:175-81	Case series n=107 FU=30 months	In a carefully chosen cohort of people for focal HIFU our results suggest acceptable oncological control with minimal postoperative morbidity. Further studies are required to establish this technique as a less morbid alternative to radical therapy.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

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Kanthabalan A, Peters M, Van Vulpen M et al. (2017) Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU international 120(2):246-56	Case series n=150 35 months	Focal salvage HIFU conferred a relatively low complication and side effect rate. Composite endpoint-free survival and biochemical control in the short to medium term were reasonable, especially in this relatively high-risk cohort, but still low compared with current whole-gland salvage therapies. Focal salvage therapy may offer disease control in men at high risk whilst minimising additional treatment morbidities	Included in the Koo, 2020 systematic review.
Kayano PP and Klotz L. (2021) Current evidence for focal therapy and partial gland ablation for organ-confined prostate cancer: systematic review of literature published in the last 2 years. Current opinion in urology 31(1):49-57	Systematic review n=12 studies	Focal therapy and partial gland ablation for organ-confined prostate cancer is an option for people with intermediate-risk disease because of its low complication profile and preservation of QoL.	More comprehensive systematic reviews included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Linares-Espinos E, Carneiro A, Martinez-Salamanca JI et al. (2018) New technologies and techniques for prostate cancer focal therapy. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 70(3):252-63	Systematic review n=9 studies	Reliable evidence for the partial-gland treatment of prostate cancer is increasing, and encouraging mid-term oncologic outcomes with the preservation of sexual and urinary functions have been reported. Accurate patient selection at the outset of treatment and careful follow up seem key attributes to achieve excellent functional results and encouraging oncological outcomes.	More recent systematic reviews included.
Maestroni U, Tafuri A, Dinale F et al. (2021) Oncologic outcome of salvage high-intensity focused ultrasound (HIFU) in radiorecurrent prostate cancer. A systematic review. Acta bio-medica: Atenei Parmensis 92(4):e2021191	Systematic review n=2 studies	Our review of the literature revealed that salvage HIFU is effective in the treatment of radiorecurrent clinically localised prostate cancer, with an overall survival of 85.2% at 5 years.	More comprehensive systematic review on salvage HIFU focal therapy included.
Mantica G, Chierigo F, Suardi N et al. (2020) Minimally invasive strategies for the treatment of prostate cancer recurrence after radiation therapy: a systematic review. Minerva Urologica e Nefrologica 72(5):586-94	Systematic review	Minimally invasive therapeutic options offer promising results in terms of biochemical control in the local recurrence setting. Unfortunately, the absence of high quality and comparative studies makes it difficult to establish which method is the best in terms of oncological and safety outcomes.	More comprehensive systematic review on salvage HIFU focal therapy included.

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Mortezavi A, Krauter J, Gu A et al. (2019) Extensive Histological Sampling following Focal Therapy of Clinically Significant Prostate Cancer with High Intensity Focused Ultrasound. The Journal of urology 202(4):717-24	Case series n=75	Focal therapy with high intensity focused ultrasound leads to a low rate of genitourinary side effects. Follow-up biopsy of treated and untreated prostates remains the only modality to adequately select men in need of early salvage treatment.	Studies with more people or longer follow up included.
Nahar B, Bhat A, Reis IM et al. (2020) Prospective Evaluation of Focal High Intensity Focused Ultrasound for Localized Prostate Cancer. The Journal of urology 204(3):483-9	Case series n=52 FU=12 months	Focal high intensity focused ultrasound is a safe and effective treatment for people with localised clinically significant prostate cancer with acceptable short-term oncologic and functional outcomes. The complications are minimal and patient selection is essential.	Studies with more people or longer follow up included.
Perez-Reggeti JI, Sanchez-Salas R, Sivaraman A et al. (2016) High intensity focused ultrasound with Focal-One R device: Prostate-specific antigen impact and morbidity evaluation during the initial experience. Actas urologicas espanolas 40(10):608-14	Case series n=64 FU=3 months	Focal-One R HIFU treatment appears to be a safe procedure with few complications. Functional outcomes proved no urinary incontinence and sexual function were maintained in 83%.	Studies with more people or longer follow up included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Ramsay CR, Adewuyi TE, Gray J et al. (2015) Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England) 19(49):1-490	Systematic review n=4 studies	Descriptive subgroup assessment within studies reporting the use of focal ablation was limited, but suggested that cancer-specific outcomes were at least comparable with those seen in full-gland therapy studies.	Small number of focal HIFU studies identified.
Rischmann P, Gelet A, Riche B et al. (2017) Focal High Intensity Focused Ultrasound of Unilateral Localized Prostate Cancer: A Prospective Multicentric Hemiablation Study of 111 Patients. European urology 71(2):267-73	Case series n=111 FU=1 year	At 1 year, HIFU-hemiablation was efficient with 95% absence of clinically significant cancer associated with low morbidity and preservation of quality of life. Radical treatment-free survival rate was 89% at 2 years.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.
Shah TT, Reddy D, Peters M et al. (2021) Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study. Prostate cancer and prostatic diseases 24(2):567-74	Propensity score matched study n=246 FU=64 months	In people with non-metastatic low-intermediate prostate cancer, oncological outcomes over 8 years were similar between focal therapy and radical prostatectomy.	More recent results presented in van Son, 2021.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Schmid FA, Schindele D, Mortezavi A et al. (2020) Prospective multicentre study using high intensity focused ultrasound (HIFU) for the focal treatment of prostate cancer: Safety outcomes and complications. Urologic Oncology: Seminars and Original Investigations 38(4):225-30	Case series n=98	Focal therapy of localised prostate cancer lesions with a robotic HIFU-probe is safe and renders an acceptable rate of minor early AEs. The inclusion of the urethra in the ablation zone leads to an increase in early complications and should be avoided whenever possible	Studies with more people or longer follow up included.
Shoji S, Hiraiwa S, Uemura K et al. (2020) Focal therapy with high-intensity focused ultrasound for the localized prostate cancer for Asian based on the localization with MRI-TRUS fusion image-guided transperineal biopsy and 12-cores transperineal systematic biopsy: prospective analysis of oncological and functional outcomes. International journal of clinical oncology 25(10):1844-53	Case series n=90 FU=21 months	The present treatment for Asian people would have similar oncological and functional outcomes to those in previous reports. Further large studies are required to verify oncological and functional outcomes from this treatment for people with localised prostate cancer.	Studies with more people or longer follow up included.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Sivaraman A, Marra G, Stabile A et al. (2020) Does mpMRI guidance improve HIFU partial gland ablation compared to conventional ultrasound guidance? Early functional outcomes and complications from a single center. International braz j urol: official journal of the Brazilian Society of Urology 46(6):984-92	Cohort study n=140 FU=12 months	HIFU focal therapy guided by MRI-ultrasound fusion may allow improved functional outcomes and fewer complications compared to ultrasound-guided HIFU focal therapy alone. Further analysis is needed to confirm benefits of MRI implementation at a longer follow-up and on a larger cohort of people	Studies with more people or longer follow up included.
Stabile A, Orczyk C, Giganti F et al. (2020) The Role of Percentage of Prostate-specific Antigen Reduction After Focal Therapy Using High-intensity Focused Ultrasound for Primary Localised Prostate Cancer. Results from a Large Multi-institutional Series. European Urology 78(2):155-60	Case series n=703 FU=41 months	The percentage of prostate-specific antigen reduction is a useful tool to assess men following focal therapy. It can assist the urologist in setting up an appropriate follow-up and during post-focal therapy patient counselling.	This cohort was captured in Stabile, 2019.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Stabile A, Sanchez-Salas R, Tourinho-Barbosa R et al. (2021) Association between Lesion Location and Oncologic Outcomes after Focal Therapy for Localized Prostate Cancer Using Either High Intensity Focused Ultrasound or Cryotherapy. The Journal of urology 206(3):638-45	Case series n=166 FU=51 months	The prostate cancer location does not significantly affect the rate of failure after focal therapy. The presence of an apical lesion should not be considered an exclusion criterion for focal therapy. Both HIFU and cryotherapy likely achieve similar medium-term oncologic results regardless of prostate cancer location.	Studies with more people or longer follow up included.
Tourinho-Barbosa RR, Sanchez-Salas R Claros OR et al. (2020) Focal Therapy for Localized Prostate Cancer with Either High Intensity Focused Ultrasound or Cryoablation: A Single Institution Experience. The Journal of urology; 203(2):320-30	Case series n=190 FU=45 months	Almost half of the men were free of focal therapy failure 5 years after treatment. Still, a significant proportion experienced recurrence at the midterm follow-up. The preoperative biopsy Gleason score and nadir prostate specific antigen were significantly associated with treatment failure.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

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Valerio M, Ahmed HU, Emberton M et al. (2014) The role of focal therapy in the management of localised prostate cancer: a systematic review. European urology 66(4):732-51	Systematic review n=12 studies	When focal therapy is delivered with intention to treat, the perioperative, functional, and disease control outcomes are encouraging within a short- to medium-term follow-up. Focal therapy is a strategy by which the overtreatment burden of the current prostate cancer pathway could be reduced, but robust comparative effectiveness studies are now required.	More recent systematic reviews included.
Valerio M, Cerantola Y, Eggener SE et al. (2017) New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. European urology 71(1):17-34	Systematic review n=13	Focal therapy has been evaluated using seven sources of energy in single-arm retrospective and prospective development studies up to Stage 2b. Focal therapy seems to have a minor impact on quality of life and genitourinary function. Oncological effectiveness is yet to be defined against standard of care.	More recent systematic reviews included.

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Valle LF, Lehrer EJ, Markovic D et al. (2020) A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER) European Urology.	Systematic review and meta-analysis	Relapse-free survival at 5 years is equivalent among salvage modalities, but reirradiation may lead to lower toxicity. This meta-analysis provides pooled estimates of surgical and nonsurgical local salvage treatments for radiorecurrent prostate cancer. Five-year recurrence-free survival was similar across modalities on meta-regression, although differences in severe genitourinary and gastrointestinal toxicity appear to favour reirradiation, particularly high-dose-rate brachytherapy	Salvage focal HIFU systematic review (Khoo, 2020) included. Meta-analysis includes whole-gland ablation as well as focal.
van Velthoven R, Aoun F, Marcelis Q et al. (2016) A prospective clinical trial of HIFU hemiablation for clinically localized prostate cancer. Prostate cancer and prostatic diseases 19 (1):79-83	Case series n=50 FU=39.5 months	Hemiablation HIFU therapy, delivered with intention to treat, for carefully selected people affords mid-term promising functional and oncological outcomes. The effectiveness of this technique should be now compared with whole-gland radical therapy.	Studies with more people or longer follow up included. Included in the Bakavicius, 2022 systematic review.

Article	Number of people/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Yap T, Ahmed HU, Hindley RG et al. (2016) The Effects of Focal Therapy for Prostate Cancer on Sexual Function: A Combined Analysis of Three Prospective Trials. European urology 69(5):844-51	Pooled analysis n=118 FU=1 year	Men who received a range of tissue preserving therapies from the 3 pertinent studies experienced small decreases in total IIEF, erectile, and individual sexual domain scores that are not significantly different to those recorded at baseline. The only determinant of erectile dysfunction after tissue preserving therapy was preoperative erectile dysfunction status. Tissue preservation confers a high probability of maintaining erectile function that appears independent of all perioperative factors with the exception of baseline status.	Studies with more people or longer follow up included.