White paper

Focal therapy for localised prostate cancer: systematic review of efficacy and functional outcomes from partial gland ablations with Low Dose Rate Brachytherapy, High Intensity Focused Ultrasound, Irreversible Electroporation, and Cryotherapy.

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Contents

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Abstract

Objective:
To compare oncological and functional outcomes of focal low dose rate I-125 brachytherapy (FB), focal high intensity focused ultrasound (HIFU), irreversible electroporation (IRE), and focal cryotherapy for the treatment of localised prostate cancer (PCa).

Methods:
A systematic review of the literature was conducted to obtain clinical reports on the focal approaches. The search was restricted to articles published from May 2015 to March 2026. Articles on primary focal monotherapy with peer-review provenance in the English language were included. Treatment efficacy outcome was incidence of clinically significant PCa (csPCa; Gleason group 2 or more) recurrence in per protocol control biopsies. Treatment-related effects were assessed from patient-reported outcome measures and physician-reported adverse events.

Results:
Ninety-seven articles were appraised including 14 on FB, 42 on HIFU, 21 on IRE, and 20 on Cryotherapy. Most studies were single-arm prospective analyses. Randomised comparisons between the focal approaches were not identified. In studies with per protocol control biopsies (N=68) the median recurrence of csPCa in-field was 3%, 6%, 10%, and 11% after FB, IRE, Cryotherapy and HIFU in 9, 17, 11, and 27 studies respectively. Urinary function reported in 51 studies was largely preserved or improved. Sexual function assessed in 54 studies was preserved in 35 (65%) studies, and decreased in 12%, 33%, 36% and 55% of FB, HIFU, IRE, and Cryotherapy studies respectively. Bowel function from 18 studies was always preserved. The median of any grade 2 adverse event was 5% after Cryotherapy, 8% after HIFU, and 9% after FB and IRE. The median of any grade 3 adverse event was 0% after FB, IRE, and Cryotherapy and 2.8% after HIFU.

Conclusion:
The real-world evidence suggests FB is more efficient at controlling localised PCa relative to HIFU, IRE, and Cryotherapy with a low impact on organ-at-risk function. Randomised comparisons are however needed to confirm long-term efficacy and safety advantages between the focal therapies, whole gland treatment, and active surveillance.

Introduction

Modern prostate magnetic resonance imaging (MRI) provides localisation of tumours together with information on their clinical aggressiveness [1]. This has paved the way for targeted diagnostic approaches and focal treatment where interventions are restricted to areas found to contain neoplasia. By preserving healthy tissues, focal therapy aims to control prostate cancer with a reduced morbidity.

The choice of treatment for localised PCa is a joint decision between the patient and the treating physician. Quality of life after treatment and medical expertise play an important role in treatment selection. However, the risk of tumour progression to more advance stages takes precedence. For low-risk tumours, patients may be enrolled in an active surveillance program in which close monitoring defers radical treatment, and attendant morbidity, unless the cancer shows signs of progression. Focal therapy may reduce uncertainty stemming from leaving tumours untreated [2]. Although not fully recognised as a standard of care it is increasingly more accepted as an option for intermediate-risk cancer when used in a clinical trial or prospective registry setting (table 1) where patients are closely monitored after treatment.

Focal therapy for prostate cancer has been extensively reviewed in the clinical literature. Valerio et al in 2017 concluded from a systematic synthesis of 37 articles on 7 sources of energy (including brachytherapy, HIFU, IRE, and Cryotherapy) that focal approaches seemed to have a minor impact on genito-urinary function but an undetermined oncological effectiveness due to short follow-up, study heterogeneity, and absence of comparator arms [3]. Ganzer et al in 2018 suggested from an expert consensus that each form of focal therapy may be preferable for different tumour locations, and that tumour risk, size, and prostate volume need consideration [4]. More recent reviews continue to support these initial observations [5-10].

This review captures those clinical studies with an update from the clinical literature to compare oncological efficacy and functional outcomes after FB with those from HIFU, IRE, and Cryotherapy.

Prostate cancer		EAU [12]	AUA/ASTRO [13]	FALCON [14]
Localised	Low-risk	?	⚠	⚠
	Intermediate-risk	?	✓*	✓
	High-risk	X	X	X
Locally Advanced		X	X	X

✓ Recommended ? Trial setting or registry ⚠ AS preferred X Not recommended
*Selected and informed patients, ideally in a prospective study. EAU: European Association of Urology, AUA: American Urology Association, ASTRO: American Society for Radiation Oncology, FALCON: FocaAL Therapy Consensus, AS: Active Surveillance

Table 1. Summary of recommendations for focal therapy in the management of prostate cancer (adapted from [11]).

Focaltreatment modalities overview

Low dose rate brachytherapy

Low dose rate (LDR) brachytherapy seeds emit ionising radiation that breaks molecular bonds in DNA resulting in cellular death by apoptosis. Each seed is a titanium tube 4.5 mm long by 0.8 mm in diameter (similarto a grain of rice) that encapsulates the radioisotope, most commonly Iodine-125 (I-125, half-life of 59.6 days) or Palladium-103 (Pd-103, half-life of 17days). The number and position of seeds is planned using dedicated software to achievethe prescription dose of 145Gyfor I-125to the target area identified from MRI and biopsy information. The seeds are permanently implanted via the perineum under real-time transrectal ultrasound (TRUS) guidance. After the implant, seed placement is verified by computerised tomography or MRI which enable a record of the doses delivered to the target area(s) and surrounding organs. See figure 1and table 2 for further technical detail and comparisons on the selected focal modalities.

High-intensity focused ultrasound (HIFU)

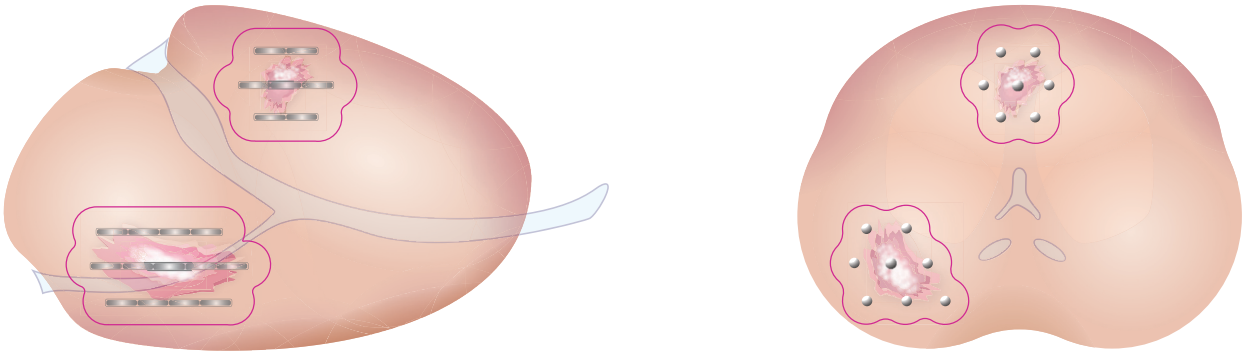
Ultrasound frequency of 0.8–7MHz transforms into mechanical energy generating temperatures between 65°C and 90°C. The thermal ablation causesprotein denaturation and coagulative necrosis. Once dimensions of the prostate are acquired and the target area identified, a 'cigar shaped' ablation volume (1.5-2.0mm wide by 15-20 mm long covering 50 to 300 mm3) is guided to the target area in real-time by means of dedicated software. Fusionof mpMRI with ultrasound images assists with lesion location, and robotic technology enhances precision. The procedure is non-invasive as energy is delivered from the ultrasound probe housed in a cooling balloon within the rectum. In large prostate glands delivery of energy to the anterior prostate may not be feasible due to the fixed focal length.

Irreversible electroporation (IRE)

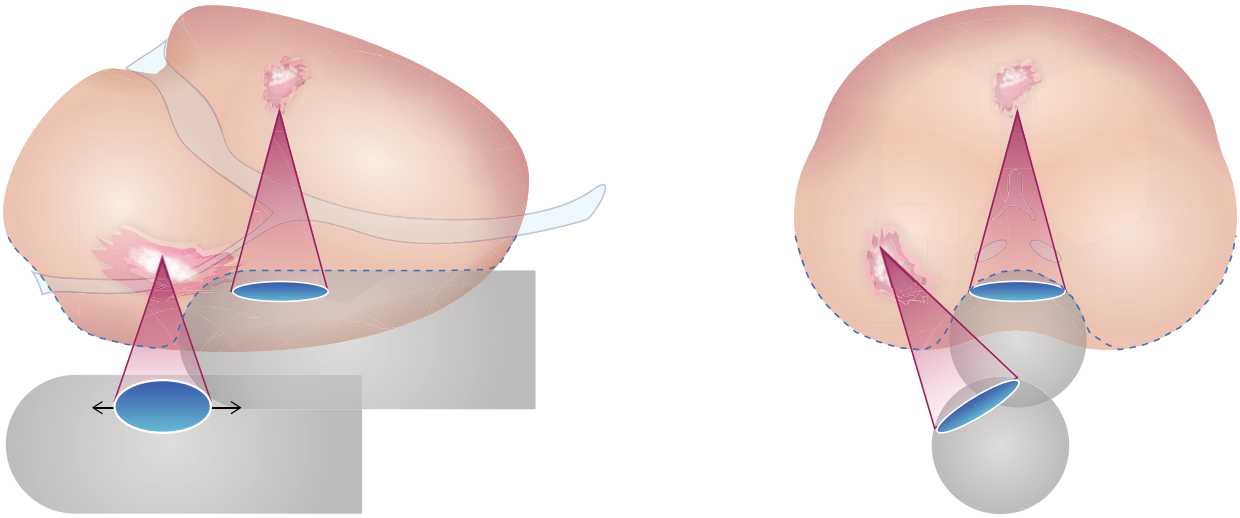
Electroporation forms nanopores in the cellular membrane that become permanent leading to loss of homeostatic regulation and cell death. Paired electrodes of anode (P+) and cathode (P-) needles are placed transperineally under TRUS guidance to deliver a seriesof short-duration high-voltage electrical pulses. The electrodes are placed 10mm to 20 mm apart to create an ablation zone that surrounds the lesion. Multiple pairs of electrodes can be sequenced to increase the size of the ablation zone (see figure 2). The active tip (exposed length) of the electrodes determines the extent of the area to be treated.

Cryotherapy

Cryotherapy involvestwo cycles of freezing and thawing. Lethal freezing temperatures (below -40°C) damage the cellular membrane and microvascular endothelium causing coagulative necrosis. Thawing creates a hypotonic environment that leads to cell swelling, further membrane damage, and oedema. Thin cryotherapy needles (cryoprobes) are inserted via the perineum. Compressed Argon gas expands within the tip of the cryo-needleto form an ice ball and helium gas enables the thawing phase. The length and diameter of the cryoprobes determine the shape and sizeof the ice ball which is monitored under TRUS guidance. Thermocouples are used to monitor temperatures in organs at risk and a warmed (40°C) balloon is placed in the rectum to control rectal temperature.

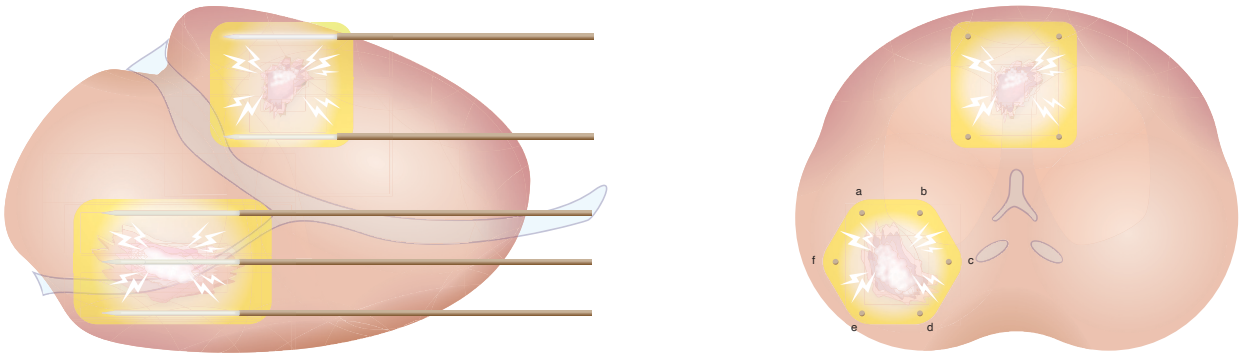


a. FB:
Low dose rate brachytherapy seeds permanently implanted in and around the target area. The image shows implants of seeds in strands. A treatment plan based on the size and location of the tumour, and proximity to organs at risk, determines strand configurations.



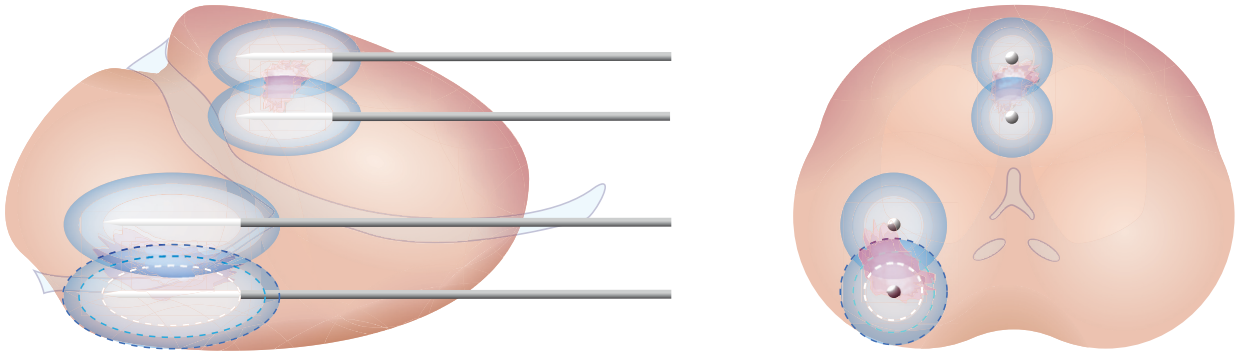
b. HIFU:
The probe emits ultrasound from the rectum with a fixed focal length, hence requires movement and rotation to reach targets in different areas of the prostate, and compress the prostate to reach tumours in the anterior part of the gland (prostate deformation shown in blue dashed line).

Figure 1 Page 6-7. Illustrations of single lesion focal treatment, example shown with lesion at mid anterior and right posterior base for each modality to highlight possible treatment approach at different locations around key organs; a. Focal Brachytherapy (FB), b. High Intensity Focused Ultrasound (HIFU), c. Irreversible electroporation (IRE), d. Cryotherapy. Shown in transverse and sagittal orientation with estimated treatment / energy margins.



c. IRE:

Four and six electrodes implanted into the prostate. Each probe is paired and sequenced e.g. a and d, b and e, c and f, etc., to generate a high voltage field around the tumour. The exposed length of the electrodes are used to match to the length and shape of the tumour.



d. Cryotherapy:

Thin needles (cryoprobes) expand Argon gas at the tip to create an 'ice ball' in the target area. The cryoprobe tip size determines the volume/shape and isotherm dimensions. Isotherm dimensions vary on the needle used, with temperatures reaching -400C, -200C, and 00C, within the white, light blue, and dark blue dashed lines, respectively.

	FB	HIFU	IRE	Cryotherapy
Treatment principle	Apoptosis by ionising radiation of DNA[1]	Apoptosis by heat/ concentrated mechanical frequency[2]	Permanent nanopores lead to loss of homeostasis, may trigger immune response[3]	Apoptosis and necrosis by tissue freeze/thaw[4]
Energy delivery	145 Gy, 59.6 days half-life[5]	200kHz and 7MHz generating 60°C to 90°C or Hyperechoic 20 to 48 Watts[2]	1500 V/cm at 90-microsecond monopolar pulses[6]	38°C to -40°C time-controlled temperature gradient[4]
Selection criteria[i.]	• Good urinary function (high IPSS)[7] • Prostate <20cc OR>60cc (100cc is technically feasible) with minimal pubic interference[11] • Prior TURP possible[7]	Prostate >40cc due to limited focal length[8]	• Pacemakers must be identified[9] • Prostate volume 65cc with minimal pubic arch interference[12]	• Prostate size between 40-60cc[10] • Men with prior TURP treatment not suitable[13]
Patient preparation[ii.]	Seperate TRUS volume study needed for pre-loaded kit ordering	• Dorsal lithotomy or right lateral decubitus • TURP maybe performed to reduce prostate volume and minimise necrotic debris from procedure[15] • Immobilisation critical[17] • Rectal cooling from balloon housing the probe[17] • Removal of gas bubbles desired to ensure uniform wave propagation[2]	Muscle relaxant to prevent contractions[16]	• Warmed urethral catheter, non-target tissue thermal protection[18] • Circulating heated rectal balloon[19] • Thermocouples placed at OAR[20]
Imaging and planning[iii.]	• TRUS real-time • Intra-operative real-time analysis after seed each implant[24]	• mpMRI fusion with TRUS real-time[21] • Ultrasound and HIFU probe are combined as one	mpMRI fusion with TRUS real-time[22]	mpMRI fusion with TRUS real-time [23]
Targeting & instrument placement[iv]	• Seeds placed in and around lesion[24] • 13 brachytherapy needles (median) inserted transperineally under TRUS[24] • 39 permanent implant seeds with the option of being encased/linked and spaced (median)[24]	• Proximal energising of lesion via software guidance[2] • Non-invasive • 50-56 mm dia visualization and treatment probe • Robotic arm to direct treatment probe within the rectum or mounted on articulated arm and fixed into position	• Lesion must be between paired probes[25] • 4-6 probes parallel configuration inserted transperineally under TRUS[25] • 10-20 mm spacing[6]	• Ice-ball formed within and around the lesion • 1-4 cryotherapy needles placed within 20 mm of each other inserted transperineally under TRUS[26] • Needle dimensions reflect ice-ball shape • Temperature probes in urethra sphincter, rectal wall, NVB[27]
Treatment margin	7 mm isotropic expansion of the focal-gross tumour volume (F-GTV)[5]	• 10 mm beyond visible lesion[28] • Margin beyond the prostate capsule when disease abuts the capsule are recommended[30]	5-7 mm beyond the visible lesion[29]	A minimum 5 mm of <20°C around the target lesion/ zone[27]
Margin: Safety from critical structures[v]	• 3 mm from urethra[24] • Urethra volume 0.1cc (V200%) receiving max dose of 164.6 Gy (mean)[5] • Rectum volume 0.05cc (V100%) receiving max dose 95.8 Gy (mean)[5] • Peri-rectal spacer placed after implant absorbed after 6 months reduces rectal dose[5]	5 mm from rectum and urinary sphincter[17]	• 5 mm from critical structure[6] • 3 mm from prostate capsule[6]	• Urethra temperatures to be maintained at 38-40°C[18] • Rectum target temp 40°C with warmer cryotherapy needles placed between the prostate and rectum, and/or rectal lumen washed with 40°C water for -10°C rectal temps[19] • NVB not below -35°C[31]
Procedure time	36 minutes (mean), real-time implant[24]	63 minutes, treatment area of 14.67mL (hemi-ablation) in 7 slices[17]	60 minutes[16]	70 minutes (median), freezing thawing 6-7 minutes in 2 cycles[27]
Post-procedure patient care activity[vi.]	• Cystoscopy post implant, visual seed check within urethra or bladder[5] • Urethral catheterisation for urinary retention, occurs in <2% of whole gland therapy procedures[5]	Bladder catheter for 5-7 days[17]	Urine catheter in place for 2 – 10 days depending on the size of the ablation zone and proximity to intraprostatic urethra[16]	• Urethral catheter 3-7 days[32] • Belladonna / opium suppositories[27]
Treatment quality assurance	CT or mpMRI post-implant dosimetry[5]	Contrast enhanced TRUS correlates with mpMRI and biopsy histology[33]	Contrast enhanced ultra-sound for perfusion defect in relation to ablation zone[34]	Visual confirmation of treated area with a follow up scan.

Common across modalities:
i. Patient exclusion include rectal fistulae and stenosis, calcification, history of abdominal perineal resection for rectal cancer, or other major rectal pathology including inflammatory bowel disease. Lesions sitting directly at the posterior apex of the prostate, near the external urinary sphincter, face restrictions. Risk of permanent urinary incontinence increased if ablation zone significantly overlaps with the sphincter.
ii. Patient preparation includes antibiotic prophylaxis, dorsal lithotomy positioning, general anaesthesia, catheter placement (or aerosolised jelly) for landmarking and drainage, complete patient mobilization is non-critical
iii. All tumours (index lesions) and critical structures mapped with software enabling targeted treatment and real-time ultrasound monitoring
iv. Procedure is minimally invasive with template and stepper used for alignment under real-time guidance
v. Margins at the discretion of the physicians.
vi. Alpha-blocker medication ranges from 6 months depending on modality
FB: Focal Brachytherapy; HIFU: High-intensity Focal Ultrasound; IRE: Irreversible Electroporation; Gy: Gray; TURP: Transurethal Resection of the Prostate; OAR: Organs At Risk; TRUS: Transrectal Ultrasound; mpMRI: multi-parametric Magnetic Resonance Imaging; NVB: Neurovascular Bundle; F-GTV: focal-gross tumour volume; CT: Computed Tomography.

See references on page 19.

Table 2. Summary of focal approaches highlighting key differences

Methods

Literature searchstrategy

The PubMed and EMBASEdatabases were queried for literature on focal approaches for the treatment of prostate cancerwith the following PICOterms:

Population – Prostate cancer

Intervention – Focaltherapy

Comparator – Energy sources

Outcome – Efficacy (oncological control) and Functional (treatment-related effects).

To obtain a broad view an initial search explored availability of reviews or clinical trials on focal therapy for prostate cancer within the last 10 years (figure 2) from 25 May 2025. The reviews guided hand searches for selection of relevant clinical studies. A second search was conducted to obtain up to date clinical studies from 25 May 2025 to 10 March 2026.

Evidence synthesis

Data from each study was collected in Excel and summarized within R statistical environment (version 4.5.1)[15] using readxl [16], tydiverse [17], gtsummary [18], and RColorBrewer [19] packages. Age means, when not reported, were obtained from available summary statistics using the Box-Coxmethod in 'estmeansd' [20].

Efficacy outcomes, in-field and out-field recurrence, were defined as the proportion of any Gleason group detected in per protocol control biopsies. Clinically significant recurrence when Gleason group 2 or more was identified. Functional outcome impact was defined by evidence of a statistically significant change from baseline of PROMs (IPSS, AUS-SS, EPIC-26, IIEF-5) beyond an acute phase (>3 months after treatment).

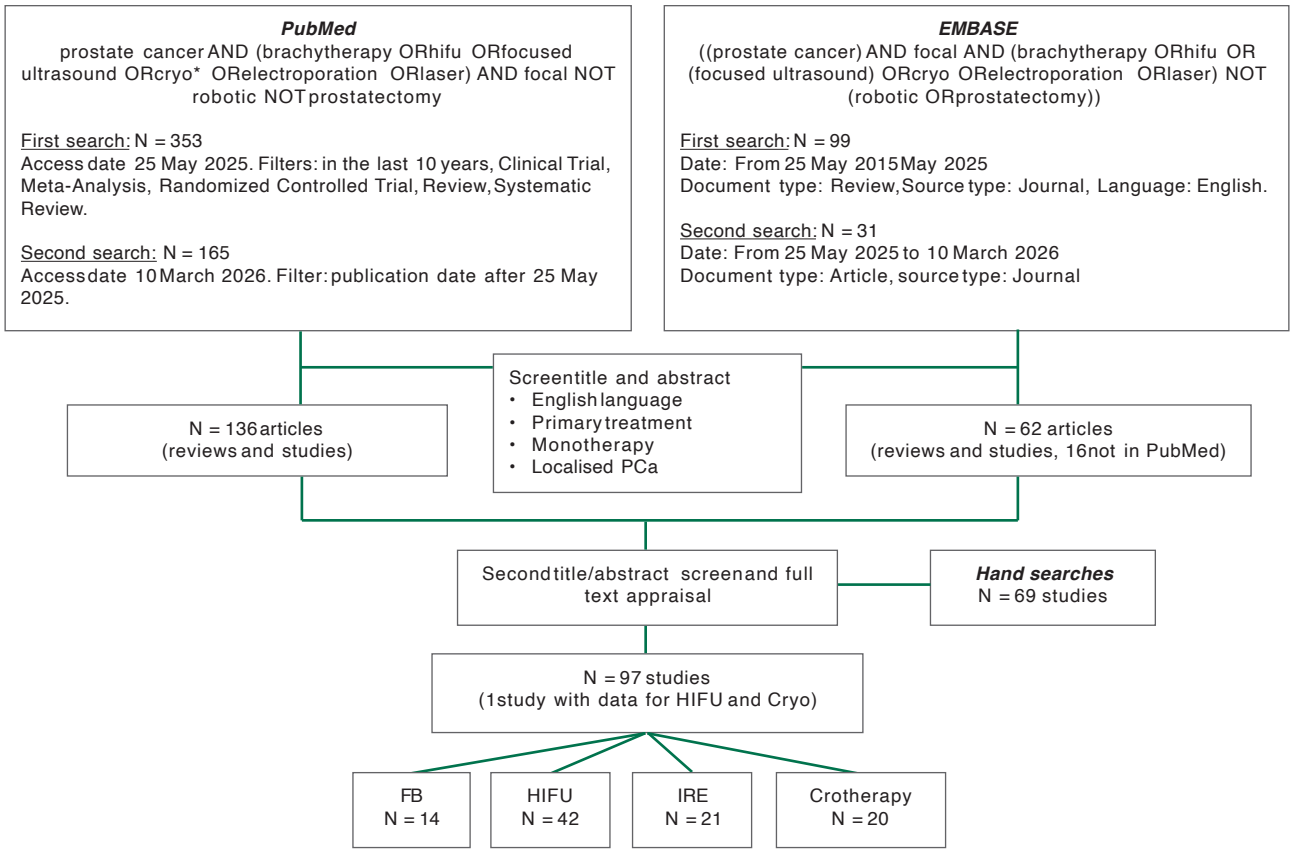


Figure 2. Overview of literature search strategy. The first search was for reviews in the last 10 years up to May 2025, and a second search for studies from May 2025 to March 2026.

Results

The literature search found 97 studies pertaining to focal therapy of localised prostate cancer with the selected energy sources (figure 2 and table 3). For FB 14 studies encompassed 865 cases with a median of 30 cases per study [21-34]. The largest body of evidence was for HIFU with 42 studies on 5,246 cases and a median of 73 cases per study [35-76]. For IRE 21 studies included 1,763 cases and a median of 50 cases per study [77-97]. For Cryotherapy there were 20 studies on 2,424 cases and a median 76 cases per study [98-116,71]. One study reported on HIFU and Cryotherapy [71].

Most reports were from prospective registries (~70%) or retrospective analyses (~30%) (table 3). The single randomised trial found compared focal versus extended IRE without a significant difference in outcomes [96]. Patient age was similar between all treatment modalities, and most studies treated men with prostate cancer of a low and intermediate risk of relapse. Inclusion of men with high-risk disease was more prevalent in reports on cryotherapy (55% of studies) and HIFU (33.8% of studies). The length of patient follow-up was short overall with FB studies reporting the longest follow up length at a median of 36 months (table 3). For all therapies the number of patients per study grew over time (figure 3).

Clinically significant PCa recurrence detected in treated (in-field) and untreated (out-field) areas in per protocol biopsies was reported by 64 and 61 studies respectively (figure 3 and table 4). The median in-field recurrence rate was 3% after FB (from 233 biopsies across 9 studies), 11% after HIFU (from 1,953 biopsies in 27 studies), 6% after IRE (from 1,108 biopsies in 17 studies), and 10% after Cryotherapy (from 761 biopsies across 11 studies). The median out-field recurrence was 3% for FB (in 9 studies), 8% for HIFU (in 27 studies), 9% after IRE (in 16 studies), and 12% after Cryotherapy (across 9 studies).

	FB	HIFU	IRE	Cryo
Study characteristic	N = 14[1]	N = 42[1]	N = 21[1]	N = 20[1]
Number of cases	30 (24, 51)[865]	73 (44, 113)[5,246]	50 (25, 106)[1,763]	76 (53, 127)[2,424]
Study type				
Prospective	10 (71%)	33 (79%)	15 (71%)	13 (65%)
Retrospective	4 (29%)	9 (21%)	5 (24%)	7 (35%)
RCT	0 (0%)	0 (0%)	1(4.8%)	0 (0%)
Focal approach				
Ultrafocal	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
Focal	8 (57%)	16 (38%)	20 (95%)	11(55%)
Focal or Partial	1 (7.1%)	13 (31%)	1(4.8%)	1(5.0%)
Partial or Hemigland	4 (29%)	13 (31%)	0 (0%)	8 (40%)
Age means (years)	67 (63, 71)	66 (65, 68)	66 (64, 67)	67 (65, 69)
Unknown	0	2	0	1
Risk groups				
Low	0 (0%)	2 (4.8%)	0 (0%)	1(5.0%)
Int	1 (7.1%)	3 (7.1%)	1(4.8%)	4 (20%)
Low-Int	12 (86%)	23 (55%)	16 (76%)	4 (20%)
Low-Int-High	1 (7.1%)	12 (29%)	4 (19%)	6 (30%)
Int-High	0 (0%)	2 (4.8%)	0 (0%)	5 (25%)
Followup length median (months)	36 (24, 65)	20 (12,30)	19 (12, 36)	27 (15, 36)
Control biopsy reason				
Per protocol	8 (57%)	30 (71%)	19 (90%)	12 (60%)
For cause	3 (21%)	9 (21%)	2 (9.5%)	7 (35%)
None	3 (21%)	3 (7.1%)	0 (0%)	1(5.0%)

[1]Median (Q1,Q3) [Sum]; n (%); Median (Q1,Q3)

Table 3.

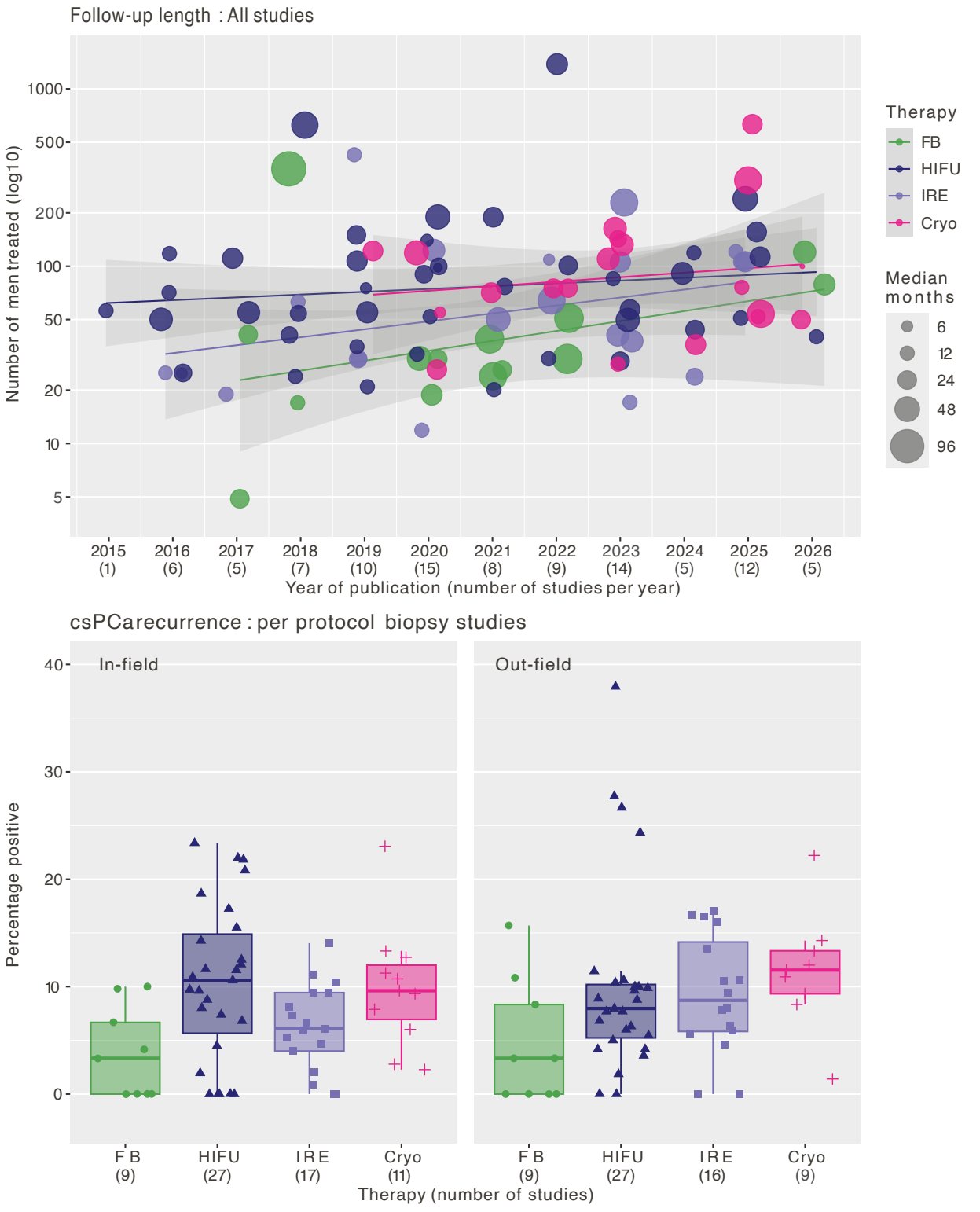


Figure 3. Overall data structure and recurrence. Top panel shows all 97 studies by year of publication and patient numbers with circle sizes by follow-up lengths. Lines represent slopes from linear regression models. Bottom panels show clinically significant (csPCa) in-field and out-field recurrence in studies with per protocol biopsies.

	FB	HIFU	IRE	Cryo
Per protocol biopsies	N = 9[1]	N = 30[1]	N = 19[1]	N = 12[1]
Number of biopsied men	26 (17,34) [233]	57 (31,90) [1,953]	40 (21,101) [1,108]	51(39, 76) [761]
In-field positive - any Gleason (%)[2]	4 (0, 10) [0:17]	15 (10,23) [0:40]	12 (6, 18) [0:37]	11(7, 20) [2:37]
In-field positive - csPCa (%)[3]	3 (0, 7) [0:10]	11(5, 15) [0:23]	6 (4, 9) [0:14]	10 (6, 13) [2:23]
Unknown	0	3	2	1
Out-field positive - any Gleason (%)[2]	12 (7, 18) [0:41]	16 (9, 24) [4:38]	16 (6, 27) [0:50]	17 (11,23) [1:40]
Unknown	0	0	0	2
Out-field positive - csPCa (%)[3]	3 (0, 8) [0:16]	8 (5, 10) [0:38]	9 (6, 15) [0:17]	12 (9, 13) [1:22]
Unknown	0	3	3	3

1 Median (Q1,Q3)[Sum]; Median (Q1,Q3)[Min:Max]
2 In men with per protocol biopsy (includes biopsies with evidence of treatment effect after brachytherapy).
3 Gleason group 2 or more.

Table 4. Summary of oncological outcomes.

Most studies that used PROMs for urinary function showed no impact on urinary symptoms (figure 4). Two studies on HIFU [35, 76], 2 on IRE [85, 92], and 3 on cryotherapy [102, 106, 109] reported better urinary symptoms post-ablation. One study showed worse urinary function after FB (6 months after implantation) [25]. The impact on patient-reported sexual function was more pronounced across all treatments; symptoms were worse in 1 FB study (12%, and clinically significant only in men with erectile disfunction at baseline at 6 months and 3 years) [21], 7 HIFU studies (33%) [46, 48, 54, 56, 57, 73, 74], 5 IRE studies (36%) [77, 78, 85, 88, 93], and 6 cryotherapy studies (55%) [100, 102, 104, 106, 108, 109]. Improvement in sexual function was never reported. An impact on bowel function was assessed in 18 studies all of which showed no significant change in patient-reported bowel symptoms.

Grade 2 and 3 adverse events were reported in 54 and 52 studies respectively (figure 5). Genitourinary (GU) events were in general low across therapies; for grade 2 GU events the median was 5% in FB, 6% after Cryotherapy, and 9% for HIFU and IRE with the top quartile below 20%. A notable outlier was one study on HIFU with 62% (18 events in 29 patients) [42]. For grade 3 GU events the median was 0% after FB, IRE, and Cryotherapy, and 4% after HIFU with the top quartile below 10%. Gastrointestinal (GI) events were rare with most grade 2 and 3 events below 1% and 0.5% of treated men respectively. A notable outlier was one study of FB with grade 2 GI of 6.6% (2 events in 30 patients) [25].

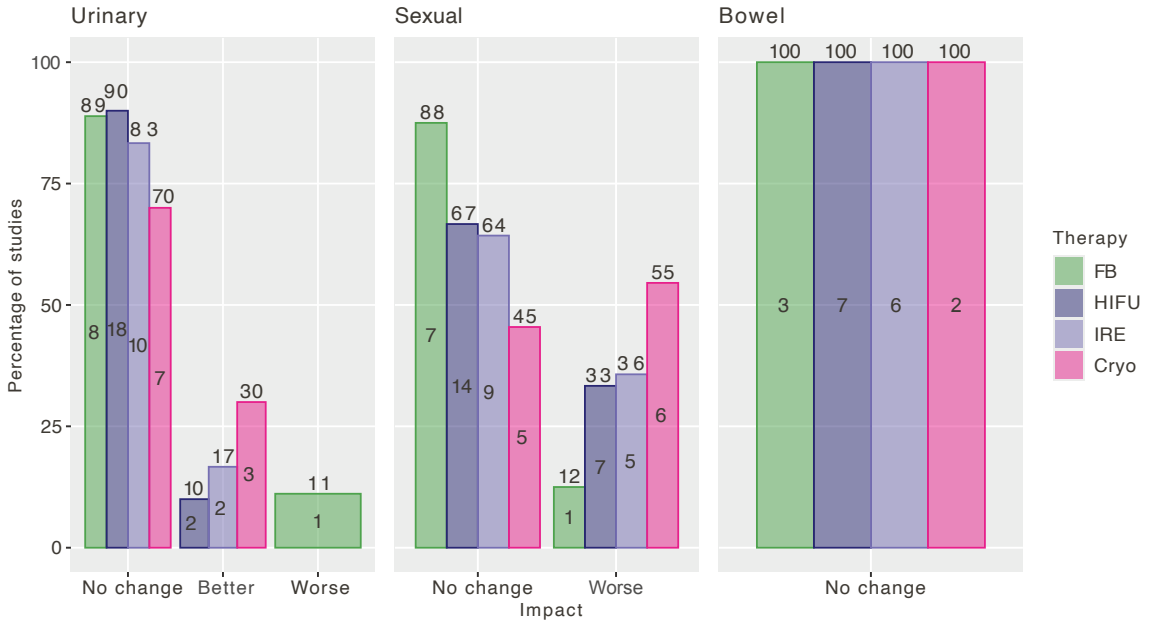


Figure 4. Focal therapy-related toxicity. Urinary, sexual, and bowel function was assessed by 51, 54, and 18 studies, respectively, that compared PROMs before and after treatment beyond a 3 months acute phase. Shown above bars are the percentage of studies with an impact on function (impact defined as a statistically significant difference relative to pre-treatment values). The number of studies are indicated inside the bars.

Discussion

The field of focal therapy continues to gain momentum with its place as a treatment option for localised prostate cancer increasingly more established [12-14]. A growing body of evidence is beginning to support the promise of equal efficacy to whole-gland radical treatment with reduced impact on nearby organ function. Hence men may find an offer of focal therapy more appealing than leaving tumours untreated, whilst accepting a risk of leaving healthy-looking areas untreated, if their quality of life is preserved. Focal therapy has also shown a favourable therapeutic ratio (effective cancer control with low morbidity) as salvage treatment [117].

Level 1 evidence is needed to compare outcomes between the different focal therapy approaches, whole gland treatment, and active surveillance. The outcomes herewith reported should be interpreted with caution. Most studies found were from single-arm prospective registries with relatively small case numbers. Patient selection criteria were not universal. Most studies assessed outcomes from mixed low and intermediate-risk cases, and several studies included men with a high risk of relapse in varying proportions; notably more than half of IRE studies included 13% to 34% high-risk cases (not shown). The ablation strategies varied from ultrafocal to partial or hemigland and several studies reported outcomes from mixed populations of focal and partial (up to 31% of HIFU studies). This has implications for both efficacy and functional outcomes. Interpretation of functional outcomes is further hampered by variation in the type of patient-reported instruments used, follow up protocols, and applied statistics.

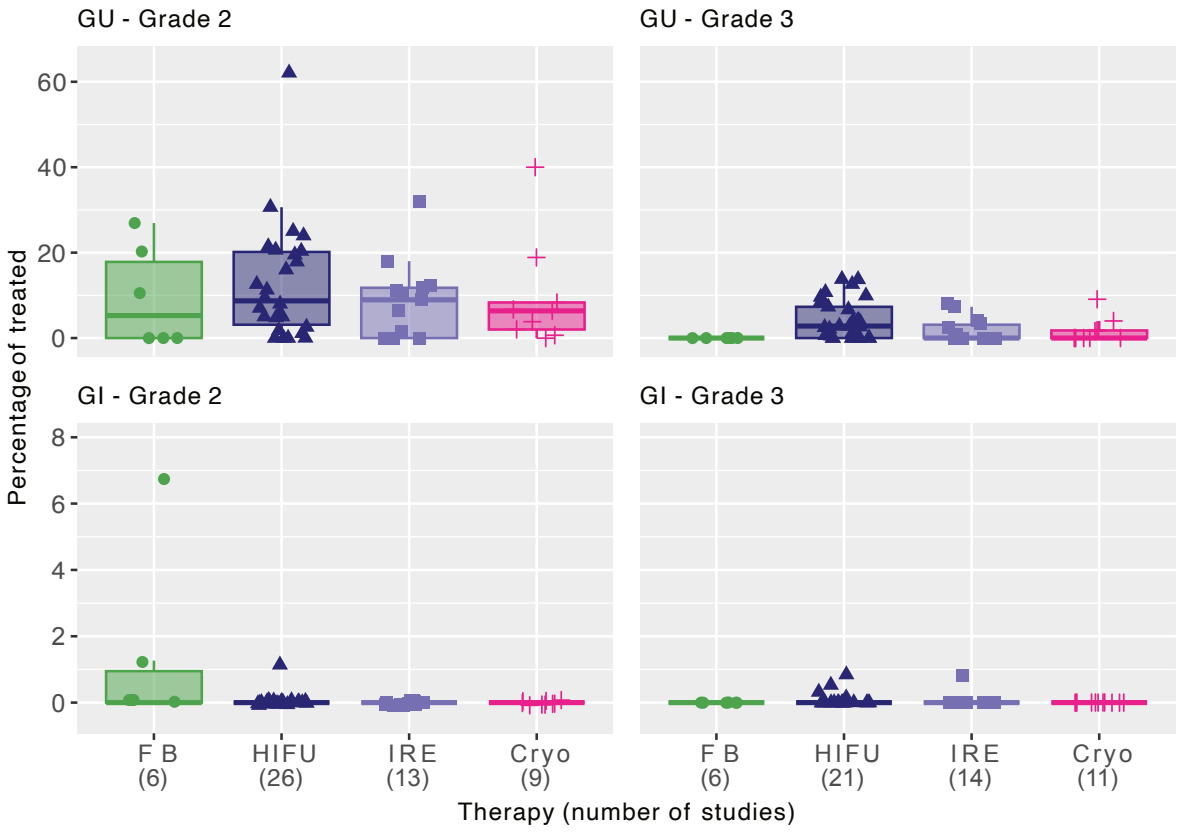


Figure 5. Adverse events. Genitourinary (GU) and gastrointestinal (GI) events are presented as the proportion of patients with an event in the study population. The number of studies reporting adverse events for each focal therapy approach is shown inside parenthesis.

This review found 97 studies on 4 sources of energy for primary focal therapy (I-125 Brachytherapy, HIFU, IRE, and Cryotherapy). A recent systematic review by Hopstaken et al published in 2022 found 72 studies on 8 sources of energy. At that time rates of in-field clinically significant cancer were reported as 0% for FB (LDR or HDR), 14.7% for HIFU, 8.5% for IRE, and 15% for cryotherapy [5]. Here, with a larger body of evidence, we obtained a similar pattern of efficacy outcomes between the sources of energy. The length of follow up also remains short which continues to challenge an assessment of the oncological effectiveness of focal therapies.

Seventy studies conducted per protocol biopsies. From these, I-125 FB showed the lowest rates of in-field and out-field recurrence. Recurrence after brachytherapy would be further reduced if presence of a radiation treatment effect in the biopsy specimen was not considered a recurrence. The strength of evidence, in terms of number of studies and study participants, was however lower for FB studies. Lower proportions of high-risk participants in the FB studies may account for the lower recurrence rates observed. Of note, exclusion of studies with high-risk men continued to show a similar pattern with median recurrence rates of 3%, 4%, 7%, and 12% for FB, cryotherapy, IRE, and HIFU, respectively (not shown).

Per protocol post-treatment control biopsies were taken from 6 months to 3 years post-ablation (in 26 studies within the first year and in 43 studies between year 1 and 3). These short-term measures of efficacy may need to be reconsidered once longer-term outcomes become available. Indeed, a number of studies abandoned 6-month biopsies due to very low incidences of significant disease. The FOCAL consensus has recommended control biopsies should be performed within the first 12 months post-treatment [14].

The impact of focal therapy on urinary, sexual, and bowel function was assessed by 51, 54, and 18 studies, respectively, that compared PROMs (IPSS, AUA-SS, IIEF-5, EPIC) before and after treatment (beyond an acute phase of 3 months). Urinary function was largely preserved, and in some instances improved. Only one study reported worse urinary function (increased IPSS) 6 months after focal/partial brachytherapy (N=30 patients), although it was significantly better than that seen in whole-gland implant controls (N=30 patients) [25]. Sexual function was more frequently negatively impacted but for the most part preserved; 65% (35/54) of studies reported no difference in sexual function (IIEF-5 and/or EPIC) relative to baseline. No study showed improvement in sexual function. Bowel function, although much less frequently assessed, was always preserved. Rectal spacers were used in one study [21].

For this review the impact of organ-at-risk function was defined by statistical significance. This may not necessarily translate into a clinically meaningful difference. The type of instrument used to quantify patient-reported symptoms may have a considerable bearing on outcome interpretation. For example, in three studies that reported a decline in sexual function there was discrepancy on statistical significance between SHIM and EPIC-SF scores at 3 years in 39 patients after HIFU [54], at 3 years in 50 patients after HIFU [74], and at 1 year on 50 patients after Cryotherapy [109]. The latter study showed the baseline score was the only significant predictor of sexual function scores after treatment. Larger study populations and longer-term follow up may be necessary to resolve these discrepancies.

Adverse event classification systems included Clavien-Dindo (38 studies), CTCAE (Common Terminology Criteria for Adverse Events) (14 studies), and RTOG (Radiation Therapy Oncology Group) morbidity scale (1 study). Adverse events were low across the 4 therapies. Two notable outliers were Duwe et al with 62% grade 2 GU events after HIFU [42] and Kim et al with 6.6% grade 2 GI events after FB [25]. The former used Clavien-Dindo and the latter the only study that used RTOG criteria for rectal toxicity. In both systems grade 2 indicates requirement for pharmacological treatment. Grade 3 GU and GI events were more frequent after HIFU but remained below 15% and 1% respectively. The timing of adverse event occurrence was only reported by one third of the studies.

In conclusion, the outcomes reported herewith on efficacy and function support findings from recent literature reviews and meta-analyses collectively comparing focal therapy approaches [5-11]. The real-world evidence suggests FB is more efficient at controlling localised PCa relative to HIFU, IRE, and Cryotherapy with a low impact on organ-at-risk function. However, considerable heterogeneity in study protocols preclude robust conclusions. Randomised comparisons between focal therapies, whole gland treatment, and active surveillance are needed to confirm the emerging consensus on a favourable therapeutic ratio of partial gland ablation.

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