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European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Andre Luis Abreu, Masatomo Kaneko, Giovanni E. Cacciamani and Amir H. Lebastchi on pp. 34–36 of this issue

An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years?

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Article info

Article history:
Accepted August 12, 2021

Associate Editor:
James Catto

Keywords:
Focal therapy
IDEAL
Prostate cancer

Abstract

Context: Focal therapy is a promising, minimally invasive strategy to selectively treat localized prostate cancer. A previous systematic review indicated that there is growing evidence for favorable functional outcomes, but that oncological effectiveness was yet to be defined.
Objective: To assess the effectiveness of focal therapy in patients with localized prostate cancer in terms of functional and oncological outcomes.
Evidence acquisition: PubMed, Embase, and The Cochrane Library were searched for studies between October 2015 and December 31, 2020. In addition, the research stages were acquired according to the Idea, Development, Exploration, Assessment, Long-term study (IDEAL) recommendations. Ongoing studies were identified through clinical trial registries.
Evidence synthesis: Seventy-two studies were identified exploring eight different sources of energy to deliver focal therapy in 5827 patients. Twenty-seven studies reported on high-intensity focused ultrasound (HIFU), nine studies on irreversible electroporation, 11 on cryoablation, eight on focal laser ablation and focal brachytherapy, seven on photodynamic therapy (PDT), two on radiofrequency ablation, and one on prostatic artery embolization. The majority of studies were prospective development stage 2a studies (n = 35). PDT and HIFU, both in stage 3, showed promising results. Overall, HIFU studies reported a median of 95% pad-free patients and a median of 85% patients with no clinically significant cancer (CSC) in the treated area. For PDT, no changes in continence were reported and a median of 90% of patients were without CSC. Both treatments were well tolerated.
Conclusions: 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.
Patient summary: Focal treatment (FT) of prostate cancer has potential, considering that it has less impact on continence and potency than radical treatment. Our systematic review indicates that despite the method being studied extensively over the past half decade, the majority of studies remain in an early research stage. The techniques high-intensity focused ultrasound and photodynamic therapy have shown most progression toward advanced research stages and show favorable results. However, more high-quality evidence is required before FT can become available as a standard treatment.

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https://doi.org/10.1016/j.eururo.2021.08.005

1. Introduction

For localized prostate cancer (PCa), active surveillance (AS) or whole gland treatment (ie, radical prostatectomy [RP] and radiotherapy) are considered standard treatment options [1,2]. However, both are associated with considerable morbidity, such as urinary incontinence, erectile dysfunction, and bowel dysfunction [3–5], contributing to decreased quality of life [3,6]. Moreover, these treatments do not necessarily improve patients' oncological outcome. The ProTecT trial has shown that the 10-yr cancer-specific survival for both RP and external beam radiotherapy for patients with low- and intermediate-risk PCa is similar to that of AS only [7]. However, AS was associated with a higher disease-progression rate and metastases. In order to improve the benefit to risk ratio, alternative therapies have been developed that aim to minimize adverse effects while maintaining a beneficial oncological outcome; focal therapy (FT) seems to be such a promising alternative.

FT aims to treat the part of the gland that harbors the index lesion, namely, clinically significant disease. Hereby, the adjacent critical structures are spared and thus morbidity is minimized. The rationale of FT is based on the theory that the lesion with the largest focus of cancer, the so-called "index lesion," determines the risk of metastases and thus the patient's prognosis [8,9]. According to consensus meetings, FT should be sought in patients with an intermediate risk of PCa; AS should be prioritized in men with low-risk disease in light of the lack of net benefit [10,11].

In the past decades, different types of energy sources in FT have been studied [12]. These consist of high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), cryotherapy, photodynamic therapy (PDT), focal laser ablation (FLA) or laser interstitial thermotherapy, radiofrequency ablation (RFA), and focal brachytherapy. A systematic review by Valerio et al [12] published in 2017 showed that FT is a safe treatment with encouraging results concerning cancer control and genitourinary function. However, the vast majority of the studies included in this review were early-stage studies (Idea, Development, Exploration, Assessment, Long-term study [IDEAL] stage $\leq$2b) [13]. It is worthwhile to investigate whether over the past half decade, studies on FTs show progression toward robust comparative studies (IDEAL stage $\geq$3).

The aim of this updated systematic review was to evaluate novel studies on FT for patients with localized PCa focusing on functional and oncological outcomes.

2. Evidence acquisition

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [14]. Its study protocol was registered in the PROSPERO database (CRD42020150781) [15].

2.1. Search strategy and selection criteria

The databases of PubMed (Medline), Embase, and The Cochrane Library were searched with "prostate cancer", "focal therapy", "ablation techniques", and the names of the energy sources. The search query is shown in the Supplementary material. We carried out the search for studies published from October 2015 to December 31, 2020, since Valerio et al [12] already performed a search up to October 2015. Current and future studies were searched in the clinical trial registries (ClinicalTrial.gov) up to January 31, 2021.

Studies were included if they reported on FT as the primary treatment and one of the following two endpoints: (1) functional outcome (eg, impotence and incontinence) and (2) oncological outcome (eg, postprocedural biopsy, prostate-specific antigen [PSA], and disease-free survival). Randomized controlled trials (RCTs), retrospective and prospective cohort studies, and single-arm studies were included. Case reports, review articles, and congress abstracts were excluded. Studies concerning salvage FT and whole gland treatment, and studies including patients who had undergone androgen deprivation therapy (ADT) or with metastatic disease were excluded. Two separate reviewers (J.H. and J.B.) screened the articles for eligibility using Rayyan software [16]. Discrepancies were discussed by the two reviewers. In case they did not agree, a third, senior author (J.F.) was asked for reaching consensus. In case studies reported on the same dataset ($\geq$50% overlap of sample size), we included the study with the longest follow-up and excluded the other. When the overlap was $<$50% of included patients, both studies were included and the possibility of duplication was mentioned in a table.

2.2. Data extraction form

From each study, the following data were extracted: (1) study design; (2) IDEAL stage; (3) type of FT; (4) type of ablation; (5) patient characteristics such as median age, retrieval of preoperative biopsy, imaging, PSA, Gleason score, and risk classification; (6) follow-up; (7) oncological outcomes (such as pre- and postprocedural PSA level, percentage of positive biopsies, biochemical recurrence [BCR], recurrence-free survival, and overall survival); (8) serious adverse events (SAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) [17] or Clavien-Dindo classification (grade $\geq$3) [18]; and (9) functional outcomes (patient-reported outcomes and questionnaire scores, percentages of leak- and pad-free continence, and erection sufficient for intercourse [ESI]). During data extraction, we used the definitions applied by the authors (eg, clinically significant cancer [CSC] and BCR).

2.3. IDEAL stages

We assessed all studies for their IDEAL stage. The IDEAL collaboration has provided a framework to evaluate research in surgery [13]. Stage 1 ("idea") describes the first use of a new procedure or proof of concept, usually in a very limited number of patients. Stage 2a ("development") describes the stage in which the innovation is further developed in small groups and assessed for safety. Stage 2b ("exploration") makes use of larger sample sizes and aims to provide an initial assessment of some clinical outcomes

(studies such as single-arm prospective cohort studies). Stage 3 ("assessment") describes the stage in which the intervention is assessed for effectiveness compared with current standards, ideally in an RCT. Stage 4 ("long-term study") concerns studies that aim to assess long-term outcomes, typically by using a registry. In case authors did not mention their IDEAL stage, the reviewers (J.H. and J.B.) assigned the corresponding IDEAL stage. In case of disagreement or doubt, a senior author (M.R.) was asked to reach consensus.

2.4. Data analysis

Continuous variables were presented either by mean and standard deviation (SD) or by median and range, as appropriate. The number of patients and percentages were given for categorical variables. In case the authors presented numbers instead of percentages on outcome measurements, percentages were calculated. For the denominator in this calculation, patients lost to follow-up or patients not undergoing a postprocedural biopsy were excluded. In case certain data could not be interpreted precisely from the manuscript, for instance, in case of a boxplot without exactly presenting mean (SD) or median (interquartile range), the corresponding author was asked to provide the additional data. In case of no response, we assigned "not interpretable" to the missing data. In a table, we present figures based on the definitions set by the authors (eg, CSC). In case of no disclosure concerning the postprocedural recurrence of cancer, the postprocedural Gleason scores were presented. In case this was not present, the data were assigned "not reported".

3. Evidence synthesis

Our search identified 8451 articles. After removal of duplicates, 5005 records were screened based on titles and abstracts. Based on this screening, 4787 articles were excluded, resulting in 218 articles. After full-text assessment for eligibility, 72 studies [19–90] were included in this systematic review. A PRISMA flowchart is depicted in Fig. 1 [14].

During full-text screening, we encountered a study by Guillaumier et al [91], which at first met our inclusion criteria, but was later excluded because we learned from the corresponding author that this study reported on the same patient population as the study by Huber et al [92] in which a pretreatment of ADT was provided. Therefore, the study of Guillaumier et al [91] was excluded, despite not specifically mentioning the use of ADT in their manuscript.

Eight different energy sources of FT were studied. Each energy source is explained in the Supplementary material (Box 1). Studies using HIFU as an energy source represented the majority of the included studies (n = 27). Nine studies reported on IRE, eight on FLA, seven on PDT, 11 on cryoablation, eight on focal brachytherapy, two on RFA, and one on prostatic artery embolization (PAE). One study [42] compared HIFU with cryoablation and was included for both HIFU and cryoablation. The majority of studies were prospective development studies in IDEAL stage 2a (n = 35), followed by stage 2b (n = 27), stage 1 (n = 4), and stage 4 (n = 1). One RCT on PDT (reported in two studies [73,74]), a feasibility RCT on HIFU, and two propensity-score matched analyses on IRE and HIFU were identified as IDEAL stage 3. The extracted data such as study characteristics, oncological outcomes, and functional outcomes are presented in Tables 1–3. Current studies on FT registered in Clinicaltrials.gov are presented in Table 4. We identified four studies reporting on a new treatment modality, that is, microwave ablation (MWA).

3.1. High-intensity focused ultrasound

Of the 72 studies reporting on FT, 27 (38%) evaluated HIFU, including a study that compared HIFU with cryoablation [42]. One study was considered IDEAL stage 1 study; the majority (n = 23) were considered stage 2 studies, of which 11 were in stage 2a and 12 in stage 2b. A propensity-score matched analysis comparing HIFU (n = 188) or cryoablation (n = 48) with robot-assisted radical prostatectomy (RARP; n = 472) and a feasibility RCT comparing HIFU with RP were considered to be in stage 3 [29,32]. One large retrospective study including 1032 patients [40] was stated to be in IDEAL stage 4. There were no RCTs assessing the effectiveness of HIFU. Most studies were single-arm, prospective cohort studies. Six studies compared HIFU with another treatment modality. Two studies, each with a different endpoint [26,45], were pooled analyses using data from three studies. One of these three studies [20] was included in this review as well. Some HIFU studies (n = 10) performed transurethral resection of the prostate (TURP) prior to HIFU treatment to prevent or reduce the risk of urinary retention or to improve treatment efficacy [22,27,31,37,43]. To study potential differences, we have reported the results separately.

3.1.1. HIFU with TURP

Ten studies (37%) included patients who had a TURP in the past or underwent TURP prior to HIFU [19,22,23,31,32,34,36,37,42,43]. The median age was 65.8 yr with a median PSA value of 6.3 ng/ml (range 5.5–8.2). The median follow-up was 25 mo (range 12–45). CSC in the treated area was reported by three studies to be 5% [37], 14% [19], and 22% [22]. Eight studies reported on SAEs and complications (median 1.9%, range 0–13.9%). Considering functional outcomes, a median of 95% of patients were pad free after treatment. Change in erectile function varied between studies, with one study reporting a 20% increase of erectile dysfunction [43] and another study reporting ESI returning to baseline after 1 yr [36]. One study [23] reported on the pre- and postprocedural use of phosphodiesterase type 5 (PDE-5) inhibitors, which increased from 6% to 17.4%.

3.1.2. HIFU without TURP

Seventeen studies (63%) performed HIFU without TURP as prior treatment. The patient population had a median age of 66 yr and a median PSA value of 6.95 ng/ml (5.1–8.3). The

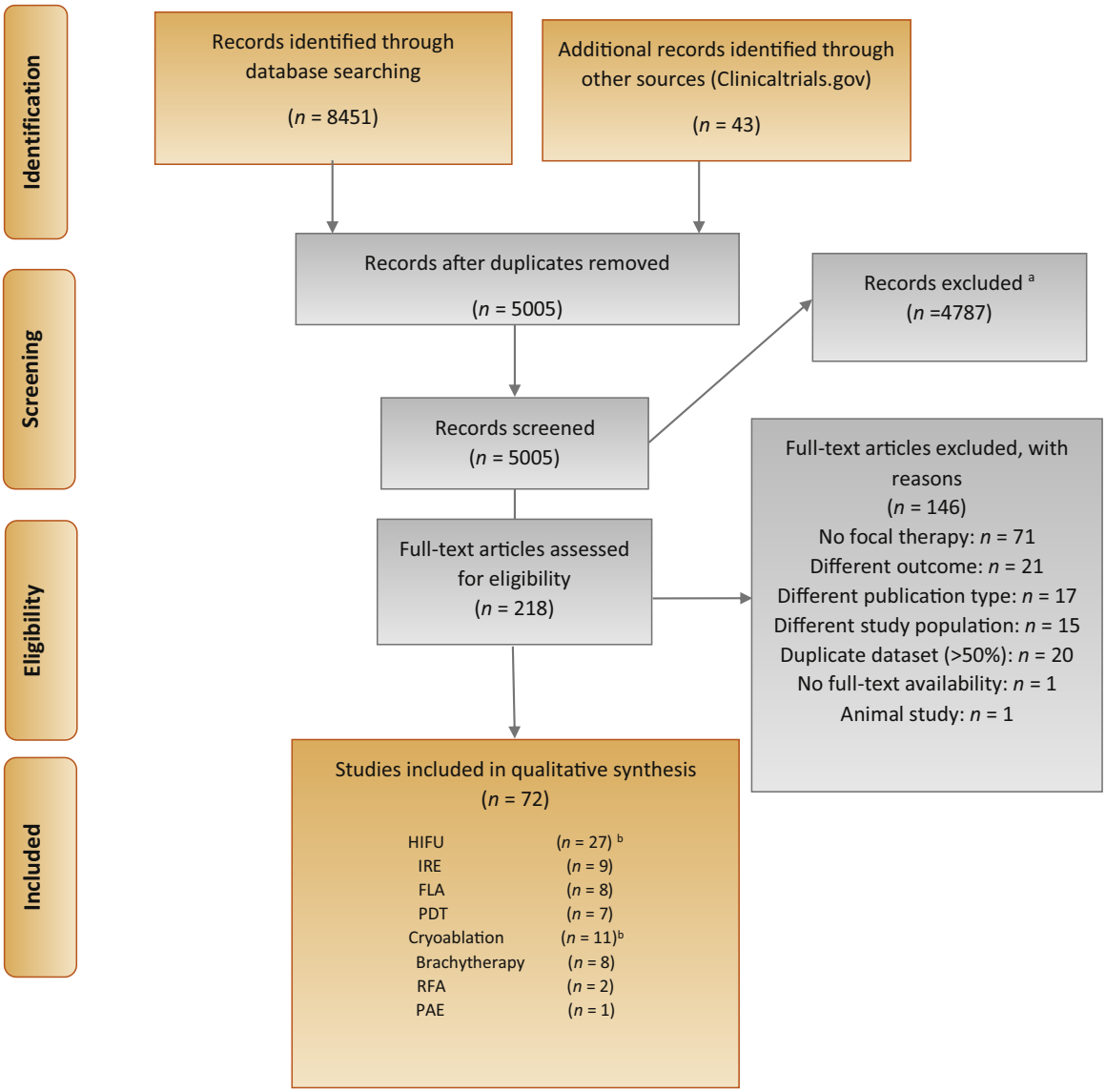

Fig. 1 – PRISMA flow diagram. FLA = focal laser ablation; HIFU = high-intensity focused ultrasound; IRE = irreversible electroporation; PAE = prostatic artery embolization; PDT = photodynamic therapy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RFA = radiofrequency ablation. [a] These consisted of records with other outcomes, other target population, and other publication types. [b] One study investigating HIFU and cryoablation was included in both the HIFU and the cryoablation group.

median follow-up was 12 mo (range 6–38). Nine of the 17 studies reported on CSC in the treated area with a median rate of 15.4%, range 0–21.8%). Eleven studies reported on complications with a median rate of 2% (range 0–4.8%). Six studies reported on the number of patients requiring a pad, with a median of 95.5% of pad-free patients. The studies reported a median decrease of erectile function of 12% (range 9.2–14%) and median ESI of 77.6% (range 44–86%). A median of 31.5% of patients used PDE-5 inhibitors after treatment, corresponding to a median increase of 17%.

3.2. *Irreversible electroporation*

The majority of IRE studies (n = 9) were prospective cohort studies. One by Scheltema et al [52] was a propensity-score matched analysis comparing IRE with RARP. This study was considered to be in IDEAL stage 3. The median sample size was 30 patients (range 12–123). The studies included low- and intermediate-risk patients with a median PSA value of 5.95 ng/ml (range 4.3–8.65). The median follow-up was 12 mo (range 7–36). CSC in the treated area was reported by four studies with a median rate of 8.5% (range 0–33%). The median percentage of pad-free patients after treatment was 100% (range 92–100%). Six studies reported a decrease in erectile function, with three (IDEAL stages 2a, 2b, and 3) reporting a "significant" decrease. The propensity matched analysis showed a higher number of pad-free patients in the IRE group (n = 96) than in the RARP group (n = 84), but this difference was not statistically significant. IRE was superior to RARP concerning preservation of ESI ($p < 0.05$) [52]. Regarding SAEs, four studies reported zero adverse events, and one study reported a myocardial infarction [53].

Table 1 – Characteristics of studies included in this review

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
FLA (*n* = 8)										
Al-Hakeem et al (2019) [55]	Prospective (development) study	2b	Focal ablation	Target and Sys	mpMRI	49	Median (range) 63 (51–73)	5.8 (3.1)	6: 13 (27) 3 + 4: 29 (59) 4 + 3: 7 (14)	cT1c-T2a
Barqawi et al (2015) [56]	Prospective (development) study	1	Focal ablation	Sys TTMB	mpMRI	7	62	Mean 5.05 ± 0.89	6: 7 (100)	NR
Chao et al (2018) [57]	Prospective (development) study	2a	Focal ablation	MRI guided	mpMRI	34	69 (range 52–88)	5.5 (2.4–9.5)	≤6: 16 (47) 3 + 4: 16 (47) 4 + 3: 2 (6)	NR
Eggener et al (2016) [58]	Prospective (development) study	2a	Focal ablation	NR	1.5 T MRI	27	62	4.4 (0.88–8.99)	6: 23 (85) 3 + 4: 3 (11) 4 + 3: 1 (4)	NR
Lepor et al (2015) [59]	Prospective (development) study	2a	NR	MRI guided	MRI	25	Median (range) 66 (49–84)	5.3 (range 2–9.4)	≤6: 11 (44) 3 + 4: 13 (52) 4 + 3: 1 (4)	NR
Natarajan et al (2016) [61]	Prospective (development) study	1	Focal ablation	MRI-US Target and Sys	mpMRI	8	Median 63	7.45	6: 1 7: 7	All intermediate risk
Natarajan et al (2017) [60]	Prospective (development) study	1	Focal ablation	MRI-US Target and template	mpMRI	11	Median 65	7.35	6: 2 7: 8	All intermediate risk
Walser et al (2019) [62]	Prospective (development) study	2b	Focal ablation	NR	mpMRI	120	Median (range) 64 (45–86)	6.05 (range 4.8–8.6)	3 + 3: 37 (30.8) 3 + 4: 56 (46.7) 4 + 3: 27 (22.5)	Low-intermediate risk
HIFU (*n* = 27)										
HIFU with TURP (n = 10)										
Abreu et al (2020) [19]	Retrospective cohort study	2b	Hemiablation	12-core Sys and Target	mpMRI	100 With TURP: 11 (11)	65 (59–70)	5.9 (4.5–7.2)	ISUP grade group: 1: 29 (29) 2: 55 (55) 3: 11 (11) 4: 5 (5)	Very low: 8 (8) Low: 20 (20) Intermediate favorable: 50 (50) Intermediate unfavorable: 17 (17) High: 5 (5)
Annoot et al (2019) [22]	Retrospective cohort study	2a	Hemiablation	TRUS and MRI Target	mpMRI	55 With TURP: NR	63	6.18 (3.72–8.64)	3 + 3: 24 (44): 7: 31 (56)	NR
Arnouil et al (2018) [23]	Retrospective cohort study	2b	Focal and hemiablation	NR	mpMRI	HIFU: 53 With TURP: NR RP: 66	HIFU: 65.11 (6.08) RP: 60.53 (5.51)	Mean (SD): HIFU: 6.32 (2.68) RP: 5.55 (2.08)	HIFU; RP: 3 + 3: 40 (75); 39 (59) 3 + 4: 10 (19); 27 (41) 4 + 3: 3 (6); 0 (0)	HIFU; RP: Low: 33 (62); 37 (56) Intermediate: 20 (38); 29 (44)
Glybochko et al (2019) [31]	Retrospective case series	2a	Hemiablation	TRUS/TTMB	CE MRI	35 With TURP: 15 (42)	65	7.8	≤7	NR
Hamdy et al (2018) [32]	Prospective, multicenter feasibility RCT study	3	Dog-leg, quadrant, & hemiablation	Target or template	mpMRI	HIFU 41 With TURP: NR RP: 41	Median (range): HIFU: 66.4 (54.2–78.2) RP: 65.5 (48.4–76.9)	Median (range): HIFU: 7.7 (2.5–17.1) RP: 6.90 (2.4–16.2)	Both arms: 3 + 4: 32 (78) 4 + 3: 8 (19.5) High-volume 6: 1 (2.4)	Intermediate

Table 1 (*Continued*)

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
Lei et al (2019) [34]	Retrospective cohort study	2b	Combination	Sys TRUS	mpMRI	12 (total cohort with WG *n* = 86) With TURP: 2 (16.7)	Zonal: 68.67 ± 6.93	Zonal: 8.23 ± 4.96	≤6: 4 7a: 6 7b: 2 ≥8: 0	Zonal: Low: 2 (16.7) Intermediate: 10 (83.3) High: 0 (0)
Nahar et al (2020) [36]	Prospective cohort study	2b	Focal, hemi, quadratic, or subtotal	12-core template + target	mpMRI	52 HIFU + TURP: 15 (28.8)	67.2 (7.6)	Median (range): 5.5 (1.6–25.9)	ISUP grade group: 1: 17 (32.7) 2: 24 (46.2) 3: 6 (11.5) 4: 3 (5.8) 5–10: 2 (3.8)	NR
Rischmann et al (2017) [37]	Prospective (development) study	2b	Hemiablation	Random and Target	mpMRI	111 With TURP: 67 (60.4)	64.8 ± 6.2	Mean 6.2 ± 2.5	≤6: 82 (74) 7: 29 (26)	NR
Tourinho-Barbosa et al (2020) [42]	Retrospective cohort study	2b	Focal ablation	Sys and Target TP	mpMRI	HIFU: 190 With TURP: NR Cryo: 119	Median (IQR): 68 (62–73)	7.1 (5.5–9.0)	3 + 3: 130 (68) 3 + 4: 56 (29) 4 + 3: 4 (2.1)	Low: 103 (54) Intermediate: 87 (46)
van Velthoven et al (2016) [43]	Prospective (development) study	2a	Hemiablation	NR	mpMRI	50 With TURP: 50 (100)	Median (IQR): 74 (70–77)	6.3 (3.9–8.3)	3 + 3: 30 (60) 3 + 4: 14 (28) 4 + 3: 6 (12)	Low: 24 (48) Intermediate: 26 (52)
HIFU without TURP (n = 17)										
Ahmed et al (2015) [20]	Prospective (development) study	2a	Combination	TPM and/or TRUS	mpMRI	56	64 (5.8)	7.4 (5.6–9.5)	3 + 3: 17 (37) 3 + 4: 25 (54.3) 4 + 3: 4 (8.7)	Low: 7 (12.5) Intermediate: 47 (83.9) High: 2 (3.6)
Albisinni et al (2017) [21]	Retrospective cohort study	2a	Hemiablation	NR	mpMRI	110	73 (7)	6.9 (4.5–9.4)	<6: 36 (65) 3 + 4: 13 (24) 4 + 3: 4 (7) >8: 2 (4)	Low: 26 (47) Intermediate: 26 (47) High: 3 (6)
Bacchetta et al (2020) [24]	Retrospective cohort study	2b	Focal/hemi/ hockey stick ablation	TTMB or TR saturation biopsy	mpMRI	32	Median (IQR): 69.0 (63–73)	7.2 (5.3–8.4)	3 + 3: 14 (42) 3 + 4: 13 (39) 4 + 3: 5 (15) 4 + 4: 1 (3)	NR
Bass et al (2019) [25]	Retrospective case series	2a	Combination	Sys and Target	mpMRI	150	65.2 (7.5)	6.4 (4.2–9.1)	3 + 3: 19 (11.5) 3 + 4: 89 (15.7) 4 + 3: 43 (25.9) 4 + 4: 12 (7.2) 4 + 5: 1 (0.6) Unknown: 2 (1.2)	Low-intermediate risk
Dickinson [b] et al (2017) [26]	Prospective (development) study	2b	Combination	NR	mpMRI	118	62.9 (range 48–77)	6.8 (5.7–9.4)	3 + 3: 31 (28) 3 + 4: 71 (64) 4 + 3: 9 (8)	NR
Feijoo et al (2016) [27]	Prospective (development) study	2a	Hemiablation	TRUS	mpMRI	71	70.2 (6.8)	6.1 (1.6–15.5)	3 + 3: 58 (86.6) 3 + 4: 9 (13.4)	NR
Ganzer et al (2018) [28]	Prospective (development) study	2b	Hemiablation	Sys TRUS	mpMRI	54	63.4 (8.3)	Mean 6.2 ± 2.1	Median (range) 3 + 3 (3 + 3 = 6 – 3 + 4 = 7)	NR

Table 1 (*Continued*)

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
Garcia-Barreras et al (2018) [29]	Propensity-score matched analysis	3	Hemiablation	TTMB	mpMRI	RARP: 472 PGA: 236	RARP: 65.10 ± 4.36 PGA: 68.28 ± 7.7	RARP: 6.99 ± 2.74 PGA: 7.12 ± 2.53	RARP; PGA: 3 + 3: 355 (75.2); 188 (79.7) 3 + 4: 117 (24.8); 48 (20.3)	NR
Ghai et al (2018) [30]	Prospective (development) study	1	Focal ablation	Sys TRUS	mpMRI	8	62 (51–68)	Mean 5.06 (0.91–8.77)	6: 6 3 + 4: 2 4 + 3: 2	Low-intermediate risk
Johnston et al (2019) [33]	Prospective (development) study	2b	Combination	TTMB	mpMRI	107	Mean (range): 66 (47–81)	Mean (range): 7.7 (1.2–26.2)	3 + 3: 32 (30) 3 + 4: 60 (56) 4 + 3: 14 (13) 4 + 4: 1 (1)	Low: 12% Intermediate: 66% High: 22%
Mortezavi et al (2019) [35]	Prospective (development) study	2a	Focal ablation	TP template saturation	mpMRI	75	Median (IQR): 67 (60–71)	5.87 (4.65–7.44)	3 + 3: 6 (8.0) 3 + 4: 53 (70.7) 4 + 3: 16 (21.3)	Low: 5 (6.7) Intermediate: 70 (93.3)
Rosenhammer et al (2019) [38]	Prospective (development) study	2a	Focal ablation	Target and Sys 12 cores	mpMRI	21	Median (IQR): 68 (62.0–73.0)	8.3 (6.2–10.2)	3 + 3: 15 3 + 4: 2 4 + 3: 4	Low: 12 (57.1) Intermediate: 8 (38.1) High: 1 (4.8)
Shoji et al (2020) [39]	Prospective (development) study	2b	Focal	Target and Sys TP	mpMRI	90	Median (range): 70 (39–85)	7.26 (range 2.48–19.95)	3 + 3: 46 (51) 3 + 4: 18 (20) 4 + 3: 14 (16) 4 + 4: 12 (13)	Low: 31 (34) Intermediate: 44 (49) High: 15 (17)
Stabile et al (2019) [40]	Retrospective cohort study	4	Combination	Sys TRUS, TTMB, Target, and Sys	mpMRI	1032	65 (IQR 60–70)	7 (4.9–9.7)	3 + 3: 203 (19.7) 3 + 4: 654 (63.4) 4 + 3: 159 (15.4) 4 + 4: 16 (1.6)	NR
Tay et al (2017) [41]	Prospective (development) study	2a	Focal ablation	TTMB	mpMRI	14	62.8 ± 4.6	Mean 8.3 ± 4.0	3 + 3: 14 (100)	Low grade
Westhoff et al (2021) [44]	Prospective multicenter study	2a	Focal	NR	mpMRI	48	68.0 (7.9)	NR	3 + 3: 26 (54.2) 3 + 4: 17 (35.4) ≥4 + 3: 5 (10.4)	NR
Yap [b] et al (2016) [45]	Pooled analysis	2b	Combination	TTMB or TR	mpMRI	118	Median (IQR): 63 (52–70)	6.8 (5.6–9.3)	3 + 3: 33 3 + 4: 73 4 + 3: 12	NR
Focal brachytherapy (*n* = 8)										
Fischbach et al (2020) [80]	Prospective (development) study	2a	Focal	Target MRIguided and random	mpMRI	9	65 (range 56–76)	9 (range 3.5–15.9)	3 + 3: 4 (44) 3 + 4: 4 (44) 4 + 3: 1 (12)	Low to intermediate risk
Graff et al (2018) [81]	Prospective (development) study	2a	Focal ablation	MRI-TRUS fusion Target and Sys	mpMRI	17	63 (8.2)	5.6	3 + 3: 13 (76) 3 + 4: 4 (24)	NR
Kim et al (2020) [82]	Retrospective cohort study	2a	Combination	NR	mpMRI	30 (focal/partial) 30 (WG)	Median (IQR) F/P: 68.0 (59.8–76.5) WG: 64.5 (59.8–75.3)	F/P: 7.6 (5.5–10.3) WG: 5.9 (4.7–10.9)	ISUP: F/P; WG: 1: 17 (56.7); 13 (43.3) 2/3: 11 (36.7); 14 (46.7) 4: 2 (6.7); 3 (10.0)	F/P; WG: Low: 10 (33.3); 4 (13.3) Intermediate: 18 (60.0); 23 (76.7) High: 2 (6.7); 3 (10.0)

Table 1 (*Continued*)

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
Langley et al (2020) [83]	Prospective (development) study	2a	Hemiablation	TTMB	mpMRI	30	65.6 (7.6)	Mean (SD): 6.7 (3.1)	3 + 3: 5 (17) 3 + 4: 21 (70) 4 + 3: 4 (13)	cT1c: 16 (53.3) cT2a: 6 (20) cT2b: 7(23.3) cTx: 1 (3.3)
Mahdavi et al (2017) [84]	Prospective (development) study	2a	Focal ablation	TRUS and TTMB	mpMRI	5	NR	NR	3 + 3: 3 (60) 3 + 4: 2 (40)	NR
Peters et al (2019) [85]	Prospective (development) study	2a	Focal ablation	TRUS, MRI guided	mpMRI	30	Median (IQR): 71 (68–73)	7.3 (5.2–8.1)	3 + 3: 16 (53) 3 + 4: 12 (40) 4 + 3: 2 (7)	Low: 4 (13) Intermediate: 26 (87)
Prada et al (2020) [86]	Prospective (development) study	2a	Focal or Hemiablation	NR	mpMRI	50	67 (range 52–81)	6 (1.9–13.4)	≤GS6: 31 (62) 7: 19 (38)	cT1c: 39 (78) cT2a: 11 (22)
Srougi et al (2017) [87]	Retrospective cohort study	2b	Index lesion ablation	TTMB	MRI	28 (apex) 13 (base)	Median (IQR): Apex: 63 (50–79) Base: 61 (55–68)	Mean ± SD: Apex: 7.0 ± 2.1 Base: 7.8 ± 3.0	Apex; base: ≤GS6: 21 (75); 12 (92) GS7: 7 (25); 1 (8)	Apex; base: cT1c: 23 (82); 11 (84) cT2a: 5 (18); 2 (16)
IRE (*n* = 9)										
Blazevski et al (2020) [46]	Prospective (development) study	2b	Index lesion ablation	TTMB ± mpMRI Target	mpMRI	123	Median (IQR): 68 (62–73)	5.725 (3.8 8.0)	3 + 3: 12 (10) 3 + 4: 88 (72) 4 + 3: 23 (19)	Low: 11 (9) Intermediate: 112 (91)
Collettini et al (2019) [47]	Prospective (development) study	2a	Focal ablation	TTMB, MRI-US fusion, TRUS (≥10 cores)	mpMRI	30	Median (IQR): 65.5 (60–68.8)	8.65 (5–11)	3 + 3: 7 (23) 3 + 4: 4 (24)	Low: 4 (13) Intermediate: 26 (87)
Enikeev et al (2020) [48]	Prospective (development) study	2a	Focal ablation	Target MRI fusion and Sys	MRI	12	64 (8.4)	Mean 6.8 ± 1.8	3 + 3: 11 (92) 3 + 4: 1 (8)	NR
Giganti et al (2019) [49]	Retrospective cohort study	2a	Focal ablation	NR	mpMRI	30	Median (IQR): 63 (60–67)	6.4 (5–8.8)	3 + 3: 7 (23) 3 + 4: 20 (67) 4 + 3: 3 (10)	NR
Murray et al (2016) [50]	Prospective (development) study	2a	Focal ablation	Target and Sys (≥12 cores) TRUS	mpMRI	27	Median (IQR): 63.1 (59.3–67.6)	4.3 (3.3–5.6)	3 + 3: 18 (72) 3 + 4: 6 (24) 4 + 3: 1 (4)	Low: 18 (72) Intermediate: 7 (28)
Scheltema et al (2018) [51]	Prospective (development) study	2a	Focal ablation	TTMB	mpMRI	60	68 (7.0)	5.9 (3.6–7.6)	3 + 3: 8 (13) 3 + 4: 40 (67) 4 + 3: 10 (17) ≥4 + 4: 2 (3)	cT1c: 3 (5) cT2a: 40 (67) cT2b: 7 (12) cT2c: 10 (17)
Scheltema et al (2018) [52]	Propensity-score matched analysis	3	Focal ablation	TR or TP	mpMRI	IRE: 50 RARP: 50	Median (IQR): IRE: 67 (62–73) RARP: 67 (64–71)	IRE: 5.9 (3.3–7.3) RARP: 6.3 (4.3–7.7)	ISUP: IRE; RARP: 1: 8 (16); 9 (18) 2: 33 (66); 31 (62) 3: 9 (18); 10 (20)	IRE; RARP: cT1c: 37 (74); 34 (68) cT2a: 12 (24); 14 (28) cT2b: 1 (2); 2 (4)
Ting et al (2016) [53]	Prospective (development) study	2a	Focal ablation	TTMB, MRI fusion/gantry biopsy, & TRUS	mpMRI	25	Median (IQR): 67 (60–71)	6.0 (4.3–8.6)	3 + 3: 2 (8) 3 + 4: 15 (60) 4 + 3: 8 (32)	Low: 2 (18) Intermediate: 23 (82)
Valerio et al (2017) [54]	Prospective (development) study	2a	Focal ablation	TTMB	mpMRI	19	Median (IQR): 60 (53–66)	7.75 (5.5–10.03)	3 + 3: 8 (42.1) 3 + 4: 11 (57.9)	Low: 7 (36.8) Intermediate: 12 (63.2)
Cryotherapy (*n* = 11)										

Table 1 (*Continued*)

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
Basourakos et al (2020) [63]	Prospective (development) study	2a	Focal	MRI/TRUS fusion Target and 12-core Sys	mpMRI	55	Median (IQR): 70 (63.4–75)	6.6 (7.7–9.2)	ISUP: 2: 32 (58.18) 3: 13 (23.64) 4: 7 (12.73) 5: 3 (5.45)	NR
Bossier et al (2020) [64]	Retrospective cohort study	2b	Combination	Sys and Target	mpMRI	Hemi: 26 WG: 40	Median (range): Hemi: 76 (71–80) WG: 74 (42–81)	Median (range): Hemi: 7.9 (3.3–11.9) WG: 6.7 (1.2–11.6)	GS: Hemi; WG: ≤3 + 3: 33%; 31% 7: 67%; 69%	Hemi; WG: Low: 15%; 20% Intermediate: 85%; 80%
Chuang et al (2020) [65]	Prospective (development) study	2b	Hemiablation	Sys and Target MRI/US fusion	mpMRI	61	Median (IQR): 69 (65–73)	6.6 (4.8–10)	ISUP: 2: 40 (66) 3: 15 (25) 4: 6 (10)	NR
Kongnyuy et al (2018) [66]	Retrospective cohort study	2b	Hemiablation	NR	NR	104	Median (IQR): 66 (62–78)	6.5 (4.7–8.1)	3 + 3: 44 (42.3) 3 + 4: 33 (31.7) 4 + 3: 19 (18.3) ≥4 + 4: 8 (7.7)	Low: 41 (39.4) Intermediate: 53 (51.0) High: 8 (7.6)
Kongnyuy et al (2017) [67]	Retrospective cohort study	2b	Hemiablation	NR	NR	163	Median (IQR): 72 (67–78)	6.2 (4.3–7.8)	≤3 + 3: 75 (46) 3 + 4: 43 (26) 4 + 3: 13 (8) ≥4 + 4: 8 (5) Missing: 24 (15)	Low: 85 (52) Intermediate: 67 (41) High: 11 (7)
Mendez et al (2015) [68]	Retrospective cohort study	2b	Combination	NR	NR	Focal: 317 WG: 317	Focal: 66.5 (6.608) WG: 66.5 (6.608)	Focal; WG: <4: 62 (20); 60 (19) 4–≤10: 255 (80); 257 (81)	Focal; WG: <7: 317 (100); 317 (100)	All low-risk
Shah et al (2019) [69]	Prospective (development) study	2b	Focal ablation	TTMB, TRUS	mpMRI	122	Median (IQR) 68.7 (64.9–73.8)	10.8 (7.8–15.6)	3 + 3: 12 (9.8) 3 + 4: 89 (73) 4 + 3: 19 (15.6) 4 + 4: 2 (1.6)	cT2a: 32 (26.2) cT2b: 3 (2.5) cT2c: 60 (49.2) cT3a: 13 (10.7) cT3b: 9 (7.4) Missing: 5 (4.1)
Sze et al (2019) [70]	Retrospective cohort study	2a	Focal ablation	Target and Sys and/or TTMB	mpMRI	17	NR	8.7 (6.7–11.76)	ISUP: 1: 12(71) 2: 5(29)	NR
Tourinho-Barbosa et al (2020) [42]	Retrospective cohort study	2b	Focal ablation	Sys and Target TP	mpMRI	HIFU: 190 Cryo: 119	Median (IQR) 66 (62–71)	6.5 (5.0–8.3)	3 + 3: 91 (76) 3 + 4: 28 (24) 4 + 3: 0(0)	Low: 79 (66) Intermediate: 40 (34)
Werneburg et al (2018) [71]	Prospective cohort study	2b	Hemiablation	TRUS	NR	Focal: 89 WG: 38 AS: 68	Focal: 69 WG: 68 AS: 66	Focal + WG: 6.1 AS: 5.0	Focal: <7: 37; 7: 39; ≥8: 12 WG: <7: 11; 7: 15; ≥8: 12 AS: <7: 53; 7: 11; ≥8: 0	NR
Wysock et al (2021) [72]	Prospective development study	2b	Focal ablation	Target and Sys 12 cores	mpMRI	83	Median (IQR): 64 (59–70)	6.18 (4.6–7.8)	ISUP: 1: 9 (11) 2: 51 (61) 3: 23 (28)	NR

Table 1 (*Continued*)

Reference	Study design	IDEAL stage	Type of ablation	Biopsy	Imaging	Patients (*n*)	Age (yr), mean (SD)	Preprocedural PSA (ng/ml), median (IQR)	Gleason, *n* (%)	Risk stratification, *n* (%)
PDT (*n* = 7)										
Azzouzi et al (2017) [73]	Prospective (development) study	3	Hemiablation	TRUS	mpMRI in PDT group	PDT: 206 AS: 207	PDT: 64.2 (6.7) AS: 62.9 (6.7)	Mean (SD): PDT: 6.2 (2.1) AS: 5.9 (2.0)	3 + 3: PDT: 206 (100) AS: 207 (100)	cT1a: PDT: 1 (<1); AS: 0 (0) cT1c: PDT: 177 (84); AS: 180 (87) cT2a: PDT: 28 (14); AS: 27 (13)
Gill [a] et al (2018) [74]	Prospective (development) study	3	Hemiablation	TRUS	mpMRI	PDT: 147 AS: 119	NR	NR	NR	NR
Lebdai et al (2017) [75]	Prospective (development) study	2b	Combination	NR	mpMRI	Hemi: 61 Subtotal: 21	Median (range): 63 (51–76)	6.1 (range 1.3–10)	2 + 3: 1 (1) 3 + 2: 4 (5) 3 + 3: 77 (94)	cT1c: 75 (91) cT2a: 7 (9)
Noweski et al (2019) [76]	Prospective (development) study	2b	Hemiablation	NR	NR	68	62.6 (5.6)	5.7	6 (100)	NR
Rastinehad et al (2019) [77]	Prospective (development) study	2a	Focal ablation	MRI/US fusion	mpMRI	16	58–79	6.7	<4 + 3	≤T2a
Rodriguez-Rivera et al (2018) [78]	Prospective (development) study	2b	Focal ablation	TTMB	NR	81	65.3 (7.38)	8.69 (5.68)	3 + 3: 69 (85.2) 3 + 4: 12 (14.8)	Low: 64 (79) Medium: 17 (21)
Taneja et al (2016) [79]	Prospective (development) study	2a	Hemiablation	12-core TR	mpMRI	30	61.6 (7.8)	NR	6 (100)	cT1c: 26 (86.7) cT1cN0Mx: 1 (3.3) cT2a: 3 (10)
RFA (*n* = 2)										
Aydin et al (2020) [88]	Prospective (development) study	2a	Focal	TP mapping	mpMRI	10	Median (range): 58 (50–64)	Range 2.9 – 7.56	3 + 3: 7 (70) 3 + 4: 3 (30)	cT1c: 10 (100)
Orczyk et al (2021) [89]	Prospective (development) study	2a	Focal	TP	mpMRI	20	Median (IQR): 66 (63–69)	7.9 (5.3–9.6)	3 + 3: 2 (10) 3 + 4: 17 (85) 4 + 3: 1 (5)	Low: 2 (10) Intermediate: 18 (90)
PAE (*n* = 1)										
Frandon et al (2021) [90]	Prospective (development) study	2a	Focal	Target & Sys	mpMRI	10	Median (range): 72 (62–77)	Median (range): 6.22 (3.28–10.14)	3 + 3: 10 (100)	cT1c: 5 (50) cT2a: 5 (50)

AS = active surveillance; CE = contrast enhanced; Cryo = cryotherapy; FLA = focal laser ablation; F/P = focal/partial; GS = Gleason score; Hemi = hemiablation; HIFU = high-intensity focused ultrasound; IDEAL = Idea, Development, Exploration, Assessment, Long-term study; IQR = interquartile range; IRE = irreversible electroporation; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; PAE = prostatic artery embolization; PDT = photodynamic therapy; PGA = partial gland ablation; PSA = prostate-specific antigen; RARP = robot-assisted radical prostatectomy; RCT = randomized controlled trial; RFA = radiofrequency ablation; RP = radical prostatectomy; SD = standard deviation; Sys = systematic; Target = targeted; TP = transperineal; TPM = template prostate mapping; TR = transrectal; TRUS = transrectal ultrasound; TTMB = transperineal template mapping biopsy; TURP = transurethral resection of the prostate; US = ultrasound; WG = whole gland.

Data from Tourinho-Barbosa et al [42] are presented in HIFU as well as cryoablation. Functional outcomes were not separately reported and are therefore a sum of these two groups.

Werneburg et al [71] and Kongnyuy et al [66] may report on the same participants, but Werneburg et al [71] describe functional outcomes, whereas Kongnyuy et al [66] report oncological outcomes.

[a] Gill et al [74] report on (long-term) data originally retrieved by Azzouzi et al [73].

[b] Contains data from Ahmed et al [20], but <50% overlap.

Table 2 – Follow-up and oncological outcome parameters

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
FLA (*n* = 8)																	
Al-Hakeem et al (2019) [55]	18	NR	0	MRI at 3 + 12 mo	NR	6 mo: MRI or MRI/US Target + Sys biopsy	NR	40/49 (82)	10/49 (20)	9/49 (18)	9/49 (18)	1/49 (2)	NR	NR	RP: 5 EBRT: 1 FLA: 1 AS: 3	NR	NR
Barqawi et al (2015) [56]	12	1/7	<1	3 T MRI	NR	TRUS		3/7	4/7 (T1c)	NR	NR	NR	Mean 3.94 ± 1.68	NR	NR	NR	NR
Chao et al (2018) [57]	24	2	NR	mpMRI	8/32 (25)	Target MRI-guided biopsy	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eggener et al (2016) [58]	12	NR	<1	MRI at 3 + 12 mo	0 (12 mo)	MRI-guided biopsy	NR	NR	3 (11) (3 + 3: 2; 3 + 4: 1)	NR	8 (30) (3 + 3: 7; 7: 1)	NR	Mean 3.4 ± 2.2	NR	RP: 1	NR	NR
Lepor et al (2015) [59]	3	0	NR	MRI at 3 mo	NR	4-core MRI-guided biopsies	NR	26/28 (96)	2/28 sites (4)	1 (4)	NR	NR	Mean 2.9	NR	NR	NR	NR
Natarajan et al (2016) [61]	6	0	6 h	mpMRI at 6 mo	NR	MRI-US biopsy	5/8 absence of any cancer		3/8 (3 + 3: 1; 3 + 4: 2)	NR	6/8 (3 + 3: 3; 3 + 4: 2; 4 + 4: 1)	NR	3.3	NR	NR	NR	NR
Natarajan et al (2017) [60]	6	1 Jul	1–2 h	3 T mpMRI at 6 mo	NR	MRI-US biopsy	NR	6/10 (60)	7/10 (3 + 3: 3; 7: 4)	4/10 (40)	NR	NR	2.55	NR	NR	NR	NR
Walser et al (2019) [62]	34	NR	NR	mpMRI	44/120	In-bore MRI guidance	NR	102/120 (85)	22/120 (18.3) (3 + 3: 4)	18/120 (15)	NR	NR	3.91 (2.36–6.46)	NR	RP: 2 (2)	NR	NR
HIFU (*n* = 27)																	
HIFU with TURP (n = 10)																	
Abreu et al (2020) [19]	Median (IQR): 20 (13–29)	NR	NR	mpMRI at 6 + 12 mo	18/61 (30)	6–12 mo: 12-core Sys +Target biopsy	32/58 (55) had cancer on biopsy		10/58 (17)	8/58 (14)	23/58 (40)	10/58 (17)	Nadir 1.3 (0.7–2.6)	2 yr: 8 (Phoenix)	NR	2 yr: 73	100
Annoot et al (2019) [22]	33	NA	NR	mpMRI at 12 mo	42/54 (78)	12 Sys biopsy and MRI Target biopsy		NR	NR	12/55 (22)	10/55 (18)	1/55	NR	NR	RP: 10/55 (18.2)	NR	100
Arnouil et al (2018) [23]	12	HIFU:2 RP: 4	NR	mpMRI	13/53 (25)	Biopsy	16/51 (30%) positive biopsy 11/51 CSC	NR	NR	NR	NR	NR	Mean: HIFU: 2.25 RP: 0.01	NR	HIFU; RP: RP: 1; 0 HIFU: 5; 0 EBRT: 2; 1	NR	NR
Glybochko et al (2019) [31]	12	NR	4	CE MRI at 6 mo	0	12 mo: NR		NR	0/35 (at 6 mo)	NR	4/35 (at 12 mo)	NR	NR	NR	NR	NR	NR
Hamdy et al (2018) [32]	36	NR	RP: 1 HIFU: 0	mpMRI at 2 wk, 12 mo, 36 mo	HIFU 2 wk: 1/7 (14)	HIFU: 12 + 36 mo: transrectal biopsy		NR	NR	NR	NR	NR	NI	NR	NR	NR	NR

Table 2 (*Continued*)

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
Lei et al (2019) [34]	12	NR	NR	mpMRI at 6 + 12 mo	Zonal: 3/12	12 mo: systematic biopsy	Absence of cancer 9 (75.0)	NR	NR	NR	NR	NR	Zonal: 2.42 ± 1.49	NR	NR	NR	NR
Nahar et al (2020) [36]	12	NR	0–1	MRI at 6 + 12 mo		6 + 12 mo: MRI/US fusion biopsy	NR	NR	5/30 (16.7)	NR	4/30 (13.3)	NR	12 mo: mean 2.23	NR	RP: 1	NR	100
Rischmann et al (2017) [37]	30	0	NR	mpMRI at 12 mo	NR	12 mo: 12-core random core & mpMRI Target biopsies		96/101 (95)	12 (12)	5/101 (5)	19 (19)	7/101 (7)	Mean 2.3 ± 1.7	NR	RP: 6 EBRT: 3	NR	98
Tourinho-Barbosa et al (2020) [42]	45	NR	NR	mpMRI at 1 & 12 mo	NR	12 mo: Sys 12-core TP biopsy	64/174 (37) (3 + 3: 24; 3 + 4: 29; 4 + 3: 8)	NR	57 (30)	NR	32 (17)	NR	Nadir 2.6 (1.4–4.5)	NR	WG: 3 (1.6) RP: 8 (4.2) RT: 30 (16) ADT: 7 (3.7)	52 (43–61)	NR
van Velthoven et al (2016) [43]	40	NR	NR	NR	NR	Only in case of increased PSA biopsy	6/8	NR	1/8 unilateral, 2/8 bilateral	NR	3/8	NR	Nadir 0.91 ± 2.1	14 (28)	RT: 3	58	87
HIFU without TURP (n = 17)																	
Ahmed et al (2015) [20]	12	NR	<1 d	mpMRI	NR	6 mo: Target TRUS biopsy		44/52 (84.6)	34/52 (65.4) (3 + 3: 12; 3 + 4: 5; 4 + 3: 1)	8/52 (15.4)	4/52 (7.7) (3 + 3: 3; 4 + 4: 1)	2/52 (3.8)	2.4 (1.6–4.1)	NR	NR	NR	100
Albisinni et al (2017) [21]	24	NR	NR	NR	NR	Type NR	2/7 recurrence, 5/7 bilateral disease (3 + 3: 2; 3 + 4: 2; 4 + 3: 2; 4 + 4: 1	NR	2/7	NR	NR	7/55 (13)	NR	NR	7/55	NR	90
Bacchetta et al (2020) [24]	NR	NR	NR	mpMRI	NR	Sys + Target biopsy when clinical suspicion	NR	NR	18 (54)	10 (30)	NR	NR	NR	NR	NR	NR	NR
Bass et al (2019) [25]	24	NR	NR	MRI at 12 mo	64 (56.1)	15 mo: MRI Target biopsies 15 mo	61/87 (70) 3 + 3: 24; 3 + 4: 23; 4 + 3: 9; 4 + 4: 4; 4 + 5: 1	NR	NR	19/87 (21.8)	NR	16/87 (18)	NR	NR	37 (25)	NR	NR
Dickinson et al (2017) [26]	12	NR	NR	MRI at 48 u + 6 mo	38/109 (35)	6 mo: cognitive targeting only treated area		71/111 (64)	41/111 (37)	21/111 (19)	NR	NR	2.0 (1.0–3.4)	NR	NR	NR	NR
Feijoo et al (2016) [27]	12	4/71 (5.6)	NR	NR	NR	12 mo: TRUS		56/67 (83.6)	11/67 (incl. 1 bilateral)	NR	6/67 (9)	NR	3.8 (2.0–5.7)	6 (9.7)	NR	NR	NR
Ganzer et al (2018) [28]	17	3	2	mpMRI at 12 mo	8/48 (16.6)	12 mo: Sys 12-core biopsy		45/49 (91.8)	13/49 (26.5)	4/49 (8.2)	17/49 (34.7)	1 (2.0)	Mean 2.9 ± 1.9	NR	10 (19.6)	NR	NR
Garcia-Barreras et al (2018) [29]	12	0	RARP: 4.29 (1.7) PGA: 2.69 (1.23)	mpMRI at 12 mo	NR	12 mo: TTMP		203/236 (86)	51/236 (22)	33/236 (14)	17/236 (7)	15/236 (6)	RARP: 0.04 ± 0.19 PGA: 4.1 ± 3.75	PGA: 21/236 (9) RARP: 29/472 (6.1)	RARP: 20/472 (4.2) PGA: 50/236 (21.2)	NR	NR
Ghai et al (2018) [30]	6	NR	<1	mpMRI at 6 mo	0/8	6 mo: Sys TRUS biopsy		NR	4/8 (50) (3 + 3: 3; 4 + 4: 1)	NR	NR	NR	3.41 (range: 0.71–5.77)	NR	RP: 1 (13)	NR	NR

Table 2 (*Continued*)

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
Johnston et al (2019) [33]	12	NR	NR	mpMRI at 12 mo	NR	NR	12/45 (26) (3 + 3: 9; 7:3)	NR	NR	NR	NR	NR	Nadir: 3.3 (–0.2 to 8.3)	16 (11)	RP: 6 (5.6) RT: 4 (3.7) ADT: 2	NR	NR
Mortezavi et al (2019) [35]	6	7	NR	mpMRI at 6 mo	8/68 (12)	6 mo: TTSPB with TRUS-guided mpMRI fusion	3 + 4: 17 4 + 3: 4 4 + 4: 7	40/68 (58.8)	NR	14/68 (20.5; incl 6 both sides)	NR	14/68	Mean 2.46 ± 1.91	NR	RP: 6	NR	NR
Rosenhammer et al (2019) [38]	12	0	NR	mpMRI at 6 & 12 mo	6/21 (28.6)	Sys 12-core biopsy, in case of PIRADS 3–5 Target biopsy		NR	4/21 (including 3/21 both sides)	1/12 (4.7)	4/21	NR	2.85	2/21	RP: 2	NR	NR
Shoji et al (2020) [39]	21 (12–42)	NR	NR	mpMRI at 2 wk & 6 mo	0 (0)	6 mo: Targeted + systematic TP biopsy	NR	90 (100)	0 (0)	0 (0)	NR	8 (8.9)	1.69 (0.05–10.90)		FT: 4 (4) RT: 2 (2) HT: 1 (1)	NR	NR
Stabile et al (2019) [40]	36	NA	NR	mpMRI at 6–12 mo	NR	Systematic TRUS with additional target zones TTPM: *n* = 424 (41)	325/1031 (31.5) (3 + 4: 189; 4 + 3: 52; 4 + 4: 12; 4 + 5: 2)	NR	NR	NR	NR	NR	NR	NR	271 (26.3) RP: 30 EBRT: 9 ADT: 20; WG HIFU: 4 Other: 3	NR	97
Tay et al (2017) [11,41]	24	2	NR	mpMRI at 6 & 24 mo	0 (0)	6 + 24 mo: TTMB	8/12 (66) (3 + 4: 1; 4 + 4: 1)	NR	4/12 (including 2 both sides) (3 + 4: 1; 4 + 3: 1)	NR	4/12 (3 + 4: 1)	NR	5	NR	NR	NR	NR
Westhoff et al (2021) [44]	38 (median)	NR	NR	mpMRI at 12 mo	NR	12 mo: biopsy	≥3 + 4: 12 (25) 3 + 3: 10 (21)	NR	NR	NR	NR	NR	NR	NR	RP: 7 EBRT: 6 HIFU: 2 ADT: 1	NR	NR
Yap et al (2016) [45]	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Focal brachytherapy (*n* = 8)																	
Fischbach et al (2020) [80]	6	0	NR	mpMRI at 6, 12, & 24 mo	0	12 mo: biopsy	NR	4/4 (100)	0/4 (0)	0	2/4 (50)	0/4	1.7	NR	NR	NR	NR
Graff et al (2018) [81]	12	0	1	mpMRI	1/17 (5.9)	12 mo: ≥12 cores (Target [≥4] + Sys)	NR	17/17 (100)	NR	0	7/17 (41.2)	1/17 (5.9)	NR	NR	RP: 1	NR	NR
Kim et al (2020) [82]	45 (median)	NR	NR	Only on clinical indication	NR	Only on clinical indication	NR	NR	NR	NR	NR	NR	NR	F/P: 2 (6.7) WG: 4 (13.3)	NR	BCRFS at 36 mo: F/P: 91.8 WG: 89.6	NR
Langley et al (2020) [83]	24	NR	<1	mpMRI at 24 mo	5 (17)	24 mo: TP template biopsy	NR	23/26 (88)	5/26 (19)	3/26 (12)	2/26(8)	0	NR	NR	NR	NR	NR
Mahdavi et al (2017) [84]	24	NR	NR	mpMRI 12 & 24 mo	1× PIRADS 3	24 mo: TTMB		2/2 (100)	0/2	0/2	0/2	0/2	NI	NR	NR	NR	NR
Peters et al (2019) [85]	48 (median)	NR	NR	PET/CT or 68 Ga-PSMA after BCR	9/10 (90)	NR		NR	2/9	NR	7/9	NR	NR	70%	NR	NR	100

Table 2 (*Continued*)

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
Prada et al (2020) [86]	32 (median)	0	0	MRI based on PSA evolution		Biopsy when biochemical failure	5 patients had positive biopsy	NR	NR	NR	NR	NR	Mean 3 (range 0.48–8.11)	7/50 (14)	NR	NR	100
Srougi et al (2017) [87]	24	0	NR	None	None	None	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IRE (*n* = 9)																	
Blazevski et al (2020) [46]	Median (IQR): 36 (24–52)	NR	NR	mpMRI at 6 mo	90/112 (80) showed no lesion on MRI	12 mo: TTMB + Target biopsies of the ablation zone		NR	NR	10/102 (9.8)	NR	13/102 (12.7)	Nadir: 3.48 (1.43–5.67)	NR	EBRT: 2 Brachy: 1 RP: 3	NR	100
Collettini et al (2019) [47]	Median (IQR): 20 (14–29)	NR	NR	mpMRI at 6 & 12 mo	NR	Target MRI-guided in bore biopsy or Target biopsy when PIRADS ≥3		NR	5/28 (17.9)	2/28 (7.1)	2/30 (6.7)	NR	6 mo: 2.70 (1–4) 12 mo: 2.35 (1–3) 24 mo: 2.35 (1–3)	NR	RP: 4	NR	NR
Enikeev et al (2020) [48]	12	NR	NR	mpMRI at 6 & 12 mo	3/15	MRI fusion targeted and systematic biopsy	NR	12 (100)	3 (25)	0 (0)	3 (25)	3 (25)	12 mo: 4.2 (mean)	NR	RP: 2 IRE: 1	NR	NR
Giganti et al (2019) [49]	Median (IQR): 16 (6–24)	NR	NR	mpMRI at 6 & 12 mo	6 mo: 6/30 (20)	Method NR; when suspicious for recurrence	3 patients had										
histopathological confirmation of recurrence	NR	NR	NR	NR	NR	NR	NR	IRE: 2 HIFU: 1 RT: 1	NR	NR							
Murray et al (2016) [50]	Median (IQR): 10.9 (6.7–19.3)	2	NR	CE MRI after 4–6 wk	NR	TRUS-guided template biopsy (>12 cores), MRI-guided Target biopsy if suspicious		NR	6 mo: 4/25 (16)	NR	3/25 (12)	NR	6 mo: 2.2 (1.1–3.8)	NR	Surgery: 3	NR	NR
Scheltema et al (2018) [51]	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Scheltema et al (2018) [52]	12	NR	NR	NR	NR	12 mo: TP biopsy	31/44 (70.5)		NR	NR	NR	NR	2.8 (0.9–4.5)	RP (PSA ≥ 0.2): 0/50	RP: 2 IRE: 3 Brachy: 1	NR	NR
Ting et al (2016) [53]	7	NR	Mean (range): 0.4 (0–5)	mpMRI	7/24	7 mo: TTMB		21/21 (100)	0	0	13/21 (62)	5/21 (24)	6 mo: 2.2 (1.0–5.0)	NR	0	NR	100
Valerio et al (2017) [12,54]	12	NR	Median (IQR): 12 h (11–22)	6 mo: mpMRI	0	TTMB (6 mo) + additional Target biopsies if Likert ≥3 lesion on MRI		12/18 (66.7)	7/18 (38.9)	6/18 (33.3)	NR	NR	12 mo: 1.71 (1.33–4.67)	NR	RP: 1	NR	100
Cryotherapy (*n* = 9)																	
Basourakos et al (2020) [63]	6	20	NR	6 mo: mpMRI	9 (29.9)	6 mo: targeted + systematic 12-core biopsy	NR	NR	NR	7 (20)	NR	6 (17)	Decrease from baseline: 4.3 (0–28.0)	NR	RP: 3 RT: 3 Cryo: 5	NR	NR

Table 2 (*Continued*)

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
Bossier et al (2020) [64]	Median (range): Hemi: 47 (1.5–99) WG: 36 (0.9–99)	NR	Median (range): Hemi: 3 (2–9) WG: 3 (3–6)	NR	NR	Biopsy after BCR	PCa in 10 pts: Hemi: 3 WG: 7	NR	NR	NR	NR	NR	NR	Hemi: 25% WG: 27%	Hemi: Cryo: 2 ADT: 1 WG: Cryo: 3 EBRT: 1 ADT: 1	4 yr: Hemi: 53% WG: 69%	NR
Chuang et al (2020) [65]	18	NR	0	mpMRI at 6 & 18 mo	17 (6 positive on biopsy)	6 mo (ipsilateral) + 18 mo (bilateral): MRI/US fusion targeted + systematic biopsy	NR	6 mo: 50/61 (82)	NR	6 mo: 11/61 (18) 18 mo: 4/27 (15)	NR	18 mo: 1/27 (4)	18 mo: 2.3 (1.3–3.6)	NR	AS: 10 Cryo: 6 Brachy: 1	NR	NR
Kongnyuy et al (2018) [66]	Median (IQR): 19 (6.3–38.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Nadir: BCR: 1.3 (0.3–8.8) No BCR: 1.0 (0.1–5.5)	39/104 (37.5)	NR	NR	NR
Kongnyuy et al (2017) [67]	Median (IQR): 36.6 (18.9–56.4)	NR	NR	NR	NR	Biopsy after BCR	PD: 14/26 (53.8) SD: 18/35 (51.4) ≥GS7: PD: 56.1% SD: 66.7%	NR	NR	NR	NR	NR	NR	44%	NR	NR	NR
Mendez et al (2015) [68]	Median: 58.3	NR	NR	NR	NR	Biopsy after BCR	8/55 (14.5)	NR	NR	NR	NR	NR		Focal: 71.3% WG: 80.1%	NR	NR	NR
Shah et al (2019) [69]	Median (IQR): 27.8 (19.5–36.7)	NR	NR	12 mo: mpMRI	NR	Biopsy if suspicion on recurrence after rising PSA (29/122)	21/29 (72.4)	NR	12/21 (57)	NR	9/21 (43)	NR	NR	NR	RP: 5 RT: 4 Systemic therapy: 4	90.5	96.1
Sze et al (2019) [70]	Median (IQR): 15 (13–17)	NR	0	12 mo: mpMRI	0/9	12 mo: targeted + systematic biopsy	NR	10/10 (100)	0 (0)	0 (0)	2/10 (20)	NR	Nadir: 0.82 (0.55–1.75)	NR	NR	NR	NR
Tourinho-Barbosa et al (2020) [42]	45	NR	NR	mpMRI at 1 & 12 mo	NR	12 mo: Sys 12-core TP biopsy	54/111 (49)	NR	44 (37)	NR	23 (19)	NR	Nadir: 2.7 (1.6–4.1)	NR	WG: 5 (4.2) RP: 13 (11) RT: 11 (9.2) ADT: 11 (9.2)	56 (46–65)	NR
Werneburg et al (2018) [71]	Median 30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wysock et al (2021) [72]	6	NR	NR	6 mo: mpMRI	7 (10)	6 mo: targeted + ipsilateral systematic biopsy	NR	NR	5 (7.1)	NR	NR	NR	6 mo: 1.42 (0.8–3.3)	NR	NR	NR	NR
PDT (*n* = 7)																	
Azzouzi et al (2017) [73]	Median (IQR): 24 (24–25)	PDT: 2 AS: 5	NR	NR	NR	12 + 24 mo: Sys TRUS-guided 12-core biopsies		PDT: 101/206 (49) AS: 28/207 (14)	PDT: 49/206 (24) AS: 91/207 (44)	NR	NR	NR	24 mo: AS: 5.27 ± 4.22	NR	NR	NR	NR

Table 2 (*Continued*)

Reference	Length of follow-up (mo)	Lost to follow-up	Hospital stay (d)	Postop imaging	Patients with suspicious areas on imaging	Post-treatment histology	Post-treatment histology (unknown area)	Absence of CSC in treated area, *n* (%)	Any cancer treated area, *n* (%)	CSC in treated area	Any cancer in untreated area, *n* (%)	CSC untreated area, *n* (%)	Postprocedural PSA level (ng/ml), median (IQR)	BCR, *n* (%)	Salvage therapy	RFS (%)	OS (%)
Gill et al (2018) [74]	48	NR	NR	NR	NR	12 + 24 mo: Sys TRUS-guided 12-core biopsies	NR	NR	PDT: 51/206 (25) AS: 134/207 (65)	PDT: 21/206 (10) AS: 60/207 (29)	PDT: 39/206 (19) AS: 25/207 (12)	PDT: 12/206 (6) AS: 14/207 (7)	NR	NR	RP: 80% RT: 14% HIFU: 5% Unknown: 1%	NR	PDT: 98 AS: 99
Lebdai et al (2017) [75]	Median (range): 68 (6–89)	NR	NR	NR	NR	6 mo: Sys 12-core biopsy	NR	6 mo: 73/82 (89)	6 mo: 20/82 (24)	6 mo: 9/82 (11)	NR	NR	3.25	NR	RP: 18 Brachy: 2	NR	NR
Noweski et al (2019) [76]	42	2	NR	MRI on irregular basis	20/32	6 mo: Sys biopsy	NR	NR	17/68 (25)	NR	17/68 (25)	NR	NI	NR	RP: 8 Brachy: 5 HIFU: 1	NR	NR
Rastinehad et al (2019) [77]	12 mo		1	mpMRI	NR	3 + 12 mo: Target & Sys 12-core biopsy	3 mo: 3 + 3: 3 3 + 4: 3 12 mo: 3 + 3: 1 3 + 4: 1	13/15 (87; at 12 mo)	2/15 (13)	2/15 (13)	NR	NR	3.9	NR	NR	NR	NR
Rodriguez-Rivera et al (2018) [78]	12 mo	10	0	NR	NR	6 + 12 mo	12 mo: 11/81 (14) 3 + 3: 9 3 + 4: 1 5 + 4: 1	NR	NR	NR	NR	NR	Median decrease: −3.28	NR	RP: 2 Unknown: 8	NR	100
Taneja et al (2016) [79]	12	2	NR	6–7 mo: mpMRI	NR	12-core biopsy at 6 mo	NR	NR	11/30 (36.7)	NR	5/30 (16.7)	NR	NI	NR	NR	NR	100
RFA (*n* = 2)																	
Aydin et al (2020) [88]	6	NR	NR	6 mo: mpMRI	NR	6 mo: TP biopsy	NR	NR	3/10 (30)	NR	2/10 (20)	NR	3.22 (1.62–6.16)	NR	RP: 1 EBRT: 1 AS: 3	NR	NR
Orczyk et al (2021) [89]	12	NR	NR	mpMRI	4	6 mo: Target TP biopsy	NR	16/20 (80)	5/20 (25)	4/20 (20)	NR	0	2.7 (0.3–3.75)	NR	AS: 2 RFA: 2		
PAE (*n* = 1)																	
Frandon et al (2021) [90]	6	NR	1	2 wk + 6 mo mpMRI	6 mo: 7/10 (70)	6 mo: Target + Sys biopsy	NR	4/10 (40)	6/10 (60)	NR	NR	NR	Range (0.3–7.6)	NR	EBRT: 1	NR	NR

ADT = androgen deprivation therapy; AS = active surveillance; BCR = biochemical recurrence; BCRFS = BCR-free survival; Brachy = brachytherapy; CE = contrast enhanced; CSC = clinically significant cancer; EBRT = external beam radiotherapy; FLA = focal laser ablation; F/P = focal/partial; FT = focal therapy; GS = Gleason score; Hemi = hemiablation; HIFU = high-intensity focused ultrasound; HT = hormonal therapy; IQR = interquartile range; IRE = irreversible electroporation; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NA = not available NI = not interpretable; NR = not reported; OS = overall survival; PAE = prostate artery embolization; PCa = prostate cancer; PD = progressive disease; PDT = photodynamic therapy; PET/CT = positron emission tomography/computed tomography; PGA = partial gland ablation; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; pts = patients; RARP = robot-assisted radical prostatectomy; RFA = radiofrequency ablation; RFS = recurrence-free survival; RP = radical prostatectomy; RT = radiotherapy; SD = stable disease; Sys = systematic; Target = targeted; TP = transperineal; TRUS = transrectal ultrasound; TTMB = transperineal template mapping biopsy; TTPM = transperineal template prostate mapping; TURP = transurethral resection of the prostate; US = ultrasound; WG = whole gland.

Table 3 – Morbidity and functional outcomes

Reference	SAE/CD grade	PROM for continence	Outcome, median (IQR)/leak free, pad free, *n* (%)		Pad free, *n* (%)		Change in continence	PROM for erectile function	Outcome, median (IQR)/ erection sufficient for penetration, *n* (%)		Change in erectile function	New use of PDE-5 inhibitors	
			Pre	Post	Pre	Post			Pre	Post		Pre	Post
FLA (*n* = 8)													
Al-Hakeem et al (2019) [55]	CD: I: 30 II: 11 IIIa: ≥0	IPSS	NR	0	NR	49/49 (100)	NS	SHIM	NR	NR	NR	NR	9/49 (18)
Barqawi et al (2015) [56]	0	AUA	NR	NR	NR	NR	NR	SHIM (2/7)	24/25 (96)	22/25 (88)	NS	NR	NR
Chao et al (2018) [57]	NR	AUASS (12 mo)	4.5 (3–12)	5 (4–9)	34/34 (100)	34/34 (100)	NR	SHIM (12 mo)	22 (20–24)	20 (16–24)	NR	NR	NR
Eggener et al (2016) [58]	NR	IPSS	9 (IQR 11.5)	10 (IQR 10)	NR	NR	NR	SHIM	21.5 (IQR 0.5)	21 (IQR 10.5)		NR	NR
Lepor et al (2015) [59]	NR	AUASS	5.5 (3–13.5)	5 (2–10.75)	0	0	NR	SHIM	20.5 (12.75–24)	21 (16–24)	NS	NR	NR
Natarajan et al (2017) [60]	0	IPSS	7.5	5.5	NR	NR	NR	IIEF-5	15.5	14.5	NR	NR	NR
Natarajan et al (2016) [61]	0	IPSS	4	3.5	NR	NR	NS	SHIM	19.5	20	NS	NR	NR
Walser et al (2019) [62]	CTCAE: II: *n* = 15 III: *n* = 1	IPSS	6.5 (3–13)	11.5 (8–17.5)	NR	NR	NS	SHIM	24 (20–25)	22 (16–24)	NS	NR	NR
HIFU (*n* = 27)													
HIFU with TURP (n = 10)													
Abreu et al (2020) [19]	III–V: 0	IPSS	9 (3–15)	6 (3–11)	NR	NR	No new-onset urinary continence	IIEF-5	22 (18–25)	21 (16–24)	NR	NR	NR
Annoot et al (2019) [22]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Arnouil et al (2018) [23]	HIFU (1.9); RP (6.1): IIIb: 1; 3 IV: 0; 1	Ingelman-Sundberg	HIFU: 100% RP: 100%	HIFU: 95.9% RP: 69.4%	HIFU: 100% RP: 100%	HIFU: 98% RP: 78.7%	NR	IIEF	HIFU: 54.7% RP: 69.7%	HIFU: 59% RP: 30%	NR	HIFU: 6% RP: 1%	HIFU: 17.4% RP: 40%
Glybochko et al (2019) [31]	0	IPSS	Mean (range): 4 (0–26)	Mean (range): 3 (1–25)	NR	NR	NR	IIEF-5	Mean (range): 20 (0–25)	Mean (range): 16 (0–25)	NS	NR	NR
Hamdy et al (2018) [32]	RP: 6/32 (19) HIFU: 4/43 (9)	EPIC/IPSS	NI	NI	NI	NI	NI	EPIC/IIEF-15	NI	NI	NR	NR	NR
Lei et al (2019) [34]	NR	IPSS	Zonal: 11 (91.7)	Zonal: 11 (91.7)	Zonal: 12 (100)	Zonal: 11 (91.7)		IIEF-5	NR	NR	NS	NR	NR
Nahar et al (2020) [36]	III: 5 (10.4)	EPIC/IPSS	TURP: 13.3 No TURP: 3.9	TURP: 8.6 No TURP: 7.1	NR	NR	NR	EPIC/SHIM	Mean: 18.8	Mean at 12 mo: 18.3	Return to baseline after 1 yr	NR	NR
Rischmann et al (2017) [37]	III: 14/101 (13.86)	IPSS	NI	NI	99%	97%	NR	IIEF-5	51/101 (IIEF ≥ 16)	40/101 (IIEF ≥ 16)	NS	NR	NR

Table 3 (*Continued*)

Reference	SAE/CD grade	PROM for continence	Outcome, median (IQR)/leak free, pad free, *n* (%)		Pad free, *n* (%)		Change in continence	PROM for erectile function	Outcome, median (IQR)/ erection sufficient for penetration, *n* (%)		Change in erectile function	New use of PDE-5 inhibitors	
			Pre	Post	Pre	Post			Pre	Post		Pre	Post
Tourinho-Barbosa et al (2020) [42]	IIIa: 7 (2.2) IIIb: 1 (0.3) IVa: 1 (0.3)	IPSS	NR	NR	NR	69/74 (93; 12 mo)	NR	NR	NR	NR	NR	NR	NR
van Velthoven et al (2016) [43]	0	Physician-reported rates	NR	NR	NR	94% (*n* = 3 persistent incontinence)	NR	Physician-reported rates	NR	NR	6 (20) developed ED	NR	NR
HIFU with TURP (n = 10)													
Ahmed et al (2015) [20]	0	UCLA EPIC	53/55 (96)	46/50 (92; 12 mo)	54/54 (100)	50/52 (96)	NR	IIEF-15	41/54 (75.9)	36/54 (66.7)	NR	7/55 (12.7)	23/54 (42.6)
Albisinni et al (2017) [21]	NR	Patient-reported rates	NR	NR	NR	52/55 (94.5)	NR	Patient-reported rates	30/54 (55)	24/55 (44)	NR	NR	NR
Bacchetta et al (2020) [24]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bass et al (2019) [25]	III: 4 (2.6)	NR	NR	NR	NR	NR	No change 131 (94.5)	NR	NR	NR	No change 115 (86.5)	NR	NR
Dickinson et al (2017) [26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Feijoo et al (2016) [27]	IIIb: 2 (2.8)	ICS, IPSS	4 (range 0–26)	NR	NR	NR	NS	IIEF-5	Median 20 (range 0–25)	Median 16 (0–25)	NR	NR	NR
Ganzer et al (2018) [28]	III: 1/51 (1.96)	ICS, IPSS	Mean ± SD: 0.9 ± 2.3	Mean ± SD: 1.4 ± 3.0	50/51 (98)	48/51 (94)	NR	IIEF-5	Mean 17.6 ± 6.1	Mean 13.6 ± 8.6	NR	7/51 (13.7)	12/51 (23.5)
Garcia-Barreras et al (2018) [29]	RARP: IIIa: 2 (0.4) IIIb: 7 (1.5) IV: 1 (0.2) PGA: IIIa: 2 (0.8) IIIb: 2 (0.8) IV: 0 (0)	IPSS	RARP: 7.26 ± 5.79 PGA: 5.44 ± 4.77	RARP: 5.03 ± 4.01 PGA: 5.61 ± 4.45	RARP: 406(86) PGA: 199 (84.3)	RARP: 300 (63.8) PGA 208 (88.1)	NR	IIEF-5	RARP: 17.81 ± 7.11 PGA: 18.01 ± 7.3	RARP: 5.71 ± 5.84 PGA: 12.83 ± 8.55	NR	NR	NR
Ghai et al (2018) [30]	0	IPSS	Mean (range): 7 (0–14)	Mean (range): 8.75 (0–19)	8/8 (100)	8/8 (100)	NR	IIEF-15	Mean (range): 50.6 (70–12)	Mean (range): 44 (67–10)	NR	NR	NR
Johnston et al (2019) [33]	0	NR	NR	NR	NR	NR	1 patient (1) new use of pads	NR	NR	15 (14) new onset of ED	NR	NR	NR
Mortezavi et al (2019) [35]	NR	EPIC, IPSS	EPIC: 91.7 (83.3–95.8) IPSS: 5 (3–12)	EPIC: 95.7 (81–97.9) IPSS: 5 (2–8)	64/64 1 pad/d or pad free	63/63 (98.4) used 1 safety pad or pad free	NS	IIEF-15	51.5 (31.8–62.8)	35 (5.8–52.0) 45/58 (77.6)	NR	NR	19 (25.3)
Rosenhammer et al (2019) [38]	IIIb 1/21 (4.76)	IPSS	7 (4–12)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 3 (*Continued*)

Reference	SAE/CD grade	PROM for continence	Outcome, median (IQR)/leak free, pad free, *n* (%)		Pad free, *n* (%)		Change in continence	PROM for erectile function	Outcome, median (IQR)/ erection sufficient for penetration, *n* (%)		Change in erectile function	New use of PDE-5 inhibitors	
			Pre	Post	Pre	Post			Pre	Post		Pre	Post
Shoji et al (2020) [39]	III: 3 (3.3)	IPSS	NI	NI	NR	NR	NR	IIEF5	43	37 (86)	NR	NR	NR
Stabile et al (2019) [40]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tay et al (2017) [11,41]	0	EPIC	NR	EPIC mean increase 2.4 points	NR	NR	NR	NR	NR	NR	NS	NR	NR
Westhoff et al (2021) [44]	NR	EPIC	NR	NR	NR	NR	NR	EPIC	NR	NR	NR	NR	NR
Yap et al (2016) [45]	NR	IPSS, UCLA EPIC	IPSS: 8 (5–12) EPIC: 92 (87–96)	NR	NR	NR	NR	IIEF-15	IIEF: 58 (32–67) IIEF-erectile: 23 (11–28)	IIEF: 47 (28–62) IIEF-erectile: 20 (9–28)	NS	12/118 (10)	44/118 (37)
Focal brachytherapy (*n* = 8)													
Fischbach et al (2020) [80]	NR	IPSS	8 (mean)	8 (mean)	NR	NR	NS	IIEF-6	22 (mean)	19 (mean)	NS	NR	NR
Graff et al (2018) [81]	0	IPSS	NR	NR	NR	NR	No change	IIEF-5	NR	NR	No change	NR	NR
Kim et al (2020) [82]	NR	IPSS	F/P: 8.0 (5.0–13.3) WG: 9.5 (5.0–13.0)	F/P: 14.0 (9.3–16.3) WG: 15.0 (9.5–19.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Langley et al (2020) [83]	NR	IPSS	NR	24 mo: Mean (SD): 8 (5.7)	NR	NR	NR	IIEF-5	NR	24 mo: Mean (SD): 12.6 (9.9)	Preserved in 73%	NR	NR
Mahdavi et al (2017) [84]	0	IPSS	NR	NR	NR	NR	No change	SHIM	NR	NR	No change	NR	NR
Peters et al (2019) [85]	1	IPSS, EORTC-PR25	5 (4–7)	7 (4–11)	NR	NR	NR	IIEF-5	19 (5–22)	6 (3–20)	50% new-onset impotence	NR	NR
Prada et al (2020) [86]	0	IPSS	Mean (range): 8.2 (0–26)	24 mo: Mean (range): 6.7 (0–18)	NR	NR	NR	IIEF-5	Mean (range): 20 (5– 25)	Mean 13	14/17 stayed potent	NR	NR
Srougi et al (2017) [87]	NR	IPSS, ICS	Mean ± SD: Apex: 4.9 ± 5.1 Base: 6.3 ± 4.9	Mean ± SD: Apex: 6.4 ± 5.2 Base: 6.2 ± 5.3	NR	NR	NS	IIEF-5	Mean ± SD: Apex: 19 ± 7.6 Base: 18 ± 6.9	Mean ± SD: Apex: 17 ± 7.7 Base: 16.5 ± 7.4	NS	NR	NR
IRE (*n* = 9)													
Blazevski et al (2020) [46]	0	EPIC-urinary	75/84 (89)	70/84 (83)	81/84 (96)	80/84 (95)	No change	EPIC-sexual	53	40	Significant decrease	NR	NR
Collettini et al (2019) [47]	0	ICIQ-MLUTS	27/30 (90%)	12/12 (100%)	29/30 (96.7%)	12/12 (100%)	NR	IIEF-5	21 (16–24) 25/30 (83.3%)	22.5 (18.5 – 22.5) 12/12 (100%)	NR	2/30 (6.7%)	3/29 (10.3%)

Table 3 (*Continued*)

Reference	SAE/CD grade	PROM for continence	Outcome, median (IQR)/leak free, pad free, *n* (%)		Pad free, *n* (%)		Change in continence	PROM for erectile function	Outcome, median (IQR)/ erection sufficient for penetration, *n* (%)		Change in erectile function	New use of PDE-5 inhibitors	
			Pre	Post	Pre	Post			Pre	Post		Pre	Post
Enikeev et al (2020) [48]	I: 4	IPSS	Mean (range): 12 (5–23)	Mean (range): 8 (0–16)	NR	NR	NR	IIEF-5	Mean (range): 14.6 (0–24)	Mean (range): 18 (0–24)	Unchanged in 11/12	NR	NR
Giganti et al (2019) [49]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Murray et al (2016) [50]	0	Prostate QoL survey	18.2	18.6	NR	23 (92%)	NR	Prostate quality of life survey	18.6	21.1	NR	2	2
Scheltema et al (2018) [51]	NR	EPIC-urinary, AUA	NR	NR	58/60	6 mo: 57/60 12 mo: 58/60	NS	EPIC-sexual	40/60 (67)	27/40 (68)	Significant decrease	NR	NR
Scheltema et al (2018) [52]	NR	EPIC-urinary, AUA	NR	NR	(%) IRE: 98 RARP: 98	(%) 12 mo: IRE: 96 RARP: 84	NR	EPIC-sexual	(%) IRE: 69 RARP: 68	(%) 12 mo: IRE: 56 RARP: 36	Significantly reduced for both groups	NR	NR
Ting et al (2016) [53]	1	EPIC-urinary	67%	67%	100%	100%	NS	EPIC-sexual	44%	56%	NS	NR	NR
Valerio et al (2017) [12,54]	0	IPSS, EPIC-urinary	16/16 (100)	16/16 (100)	16/16 (100%)	16/16 (100%)	No change	IIEF-15	12/16 (75%)	11/16 (69%)	No change	2	2
Cryotherapy (*n* = 9)													
Basourakos et al (2020) [63]	2: 22 3: 5 (9)	EPIC	Mean (SD): 0.71 (1.37)	9 mo: Mean (SD): 1.21 (1.72)	NR	NR	NR	EPIC	Mean (SD): 3.41 (3.32)	Mean (SD): 3.83 (3.76)	NR	NR	NR
Bossier et al (2020) [64]	≤2: Hemi: 23% WG: 48% ≥3: 0%	NR	NR	NR	Hemi: 100% WG: 100%	Hemi: 83% WG: 83%	NR	NR	Hemi: 43% WG: 20%	Hemi: 54% WG: 25%	NR	NR	NR
Chuang et al (2020) [65]	2: 5 ≥3: 0	IPSS	8 (4–12)	5.5 (4–7)	NR	100%	NR	EPIC-CP sexual	Median: 5	6 mo: Median: 6	NR	NR	1
Kongnyuy et al (2018) [66]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kongnyuy et al (2017) [67]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mendez et al (2015) [68]	NR	NR	NR	NR	NR	Focal: 100% WG: 98.7%	NR	NR	100%	Focal: 68.8% WG: 46.8%	NR	NR	NR
Shah et al (2019) [69]	III: 2 (1.6)	IPSS	NR	NR	NR	69/69 (100)	NR	IIEF-15	33 (14–56) 31/122 (25.4)	22 (9–45) 26/122 (21.3)	NS	NR	NR
Sze et al (2019) [70]	0	IPSS	5 (2–0)	4 (2–4)	NR	100%	NR	IIEF-5	19.5 (16–17)	12 mo: 19 (14–18)	NR	NR	NR
Tourinho-Barbosa et al (2020) [42]	IIIa: 7 (2.2) IIIb: 1 (0.3) IVa: 1 (0.3)	IPSS	NR	NR	NR	69/74 (93; 12 mo)	NR	NR	NR	NR	NR	NR	NR
Werneburg et al (2018) [71]	NR	EPIC	NI	NI	NI	NI	NS	IIEF	NI	NI	NS	Focal: 42 WG: 14	NR
Wysock et al (2021) [72]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 3 (*Continued*)

Reference	SAE/CD grade	PROM for continence	Outcome, median (IQR)/leak free, pad free, *n* (%)		Pad free, *n* (%)		Change in continence	PROM for erectile function	Outcome, median (IQR)/ erection sufficient for penetration, *n* (%)		Change in erectile function	New use of PDE-5 inhibitors	
			Pre	Post	Pre	Post			Pre	Post		Pre	Post
PDT (*n* = 7)													
Azzouzi et al (2017) [73]	Grade ≤ III: PDT: 59 AS: 24	IPSS	NR	NR	NR	NR	NS	IIEF-15	NR	NR	NS	NR	NR
Gill et al (2018) [74]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lebdai et al (2017) [75]	Grade 3: 1	IPSS	Median 4	Median 4	NR	NR	NR	IIEF-5	Median 23	Median 22.5	NR	NR	NR
Noweski et al (2019) [76]	Grade ≥3: 3	NR	NR	NR	NR	NR	NR	NR	NR	12 mo: 9 (15.8)	NR	NR	NR
Rastinehad et al (2019) [77]	Grade 3: 0	IPSS	8	8	NR	NR	NR	SHIM	23.5	20.5	NR	NR	NR
Rodriguez-Rivera et al (2018) [78]	4 (4.9)	IPSS	10.8	7.7	NR	NR	NR	IIEF	19.6	15.8	NR	NR	NR
Taneja et al (2016) [79]	0	IPSS	NI	NI	NR	NR	NR	IIEF-5	NI	NI	Decreased	NR	NR
RFA (*n* = 2)													
Aydin et al (2020) [88]	I: 5 II: 3 III: 1	AUA	Median: 6.5	6 mo: Median: 5	NR	NR	NR	IIEF-5	Median: 22	6 mo: Median: 10	4× ED after treatment	NR	NR
Orczyk et al (2021) [89]	1: 11 (27.5%) 2: 29 (72.5%)	EPIC	NR	12 mo: 16/18 (89)	NR	NR	NR	IIEF-15	NR	12 mo: 11/12 (91.7)	NR	NR	NR
PAE (*n* = 1)													
Frandon et al (2021) [90]	I: 2 (20) II: 1 (10)	IPSS	Median (range): 5 (1–16)	Median (range): 1 (1–19)	NR	NR	NS	IIEF-6	Median (range): 24 (1–30)	Median (range): 27 (0–30)	NS	NR	NR

AS = active surveillance; AUA = American Urological Association; AUASS = American Urological Association Symptom Score; CD = Clavien-Dindo; CRYO = cryotherapy; CTCAE = Common Terminology Criteria for Adverse Events; ED = erectile dysfunction; EORTC = European Organisation for Research and Treatment of Cancer; EPIC = Expanded Prostate Cancer Index Composite; FLA = focal laser ablation; F/P = focal/partial; Hemi = hemiablation; HIFU = high-intensity focused ultrasound; ICIQ-MLUTS = International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms Module; ICS = International Continence Society; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; IRE = irreversible electroporation; NI = not interpretable; NR = not reported; NS = not significant; PAE = prostatic artery embolization; PDE-5 inhibitor = phosphodiesterase type 5 inhibitor; PDT = photodynamic therapy; PGA = partial gland ablation; PROM = Patient-reported outcome measure; QoL = quality of life; RARP = robot-assisted radical prostatectomy; RFA = radiofrequency ablation; RP = radical prostatectomy; RT = radiotherapy; SAE = serious adverse event; SD = standard deviation; SHIM = Sexual Health Inventory For Men; TURP = transurethral resection of the prostate; UCLA = University of California, Los Angeles; WG = whole gland.

Table 4 – Current and future studies identified in ClinicalTrials.gov (up to January 31, 2021)

Source of energy	Investigator	IDEAL stage	Recruitment status	Sample size	Gleason score	Clinicaltrials.gov identifier
FLA (n = 7)	Ghai et al, University Health Network, Toronto, Canada	2a	Recruiting	23	≤7	NCT03650595
	Manenti et al, University of Rome Tor Vergata, Rome, Italy	2a	Recruiting	50	≤7	NCT04045756
	Pantuck et al, University of California at Los Angeles, Los Angeles, CA, USA	2a	Active, not recruiting	10	≤ T2b, with Gleason score 7	NCT04305925
	Futterer et al, Radboudumc, Nijmegen, The Netherlands	2b	Recruiting	53	≤7	NCT04379362
	Oddens et al, Amsterdam UMC, Amsterdam, The Netherlands	1	Recruiting	15	NS	NCT04170478
	Woodrum et al, Mayo Clinic, Rochester, MN, USA	1	Recruiting	20	≤7	NCT02600156
	Wood et al, National Institutes of Health Clinical Center, Bethesda, MD, USA	1	Enrolling by invitation	9	Low to favorable intermediate	NCT02759744
HIFU (n = 14)	Eberli et al, Klinik für Urologie, Universitätsspital Zürich, Germany	2b	Unknown	100	Gleason ≤4 + 3, T1-T2cN0M0	NCT02265159
	Sven Löffeler et al, Hospital of Vestfold, Tønsberg, Vestfold, Norway	2b	Recruiting	250	Clinical/ radiological stage < T2c	NCT04549688
	Robertson et al, Duke University Medical Center, Durham, NC, USA	2b	Unknown	141	Clinical stage T1a, b, or c or T2a	NCT00295802
	Yee et al, Chinese University of Hong Kong	2a	Recruiting	20	7	NCT03927924
	Bladou et al, Urology Department, Jewish General Hospital, Montreal, Quebec, Canada	2a	Unknown	25	≤7 (3 + 4)	NCT02016040
	Hospices Civils de Lyon, Lyon, France	2a	Recruiting	170	3 + 4	NCT03568188
	Crouzet et al, Hospices Civils de Lyon, Lyon, France	3	Recruiting	146	6	NCT03531099
	Vrabec et al, Abbotsford Regional Hospital Cancer Center, BC, Canada	2b	Not yet recruiting	20	≤7	NCT00573586
	Elet et al, Edouard Herriot Hospital, Lyon, France	2a	Active not recruiting	180	T1 or T2	NCT03632980
	Emberton et al, University College London, London, UK	2b	Recruiting	354	≤3 + 4	NCT01194648
	Schoenberg et al, Johns Hopkins Medical Institution, Baltimore, MD, USA	2b	Active, not recruiting	466	T1c or T2a	NCT00770822
	Hospital de Transplante Euryclides de Jesus Zerbini, São Paulo, Brazil	2b	Active, not recruiting	130	Low or intermediate	NCT03255135
	Marks et al, University of California, Los Angeles, CA, USA	2b	Enrolling by invitation	30	NS	NCT03620786
	Baco et al, Oslo University Hospital, Oslo, Norway	3	Recruiting	250	3 + 3 and 3 + 4	NCT03668652
Focal brachytherapy (n = 6)	Strnad et al, University of Erlangen-Nürnberg Medical School, Erlangen, Germany	2a	Recruiting	50	≤6	NCT02391051
	Fernandez et al, St George Hospital, Sydney, Australia	2a	Recruiting	20	6	NCT02643511
	Song et al, John Hopkins University, Baltimore, MDs, USA	1	Not yet recruiting	20	6 & 7	NCT03861676
	Benoit et al, University of Pittsburgh Medical Center, Pittsburgh, PA, USA	2b	Recruiting	100	≤ 6	NCT02290366
	Morris et al, British Columbia Cancer Agency, Vancouver, BC, Canada	1	Unknown	10	≤3 + 4	NCT01830166
	Berlin et al, Princess Margaret Cancer Centre Toronto, ON, Canada	2a	Recruiting	30	Low to favorable intermediate	NCT02918253
IRE (n = 5)	De La Rosette et al, Clinical Research Office of the Endourological Society	2b	Active, not recruiting	106	6 or 7	NCT01835977
	Sun et al, Second Military Medical University, Shanghai, China	2b	Active, not recruiting	119	NS	NCT03838432
	Enikeev et al, I.M. Sechenov First Moscow State Medical University, Moscow, Russia	2a	Recruiting	12	3 + 3 = 6; 3 + 4 = 7	NCT04192890
	Wang et al, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China	3	Not yet recruiting	438	<8	NCT04278261
	Emberton et al, University College London Hospitals, London UK	2a	Unknown	20	≤7	NCT01726894
PDT (n = 3)	Coleman et al, Memorial Sloan Kettering Cancer Center, New York, NY, USA	2b	Active, not recruiting	50	3 + 4	NCT03315754

Table 4 (*Continued*)

Source of energy	Investigator	IDEAL stage	Recruitment status	Sample size	Gleason score	Clinicaltrials.gov identifier
	Azzouzi et al [73,103], Centre Hospitalier Universitaire, Angers, France	4	Active, not recruiting	200	≤6	NCT03849365
	Nanospectra Biosciences, Inc.	2a	Active, not recruiting	45	≤7	NCT02680535
Cryotherapy (n = 3)	Tay et al, Singapore General Hospital, Singapore	2a	Recruiting	30	≤4 + 4	NCT04138914
	Marks et al, University of California, Los Angeles, CA, USA	2b	Enrolling by invitation	100	≤7	NCT03503643
	Guazzoni et al, University "Vita e Salute" San Raffaele Milano, Italy	2a	Unknown	100	T1c or T2a	NCT00928603
MWA (n = 4)	Chiu et al, Chinese University of Hong Kong	2a	Recruiting	30	Low or intermediate	NCT04113811
	Delongchamps et al, Assistance Publique – Hôpitaux de Paris, Paris, France	2a	Active, not recruiting	11	3 + 4	NCT03023345
	Oderda et al, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Italy	2a	Recruiting	11	≤3 + 4	NCT04627896
	Fontanelli et al, Koelis, Belgium and France.	2b	Not yet recruiting	65	3 + 4	NCT04582656
PAE (n = 1)	Frandon et al, Nîmes University Hospital, Nimes, France	2a	Not yet recruiting	12	9–10	NCT04423913
RFA (n = 0)						

FLA = focal laser ablation; HIFU = high-intensity focused ultrasound; IDEAL = Idea, Development, Exploration, Assessment, Long-term study; IRE = irreversible electroporation; MWA = microwave ablation; NS = not specified; PAE = prostatic artery embolization; PDT = photodynamic therapy; RFA = radiofrequency ablation.

3.3. Focal laser ablation

Eight studies on FLA were identified. Three studies were in IDEAL stage 1, three in IDEAL stage 2a, and two were in IDEAL stage 2b. The median sample size was 26 (range 7–120). Study population consisted of low- to intermediate-risk patients with a median preprocedural PSA value of 5.8 ng/ml (range 4.4–7.5). The median follow-up was 12 mo. Most studies reported postprocedural Gleason scores and did not specify CSC in the treated area. Four studies reported these outcomes with a median CSC rate of 16.5% (range 4–40%) in the treated area. Three studies reported zero SAEs, one study reported one CTCAE grade III event, that is, urinary tract infection, and 15 grade II events of which two were rectourethral fistulas both of which resolved after 4–6 wk with a urinary catheter. Two studies reported on pre- and postprocedural pad-free continence, with zero patients requiring pads after FLA. Pre- and postprocedural Sexual Health Inventory for Men (SHIM) scores remained constant with no significant changes being reported (Table 3).

3.4. Cryoablation

Eleven studies on cryoablation were identified, of which six were retrospective studies, one of which compared HIFU with cryoablation [42], and five were prospective studies. All studies were in IDEAL stage 2. The median number of patients who were included was 89 (range 17–317). The median follow-up was 19 mo. Three studies reported on postprocedural CSC, with 0%, 15%, and 20% of patients having CSC in the treated area [63,65,70]. Five studies reported on SAEs, with three reporting zero grade III SAEs and two reporting 1.6% and 9% grade III SAEs. Change in continence was reported by five studies, with four studies reporting 100% pad-free continence. Two studies compared whole gland cryoablation with focal ablation: one reported no difference in pad-free continence between groups (both 83%) [64] and the other reported a significant difference in favor of focal cryotherapy (24 mo continence 100% vs 98.7%, p = 0.02) [68]. The latter also reported significantly better erectile function for the focally treated patients (at 24 mo 68.8% vs 46.8% ESI, p = 0.001). The other studies did not report significant decline in International Index of Erectile Function (IIEF) and Expanded Prostate Cancer Index Composite (EPIC) scores.

3.5. Photodynamic therapy

Of the seven studies on PDT, two were in IDEAL stage 2a, three in IDEAL stage 2b, and two in as IDEAL stage 3. However, both studies [73,74] reported on the same trial (NCT01310894). Azzouzi et al [73] reported on safety, functional outcomes, and postprocedural biopsies at 24 mo, and Gill et al [74] reported on the risk of RP after 4 yr. However, this latter study also reported on postprocedural biopsies after 24 mo in a post hoc analysis, arguably accounting for data overlap. Since both articles provide separate, useful information for this review, we reported both.

In this trial, 413 patients were randomly assigned to receive PDT or AS. Patients were followed for 24 mo on functional outcome (International Prostate Symptom Score [IPSS] and IIEF-15) and oncological outcome by means of a systematic transrectal ultrasound–guided biopsy. The RCT reported SAEs in 59 PDT patients, compared with 24 patients in the AS group. The most common treatment-related adverse events were urinary retention and prostatitis (2%). Concerning oncological outcomes, there were more

patients with a negative biopsy in the PDT group than in the AS group (PDT 101 [49%] vs AS 28 [14%], hazard ratio 3.67, 95% confidence interval 2.53–5.33, $p < 0.0001$) and significantly more patients required subsequent radical treatment in the AS group (PDT 12 [6%] vs AS 60 [29%]). IIEF-15 and IPSS scores were reported to be similar for both groups after 24 mo. The other studies reported lower incidences concerning adverse events, with respectively 0–5% adverse events. CSC in the treated area was reported by three studies, reporting 11% (9/82) at 6 mo, 13% (2/15) at 12 mo, and 10% (21/206) at 24 mo. Concerning functional outcomes, no changes in continence were reported. One study reported a decline of erectile function after 12 mo [79] but did not present exact numbers, the others reported no change or no data.

3.6. Focal brachytherapy

Eight studies on brachytherapy were included, seven in stage 2a and one in stage 2b. Sample sizes were small with a median of 30 patients (range 5–50). The median follow-up was 24 mo. Three studies reported a 100% absence of CSC in the treated area; one study [83] reported that 12% of the patients had CSC after treatment. Treatment was well tolerated, with only one study reporting one grade 3 complication, namely, acute prostate hemorrhage due to incorrect catheter removal [85]. Concerning continence, no differences for pre- and postprocedural continence scores were reported; only one study [82] reported a significant increase in IPSS score from 8 to 14 at 6 mo. Four studies reported on erectile function, with two presenting a decline and one study [85] reporting a significant decrease in IIEF scores from 19 (5–22) at baseline to 6 (3–20) at 6 mo, corresponding to a 50% rate of new onset of severe erectile dysfunction [85].

3.7. Radiofrequent ablation

Two IDEAL stage 2a studies on RFA were included [88,89] with ten and 20 patients and 12- and 6-mo follow-up, respectively. CSC in the treated area was reported in 4/20 patients (20%) by Orczyk et al [89]. The other study by Aydin et al [88] did not report on CSC but reported cancer in the treated area in 3/10 patients. One grade 3 SAE was reported, that is, gross hematuria that required diagnostic cystoscopy without the need for coagulation. No new pad use was reported by Aydin et al [88], while Orczyk et al [89] reported that 2/18 required a pad after RFA. Concerning erectile function, Aydin et al [88] reported significantly decreased IIEF-5 scores at 6 mo and Orczyk et al [89] reported absence of new erectile dysfunction in 11/12 patients.

3.8. Prostatic artery embolization

One prospective pilot study on PAE (IDEAL stage 2a) was identified [90], In this study, ten patients, consisting of men with a median age of 72 yr and a Gleason score of 6, were treated with PAE. No SAEs were reported. After 6 mo, 6/10 patients had CSC of the treated area at biopsy. No significant changes in urinary continence (IPSS score from median 5 to 1 [$p = 0.32$]) or erectile function (IIEF-6 score from median 24 to 27 [$p = 0.97$]) were reported.

3.9. Current and future studies

Forty-three studies were identified in the trial database of Clinicaltrials.gov (up to January 31, 2021) concerning FT as a primary treatment for men with localized PCa (Table 4). In addition to the earlier mentioned modalities, studies on MWA ($n = 4$) were identified. Most modalities will remain to be studied in stage 2. Only for HIFU and PDT, progression toward advanced research stages 3 and 4 can be seen. An overview of IDEAL-stage progression from studies identified in this review and studies identified on clinicaltrials.gov (>2020) is depicted in Fig. 2.

3.10. Discussion

In this systematic review, we identified 72 studies, describing eight sources of energy for primary FT in 5827 patients with localized PCa. The majority of studies were in an early research stage, with IDEAL stage 2a ($n = 35$) followed by IDEAL stage 2b ($n = 27$), although IDEAL stages 3–4 were identified in five studies. Currently registered studies ($n = 43$) show similar trends to those observed in studies of the past 5 yr, that is, most studies being in IDEAL stage 2 and the majority investigating HIFU.

Concerning oncological effectiveness, almost all studies reported that they performed control biopsies, but most studies did not report on CSC. CSC in the treated area was described with a median of 14.7% (HIFU), 8.5% (IRE), 10% (PDT), 15% (cryoablation), 17% (FLA), 20% (RFA), 60% (PAE), and 0% (focal brachytherapy) of treated patients. However, these numbers need to be interpreted with caution as only two studies in focal brachytherapy presented the numbers of CSC and only one study reported CSC in PAE and RFA. Moreover, in general, the follow-up was rather short, with, for example, a median follow-up of 12 mo (range 6–45) for HIFU, which makes the assessment of oncological effectiveness challenging. Functional outcomes were generally favorable for all modalities of FT. No significant changes in urinary continence and ESI were reported for studies using HIFU, FLA, cryoablation, and PDT. Although a reliable comparison between modalities is challenging to draw, HIFU and PDT seem to be studied most extensively and in advanced research stages (2b-3).

Valerio et al [12] included 37 studies, whereas we have identified 72 studies, indicating that over the past 5 yr more studies have been investigating FT. Some differences between the two reviews could be discussed. First, the new review includes larger series for HIFU, IRE, FLA, and PDT, and a longer median follow-up with a median of approximately 15 mo. Second, the identified studies included patients with low-risk PCa, but we observed an increase in the proportion of patients with a Gleason score of 7 undergoing FT. Third, HIFU remained the most studied modality, and for both HIFU and IRE, we found studies with

advancement toward stage 3. FLA showed progress toward stage 2b. Cryoablation and brachytherapy remained in stage 2b. The current review identified seven PDT studies, whereas Valerio et al [12] reported three PDT studies. Two of the currently identified PDT studies reported results from an RCT. Surprisingly, PDT was not the most extensively studied energy source over the past decades. The first pilot study on PDT for patients with low-risk PCa was conducted in 2006 [93], in an era where cryoablation and HIFU had already proceeded to stage 2 and where the first pilot study on RFA for PCa patients was performed almost 10 yr before [94]. A possible reason for the quick advancement of studies on a certain modality could be the continuous commitment of a research group to gain evidence for a certain treatment modality. Fourth, some differences in energy sources were found, that is, Valerio et al [12] included no study using PAE, whereas we identified one stage 2a study. Fifth, we identified seven studies with a comparator arm composed of standard care [23,29,32,42,52,71,73], whereas Valerio et al [12] identified none. Similar to Valerio et al [12], we encountered considerable heterogeneity of studies, including differences in patients (inclusion of Gleason 6 patients), type of ablations (ie, hemiablation and hockey stick ablation), biopsy method, follow-up, functional outcomes reported, and different definitions of CSC. Despite numerous consensus meetings describing these aspects [10,95–97], still a considerable variety is observed between studies. In addition, some studies reported the addition of TURP prior to HIFU, which was the case for 37% of the HIFU studies included in this review. We described these results separately, because we could not exclude that the previous TURP influenced the functional and oncological outcomes. Based on this review, a majority of HIFU procedures are performed without the addition of TURP. The most recent guideline report and consensus statement do not mention the addition of TURP prior to FT [2,98]. Nomenclature changes were not observed, although it is remarkable that partial gland ablation is more often used in studies involving cryoablation. Furthermore, we have identified 43 ongoing trials, whereas Valerio et al [12] identified 17 trials, indicating an increase in the number of trials involving FT for localized PCa.

To our knowledge, this is the first systematic review on FT without a language bias, which has, in addition to functional and oncological outcomes, provided insight into the research stage advancement of FT over the past 5 yr. Although this has led to an updated comprehensive overview of the current literature, there are some limitations that should be discussed. First, the heterogeneity of studies precluded an adequate risk of bias assessment and an adequate comparison between studies by means of a pooled analysis. In addition, there are several factors that challenge adequate interpretation of the results. Some studies reported significant differences but did not present the data. Other studies reported not to have observed statistically significant differences but presented data that could well present a clinically relevant difference. For instance, a study stated no significant differences in erectile function before and after treatment, while after treatment, the incidence of erectile dysfunction increased from 10% to 37% [45]. Moreover, these stage 2 studies were not powered to assess for clinically relevant differences. Another limitation consists of the possibly selective reporting of functional outcomes when patients would not reach the intended follow-up. For example, in a study [47] in which only 12/30 patients were able to reach the follow-up, all 12 reported leak- and pad-free continence. These data were presented as 100% pad-free continence, but this does not adequately reflect the functional outcome of the treated population.

In 2014, it was already stated that for FT to become an established treatment, studies needed to proceed from developmental studies toward stage 3 trials [99]. Although progress toward advanced research stages is seen in this review, a majority of studies still remain in stage 2. In addition, rather than progression of one particular energy source toward IDEAL stage 3 studies, multiple new energy sources are appearing, such as PAE and MWA. These modalities inevitably require to start off in an early research stage. There are several reasons that may explain why delivering a robust explanatory RCT is challenging. Some authors [100] suggest that not all patients are willing to be randomized into an experimental treatment group. The reason for this belief is the termination of several RCTs due to poor accrual. It is, therefore, suggested that the employed study design should be changed to that of a patient-preference study [12,100]. However, the PART feasibility RCT, which aimed to investigate the barriers of recruitment in HIFU, showed that patients were in fact willing to be randomized and that such a trial is feasible, albeit in a specific context. Indeed, the “expert” centers offering HIFU off trial had a low acceptance rate because most patients referred to these centers had strong preference for HIFU and therefore did not agree to be randomized [32]. A second challenge concerns the desired outcome variable that is to be studied. High-quality evidence gained through two different RCTs (PART for HIFU and PDT) shows that the genitourinary morbidity of FT is significantly lower [12]; however, evidence for oncological outcome is much more difficult to obtain. This will require a considerably large sample size and longer follow-up ($>$10 yr) given the inherent challenges with localized PCa treatment assessment. Defining oncological outcome by means of progression-free survival measure might reduce the follow-up of an RCT, but it is unlikely that a time scale of $<$10 yr would provide any definitive results.

4. Conclusions

Over the past 5 yr, 72 studies on FT have been conducted. With two RCTs and two propensity-score matched analyses, evidence generated by IDEAL stage $\geq$3 studies has been delivered. However, the majority of studies concerning FT for localized PCa are still in an early research stage. Although there is high-quality evidence that FT improves functional outcomes and minimizes adverse events, definitive proof of oncological effectiveness of FT against standard of care is still pending. To fully comprehend the role of FT in patients with localized PCa, more definitive studies are required.

***Author contributions*:** Jana S. Hopstaken and Joyce G.R. Bomers had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hopstaken, Bomers, Fütterer, Rovers.
Acquisition of data: Hopstaken, Bomers.
Analysis and interpretation of data: Hopstaken, Bomers, Fütterer, Rovers.
Drafting of the manuscript: Hopstaken, Bomers.
Critical revision of the manuscript for important intellectual content: Sedelaar, Valerio, Fütterer, Rovers.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Sedelaar, Valerio, Fütterer, Rovers.
Other: None.

***Financial disclosure*:** Jana S. Hopstaken certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Professor Dr. Rovers and Professor Dr. Fütterer report grants from Profound Medical, during the conduct of this study, and grants from Siemens Healthineers, outside the submitted work.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.08.005.

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