REVIEW ARTICLE

Oncological results and cancer control definition in focal therapy for Prostate Cancer: a systematic review

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INTRODUCTION: Focal therapy (FT) is a promising alternative to whole-gland treatments for Localized Prostate Cancer. Ten different FT modalities have been described in literature. However, FT is not yet recommended by the International Guidelines, due to the lack of robust data on Oncological Outcomes. The objective of our Narrative Review is to evaluate the oncological profile of the available FT modalities and to offer a comprehensive overview of the definitions of Cancer Control for FT.
MATERIAL AND METHODS: Literature search was performed on 21st February 2023 using PubMed, EMBASE, and Scopus, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). Articles reporting whole gland-treatments were excluded. All articles reporting oncological outcomes were included.
RESULTS: One-hundred-twenty-four studies, reporting data on more than 8000 patients treated with FT, were included. Overall, 40 papers were on High Intensity Focal Ultrasound (HIFU), 24 on Focal Cryotherapy, 13 on Irreversible Electroporation (IRE), 11 on Focal brachytherapy, 10 on Focal Laser Ablation (FLA), 8 on Photo-Dynamic Therapy (PDT), 3 on Microwave ablation, 3 on Robotic Partial Prostatectomy, 2 on bipolar Radio Frequency Ablation (bRFA), 1 on Prostatic Artery Embolization (PAE) and 9 comparative papers. Overall, the Biochemical Recurrence (BCR) rate ranged from 0% (Focal Brachytherapy) to 67.5% (HIFU); the Salvage treatment rate ranged from 1% (IRE) to 54% (HIFU) considering re-treatment with FT and from 0% (Focal Brachytherapy) to 66.7% considering standard Radical Treatments. There is no univocal definition of Cancer Control, however the "Phoenix criteria" for BCR were the most commonly used.
CONCLUSIONS: FT is a promising alternative treatment for localized prostate cancer in terms of Oncological Outcomes, however there is a wide heterogeneity in the definition of cancer control, the reporting of oncological outcomes and a lack of high-quality clinical trials. Solid comparative studies with standard treatments and an unambiguous consensus on how to describe Cancer Control in the field of Focal Therapy are needed.

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BACKGROUND

Whole-gland treatments, such as Radical Prostatectomy (RP) and Radiotherapy (including both External Beam Radiation Therapy (EBRT) and Brachytherapy), have historically been considered the standard of care for the treatment of Localized Prostate Cancer (PCa). With technological innovations and improving diagnostic accuracy, the detection of PCa has improved manifold. This has a far-reaching impact on incontinence and erectile dysfunction which overall impacts patients' QoL [1–5].

Active Surveillance (AS) is recommended by the EAU Guidelines as the standard of care for Low-risk patients and it is proposed as a possible management strategy for highly selected intermediate-risk patients, aiming to avoid unnecessary treatment and its related side effects [6, 7]. However, it is associated with a higher disease-progression rate and metastases, suggesting the need to find other therapeutic options for patients with clinically Localized PCa keen to preserve functional outcomes [8].

Since the early 2000s, Focal Therapy (FT) has gained popularity as an alternative option to whole-gland treatment and AS. The assumption of FT is that a single focus, called the "index lesion", drives the tumor growth and the risk of metastasis [9]. By targeting the index lesion or just a portion of the gland, avoiding the surrounding tissues, FT should significantly reduce treatment-related side effects on the urinary and sexual functions, resulting in a better health-related quality of life, without jeopardizing short-term cancer control [10, 11]. This has led to a progressive

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Table 1. Overview of the principal FT techniques, energy sources, mechanisms of action and approaches.

FT Modality	Energy source	Mechanism of action	Approach
HIFU [65]	Ultrasonic waves converted into heat (>65 °C)	Acoustic cavitation and coagulative necrosis	Transrectal probe under TRUS guidance
Cryotherapy [66]	Thermic Energy (−40 °C)	Protein degeneration, vascular damages, disruption of the cell membrane and cell lysis	Transperineal fibers under TRUS guidance
PDT [67]	Photosensitizing agent with vascular targeting	Infrared-activated generation of reactive oxygen species leading to vascular thrombosis and coagulative necrosis	Oral/intravenous drug + transperineal fibers under TRUS guidance
IRE [68]	Electric current	Formation of pores in prostate cell walls and cellular disruption	Transperineal needles under TRUS guidance
FLA [69]	Electromagnetic radiations inducing photothermal effect (>42 °C)	Protein denaturation and coagulative necrosis (without cavitation)	Transrectal/transperineal fibers under TRUS/MRI guidance
Focal brachytherapy [70]	Iodine-125 (I-125) radioactive seeds	DNA damage inducing mitotic arrest and cell death	Transperineal needles under TRUS/MRI guidance
Microwave ablation [43]	Microwaves inducing thermal effect	Coagulative necrosis with "heat-sink" effect	Transrectal/transperineal fibers under TRUS guidance
bRFA [71]	High-frequency alternating current	Heating with subsequent protein denaturation	Transperineal needles under TRUS guidance
PAE [50]	Microspheres injected into prostatic arteries	Local anoxia resulting in ischemic necrosis and inflammatory reactions	Superselective percutaneous angiography
Partial Prostatectomy [47]	-	Surgical partial removal of the prostate/ target lesion	Robotic Transperitoneal or Transvesical approach

HIFU high intensity focused ultrasound, *PDT* photodynamic therapy, *IRE* irreversible electroporation, *FLA* focal laser ablation, *bRFA* bipolar radiofrequency ablation, *PAE* prostatic artery embolization, *TRUS* transrectal ultrasound.

trend to partial gland ablative treatments over whole gland approach.

Ten different FT modalities have been described: High Intensity Focused Ultrasound (HIFU), Focal Cryotherapy, Irreversible Electroporation (IRE), Focal Brachytherapy, Focal Laser Ablation (FLA), Photodynamic Therapy (PDT), Microwave ablation, Partial Prostatectomy, bipolar Radio Frequency Ablation (bRFA) and Prostatic Artery Embolization (PAE). The main characteristics for each approach are summarized in Table 1. However, despite numerous studies have been carried out to evaluate the oncological and functional outcomes of FT, due to the absence of reliable evidence of long-term efficacy, the EAU Guidelines still recommend offering whole-gland as well as focal ablative therapies within clinical trials or registries [6].

Moreover, while it is well known how to evaluate the overall performance of radical treatments with curative intent for Localized PCa such as RP or RT using trifecta and pentafecta, these have never been discussed for FT [12, 13]; therefore, there is still no tool to objectively judge neither the individual treatments nor the various FT modalities between them. In Trifecta, the oncological outcome is defined as Cancer Control; however, in the FT field, there is no consensus on how to report the Cancer Control outcome, despite numerous consensus meetings, which focused more on standardization of follow-up and indications.

The aim of this systematic review was to provide a comprehensive overview of the results in terms of Oncological outcomes of the avaialable different modalities of Partial-gland FT and how in the current literature Cancer Control is defined in the field of FT.

EVIDENCE ACQUISITION

Literature search

This Systematic Review was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method [14]. Literature search was performed on 21 February 2023 using PubMed, EMBASE, and Scopus. No date limit was imposed on the literature search. The following term and Boolean operators were used: (focal brachytherapy OR Irreversible Electroporation OR High-Intensity Focused Ultrasound OR cryotherapy OR microwave ablation OR partial prostatectomy OR focal laser therapy OR photodynamic therapy OR radiofrequency ablation) AND (prostate OR prostatic) AND (cancer OR tumor). The complete and more comprehensive research strategy is provided in Appendix 1.

Selection criteria

The PICO (Patient, Intervention, Comparison, Outcomes) model was used to frame and answer the clinical question:

P: Patients with Localized PCa
I: Focal therapy including HIFU, Cryotherapy, IRE, Microwave ablation, FLA, PDT, bRFAn, Focal Brachytherapy, Partial Prostatectomy, PAE
C: Single-arm or comparative studies
O: Oncological outcomes including Biochemical Recurrence (BCR), Overall Survival (OS), Disease Free Survival (DFS), Salvage-free survival, Cancer in Treated area rates, Cancer in untreated area rates, Clinically Significant Cancer in treated area and Salvage rates

Study screening and selection

Studies were accepted based on PICOS eligibility criteria. Preclinical and animal studies were excluded. Only Partial gland ablations were included (including: Hockey sticks, hemi-gland, quadrant and subtotal), studies on whole-gland treatments where excluded. Reviews, letters to the editor, case reports, and meeting abstracts were also excluded. Only English papers were accepted. Retrospective, prospective and prospective randomized studies were accepted.

All retrieved studies were screened by two independent authors through Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). A third author solved

discrepancies through discussion. The full text of the screened papers was selected if found pertinent to the aim of this review.

EVIDENCE SYNTHESIS

Literature screening

Literature search found 13,516 papers. Among these, 2648 duplicates were automatically removed, and 10868 papers were screened against title and abstract. Among the latter, 10,576 papers were further excluded because unrelated to the purpose of the present review. The remaining 292 full-text papers were screened for appropriateness and 169 papers were excluded. Finally, 124 papers were accepted and included. Figure 1 shows the flow diagram of the literature search.

Study characteristics

There were 40 papers on HIFU, 24 on Focal Cryotherapy, 13 on IRE, 11 on Focal brachytherapy, 10 on FLA, 8 on PDT, 3 on Microwave ablation, 3 on partial prostatectomy, 2 on bRFA and 1 on PAE. There were 9 comparative studies. Among them, 1 was a pooled analysis on PDT and 2 studies reporting 2 and 4-years oncological outcomes of a single RCT comparing PDT and Active Surveillance (AS); all the other articles were prospective and retrospective cohorts. It was therefore not possible to perform a Meta-Analysis. The complete list of the studies is available in Appendix 2. The general characteristics of the included articles are summarized in Supplementary Table 1, while all oncological outcomes are available in Supplementary Table 2.

An overview of the ranges of BCR, focal re-treatment and radical treatment sorted by modality and of the number of studies reporting these parameters is available in Table 2. A summary of the modalities in which these parameters are defined between the various studies is presented in Table 3.

Comparative studies

Thirteen of the 124 studies retrieved were comparative and, among them, two referred to the same RCT. Overall, 3 of them compared the results of FT vs AS, 5 compared FT vs Robot Assisted Laparoscopic Prostatectomy (RALP) and 5 compared different FT modalities. However, only 9 studies (2 FT vs AS, 2 FT vs RALP and 4 FT vs FT) reported oncological outcomes and were therefore included in this analysis.

FT vs AS. The two available articles referred to a single Randomized Clinical Trial (RCT) d(PCM301) by the PMC301 study group [15, 16], including 206 patients in PDT arm and 207 in AS arm, reporting the 2- and 4-year oncological outcomes. All patients had a low-risk disease. Treatment failure was defined as the progression of disease from low- to moderate- or high-risk PCa. Re-treatment was permitted at 1 year in areas with positive biopsy. At the 2 years follow-up, negative biopsies were reported in 49% of men treated with PDT and 14% on AS. At 4 years, PDT was associated with significantly lower rates of cancer progression (HR 0.42) and conversion to radical treatment compared to AS (24% for PDT vs 53% for AS). PDT was not approved by the US FDA in 2020 due to missing biopsy data (13%), high rate of complications, and potential danger of large numbers of men with low risk PCa amenable for AS receiving unnecessary treatment.

FT vs RALP. Only three articles comparing the oncological outcomes of FT to RALP are available in the literature: one comparing radical prostatectomy to HIFU, the other comparing it to HIFU and focal Cryotherapy and lastly RALP vs IRE. However, Hamdy's work [17] is only a feasibility study, it does not report any results and were therefore excluded. In a match paired analysis, Garcia- Barreras et al. [18] compared 236 patients undergoing FT (HIFU or Cryotherapy) with 472 patients undergoing RALP: at a mean follow up of 38.4 months, FT failure (defined as positive control biopsy after treatment) was observed in 68 men (28.8%), of which 53 (28.1%) after HIFU and 15 (31.2%) after cryotherapy. FT ablation was associated with a higher risk of salvage treatment (HR 6.06, $p < 0.001$) compared to standard radical treatment. In a match-paired analysis, Scheltema et al. [19] aimed to compare the effect of RALP versus focal IRE on patient-reported quality of life (QoL) and early oncological control using propensity-scored matching (50 patients each). In total, 70.5% (31/44) men were free of significant PCa. Of those with residual significant PCa (29.5%, 13/44), five were monitored actively, three underwent salvage IRE, three salvage RALP, one salvage low-dose rate brachytherapy. One patient was diagnosed with metastatic disease directly after IRE due to persisting elevated PSA (>10 ng/mL) that refused pre-treatment template-mapping biopsies and staging imaging. The median decline in PSA after IRE was 51% (IQR 28–85%) when the median post-IRE nadir PSA (2.8 ng/mL, IQR 0.9–4.5) was compared with the median pre-IRE PSA (5.9 ng/mL, IQR 3.3–7.3). None of the RALP patients experienced biochemical failure (PSA ≥ 0.2 ng/mL) within the first 12 months of follow-up.

Comparison between different modalities of FT. Among four studies comparing the oncological results of different FT modalities, three compared HIFU to Cryotherapy while one compared HIFU, Focal Brachytherapy, Cryotherapy, and PDT. However, two of these [20, 21] reported results from the same retrospective cohort, with similar variables for 3- and 5-year outcomes: at 1, 3 and 5 years the cumulative failure-free survival rate was 95%, 67% and 54%, while the radical treatment-free survival rate was 99%, 79% and 67%, respectively. The 5-year metastasis-free survival rate was 98% and no PCa-specific death was registered in this cohort. On the other hand, the observational prospective study by Dias et al. [22], with a cohort of 150 patients (37 and 113 treated with Cryotherapy and HIFU respectively) and a median follow-up of 61 months, reported failure-free survival (FFS) at 2 and 4 years of 75.6% and 53.6%, respectively, while salvage-free survival at 2 and 4 years was of 78.9% and 53.9%, respectively. Finally, in the retrospective study by Barret et al. [23], the post-treatment PSA levels were 3.1, 2.9, and 2.7 ng/ml at 3, 6 and 12 months respectively; no other oncological outcomes were reported.

Single-arm studies

Focal HIFU. Oncological outcome of HIFU ablation were reported by 40 studies. Six of them reported outcome of hemi-gland ablation. All studies used ultrasound-guided HIFU ablation except one series by Tay et al. reporting outcome of Magnetic Resonance (MR)-guided HIFU treatment. There was no RCT assessing the outcome of HIFU ablation for PCa. Overall, 28 studies were prospective, while 15 studies were retrospective case series. Median follow-up ranged from 6 to 127 months. While El Fegoun et al. [24] reported the series with the longest follow-up period of 127 months, this series only included 12 patients. On the other hand, Reddy et al. [25] reported the outcome of 1379 patients from 13 centers in the United Kingdom with a median follow-up of 32 months, while Stabile et al. [26] retrospectively reported a multicentric cohort of 703 patients in Europe with a median follow-up of 41 months.

Eighteen studies used MRI-USG fusion biopsy for diagnosis of PCa before HIFU ablation. All studies reported a mean PSA < 10 ng/mL before HIFU ablation. Sixteen series included ISUP grade group 4. After the treatment, 23 studies reported a routine mpMRI at 6–12 months together with a template or MRI-USG fusion biopsy at 6–12 months. The risk of any PCa recurrence upon follow-up control biopsy was 6% to 30% in majority of the studies. Some studies reported a recurrence rate of 30–50%. Abreu et al. [27] reported a 10% in-field recurrence and 8% out-of-field recurrence of ISUP grade group 2 or above PCa, which is similar to

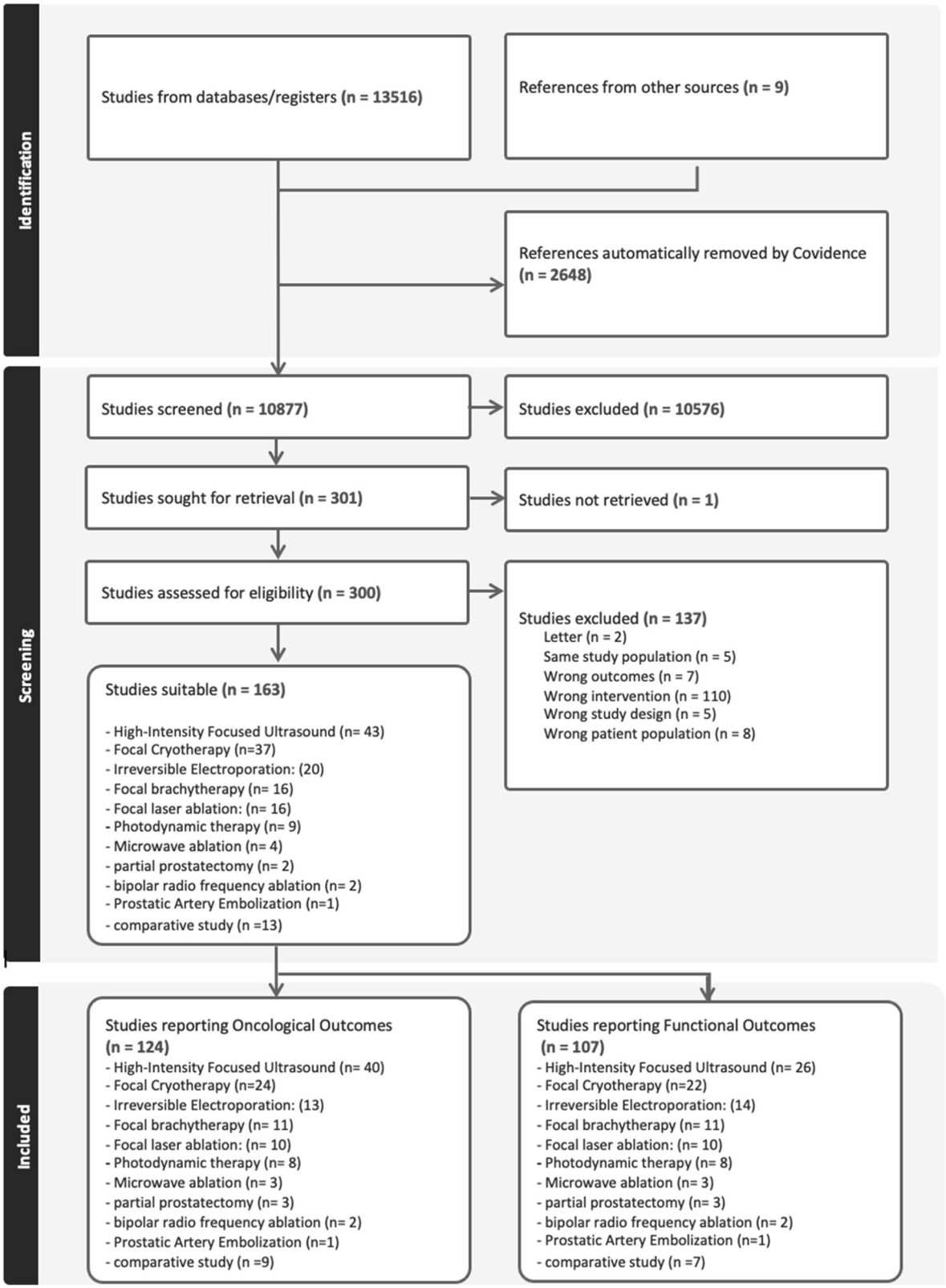

Fig. 1 PRISMA flowchart. Preferred reporting items for systematic review and meta-analysis flowchart.

Nahar et al. [28]. Shoji et al. [29] reported 8.9% of the patients having significant cancer detected in the un-treated area, but none in the treated area. Overall, the need for more than one ablative session ranged from 3.8% to 30%, and the need for further radical treatment (radical prostatectomy or whole-gland radiotherapy) ranged from 2.2% to 25%. Reddy et al. [25] reported 18.3% of their patients requiring repeated FT due to residual or recurrent cancer and 6.7% of their patients requiring salvage whole-gland treatment. Stabile et al. [26] reported an overall rate of 30% patients having additional treatment with 13% having

Table 2. Overview of the Oncological Result for FT.

FT Modality	BCR range (%)	Studies reporting BCR, n (%)	Focal re-treatment range, %	Studies reporting re-treatment, n (%)	Salvage treatment range, %	Studies reporting salvage treatment, n (%)
HIFU	2–67.5	22/40 (55)	2.3–54	14/40 (35)	3.3–38	26/40 (65)
Cryotherapy	2.6–62	12/24 (50)	1.6–19.9	14/24 (58.3)	1.3–44	15/24 (62.5)
PDT	4.9–33	3/8 (37.5)	1.5–23	4/8 (50)	8.3–66.7	4/8 (50)
IRE	NR	0/13 (0)	1–10.5	10/13 (73.9)	2–16.2	12/13 (92.3)
FLA	NR	0/10 (0)	2–33.3	5/10 (50)	1.7–16.7	4/10 (40)
Focal brachytherapy	0–29	6/11 (54.5)	6.7–17	4/11 (36.3)	0–16.7	6/11 (54.5)
Microwave ablation	NR	0/3 (0)	NR	0/3 (0)	10–13	2/3 (66.7)
RFA	NR	0/2 (0)	10	1/2 (50)	20	1/2 (50)
PAE	NR	0/1 (0)	NR	0/1	10	1/1 (100)
Partial Prostatectomy	11.1	1/3 (33.3)	NR	0/3 (0)	7.3–24	2/3 (66.7)

BCR, retreatment and salvage treatment ranges sorted by modality and the number of studies reporting the parameters.

Table 3. Overview of Cancer Control definitions in FT.

Cancer Control definition	Definition	Number of studies reporting the parameter
BCR ASTRO '97	Three consecutive rises of PSA above the Nadir	3
BCR Phoenix	Rise of PSA ≥ 2 ng/ml above the Nadir	29
BCR Stuttgart	PSA Nadir + 1.2 ng/mL	4
BCR Huber	PSA 1.0 ng/mL at 12 months and 1.5 ng/mL at 24–36 months	1
BCR Nadir + 0.5 ng/mL	PSA Nadir + 0.5 ng/mL	1
BCR AUA criteria for BCR after RP	Post-operative PSA ≥ 0.2ng/mL followed by a second confirmatory PSA ≥ 0.2ng/mL	1
Salvage - Focal re-treatment	Need for a new FT treatment (same or different FT modality)	52
Salvage - Radical treatment	Need for Radical treatment (ADT, RT, Prostatectomy)	73

Definitions of BCR and re-treatment and number of studies reporting each parameter.

radical treatment over the study period. Some studies adopted the ASTRO definition as BCR (2 studies before 2008) while some adopted Phoenix (11 studies) or Stuttgart (3 studies) criteria. The BCR by Phoenix criteria ranged from 7.8% to 26.6%. Men with bilateral PCar at diagnosis and a higher PSA nadir had a higher likelihood of treatment failure. Furthermore, HIFU treatment for anteriorly locating tumor has lower success rate.

Cryotherapy. Oncological outcomes of Cryotherapy were reported by 24 studies of this review. Of them, seven were prospective study, while fourteen were retrospective, for a total of more than 2800 patients treated. No RCT was available. The largest series was reported by Ward et al. [30], with more than a thousand patients enrolled, while all the other studies included less than 200 patients. Median follow-up ranged from 24 to 60 months, with the longest of 85 months reported by Marra et al. [31]. Nineteen studies used MRI-USG fusion biopsy for diagnosis of PCa before Cryosurgical ablation. All studies reported a mean PSA < 10 ng/mL before ablation except for Shah et al. [32] (mean PSA 10.8 (7.8–15.6) ng/mL) and Ward et al. [30] (156 patients with PSA > 10 ng/mL). Eleven series included ISUP grade group 4 or higher. After the treatment, 16 studies reported the use of a routine mpMRI at 6 to 12 months together with a template or MRI-USG fusion biopsy at 6 to 12 months. At a median follow up of 24 months, OS ranged from 97% to 100%. Conversely, the risk of any PCa recurrence at follow-up biopsy on treated areas ranged from 0%, as reported by Onik et al. in [33], to 56%, as reported by Ohishi et al. in [34]. Recurrence in untreated areas ranged from 0 to 24%. In terms of cancer control, BCR rate was reported by approximatively half of the studies. Some adopted the ASTRO definition for BCR (2 studies before 2008), while others adopted the Phoenix criteria (8 studies) or even a self-proposed definition of Nadir + 0.5 ng/mL as threshold. BCR according to Phoenix criteria ranged from 4% to 37.5%. The need for more than one focal ablative treatment ranged from 2.7% to 13%, while the need for subsequent radical treatment (radical prostatectomy or whole-gland radiotherapy) ranged from 1.3% to 44%.

IRE. Thirteen studies on IRE were identified, of which seven were retrospective and five were prospective. The median number of patients included was 45 (range 10–429). The follow-up ranged from 6 to 60 months. In all studies an MRI was performed before control prostate biopsy, which was a template mapping biopsy in 8 studies, whilst MRI-targeted biopsy was performed in 9 studies. All the repeated biopsies were performed 6–12 months post-IRE. Cancer in the treated area was reported by 10 studies with a rate of positivity ranging from 0 to 33.3%. The rate of clinically significant PCa in the untreated area was 5–31%. Blazevski et al. [35] reported that at 3 years, the overall failure-free survival was 96.8%, metastasis-free survival was 98.5% and overall survival was 100%. Scheltema et al. [36] reported failure-free survival of 91% at 3 years, 84% at 5 years and 69% at 8 years. Moreover, there were no significant differences in failure-free survival rates per ISUP Grade. Only 2 studies reported the rate of BCR. In one study, the

Phoenix definition was used, while in another one BCR was defined as Nadir + 0.5 ng/mL. BCR rate was 4.6% and 11%, respectively. Only one paper did not report the rate of Salvage therapy; notably in 6 studies a re-treatment after failure with IRE was administered.

Focal Brachytherapy. We identified 11 studies reporting oncological outcomes of focal brachytherapy, for a total of 576 patients included. Overall, the median follow-up ranged from 6 to 72 months. 3 studies had a median follow-up >60 months. Six studies reported 0% of clinically significant cancer in the treated area, while one reported that 5% of the participants had clinically significant cancer after treatment. Two studies reported a biochemical failure-free survival of 100%. The longer-term studies demonstrated promising results. Saito et al. [37] and Ta et al. [38] showed a 5-year treatment failure-free survival of 90% and a 5-year biochemical recurrence-free survival of 96.8%, respectively. In the study conducted by Nguyen et al. [39], both low- and intermediate-risk groups had a favorable PSA failure-free survival (at 5 years: 95.1% and 73.0%, respectively; at 8 years: 80.4% and 66.4%, respectively). Only 6 studies reported the rates of BCR, with the Phoenix criteria being the only definition used. Only 4 studies reported the rates of salvage treatment, with brachytherapy re-treatment as the most common salvage treatment used, along with External Beam Radiotherapy.

FLA. Ten studies on Focal Laser Ablation (FLA) were identified. All of them were prospective, for a total of 344 patients included. No RCT was available. The sample size ranged from 7 to 120 patients. Overall, at follow-up time ranging from 3 to 71.5 months, the percentage of residual cancer in the treated area was 15–70%. One study reported residual PCa in the treated area of only 4% (Lepor et al. [40]), in contrast with all the other studies that were based on longer follow-up. In 6 out of 12 studies, a systematic sampling of the prostate was combined with targeted biopsy samples during follow-up, reporting a percentage of cancer in untreated areas ranging from 6.7% to 75%. None of the studies reported BCR rates. Salvage therapies were performed in up to 50% of the cases.

PDT. Eight studies reported oncological outcomes of PDT, with only one of them being retrospective, while all other seven were prospective. A total of 366 patients were included. Azzouzi et al. [41], in a pooled analysis of three phase 2 studies including 117 men with low-risk PCa treated with PDT hemi-ablation in the lobe with cancer and bilateral subtotal ablation in case of bilateral disease, reported 6-month biopsy positivity rate of 31.6%. In the study by Noweski et al. [42], a medium-term phase 2 study on 68 optimally treated patients with 3.5 years of follow-up, 50% of the cohort had positive follow-up biopsy (25% in the treated and 25% in the untreated lobe). Only one study reported the BCR-Phoenix rate (4.8%), while 5 studies reported Salvage treatment rates, for a total of 18 patients re-treated with FT.

Microwave ablation. Three studies on microwaves reported oncological outcomes, and all of them were single-center prospective trial, for a total of 36 patients included. The "Fostine trial" is the first feasibility and safety study conducted by Delongchamps et al. [43] using transrectal microwave needle ablation guided by MRI-Ultrasound fusion with organ-based tracking mechanism; the primary outcome was the ablation zone necrosis at one-week post-operative MRI. Another phase 1 trial on TMA by Oderda et al. [44] was performed in 11 patients via transperineal route, and oncological outcomes are awaited. The oncological outcomes of the first 15 patients in the first efficacy trial ($n = 30$) on TMA by Chiu et al. [45] was reported in 2022. Twenty-three tumor regions in 15 patients were ablated, with PSA dropping from a median of 7.7 to 2.4 ng/mL in 6 months. The primary outcome of per-protocol 6-month biopsy outcome of both treated (targeted biopsy of 3–4 cores per lesion) and untreated (systematic biopsies of at least 18 cores) areas showed that 91.3% of the treated areas had no cancer. In per-patient analysis, 5 patients (33.3%) had in-field or out-of-field recurrences; of those, 4 were amenable for AS and 1 had radical RT.

Partial Prostatectomy. Three studies on robotic-assisted Partial Prostatectomy where included, for a total of 51 patients. All patients had GS 7 or less. Villers et al. [46] performed a technical feasibility study of anterior Partial Prostatectomy (APP) for isolated anterior PCa, proven at targeted biopsy (two cores per lesion) and determined to be at low or intermediate risk. Twenty-eight patients fulfilled the study criteria, but only 17 (60%) gave the consent to participate. Nine (53%) of them had positive surgical margins. Overall, five patients showed residual tumor at post-operative biopsy. Overall, robotic-assisted Partial Prostatectomy for isolated anterior cancer resulted in 86% BCR-free survival at 24 months of follow-up. In 2022, Kaouk et al. [47] reported perioperative retrospective outcomes of the first 9 consecutive partial prostatic gland excision through a transvesical approach, with a robotic single port device. Focally positive margins were found in 4 patients (44%), even if all patients had negative margins at frozen sections. Two studies reported salvage treatment rates (5.5 and 24%, respectively).

bRFA. Two studies on bRFA were included. The one by Aydin et al. [48] retrospectively reviewed data on two prospective pilot trials of bRFA for localized PCa, enrolling a total of 10 patients with a median follow-up of 6 months, while the other by Orczyk et al. [49] enrolled 20 patients (2 D'Amico Low-Risk and 18 Intermediate-Risk), with a median 12-month follow-up. In both studies, follow-up with transperineal prostate biopsy was carried out at a median of 6 months from bRFA: Aydin et al. [48] reported no cancer in the treated zones in 70% of patients, while the absence of significant PCa was achieved in 16 patients (80%) in the study by Orczyk et al. [49]. Among the seven patients who had no residual disease in the ablated zone, as reported by Aydin et al. [48], two showed minimal (<5% of the positive core) low-risk (GS = 6) de novo lesions outside the treated area. While the BCR rate was not reported, the rate of salvage treatment was 10% and 20% in the two studies.

PAE. Only one single prospective pilot study by Frandon et al. [50] was included, enrolling 10 patients with a median age of 72 years (range 62–77 years), with unilateral focal low-risk PCa under AS, who were treated with unilateral PAE in the affected prostatic lobe. At 6-months biopsy, 60% of patients had residual cancer in the treated area. At one year, 9 patients (90%) were still under surveillance, while one underwent radiotherapy for PCa progression outside the target lesion. No BCR rate were reported.

DISCUSSION

In this systematic review about oncological outcomes of FT, we identified 124 studies for a total of more than 8000 patients. We described 10 different FT modalities for PCa: HIFU, Cryoablation, FLA, microwaves, bRFA, PDT, focal brachytherapy, PAE and Partial Prostatectomy. The median follow-up was 24 months (IQR 12-36.7).

In terms of follow-up, most studies used an MRI at 6–12 months; the type of biopsies performed varied across the different studies both in terms of approach (targeted vs systematic, Transrectal vs Transperineal), timing and triggers (i.e., at BCR, or when there is any suspicion on MRI scan, etc.). The importance of correct pre-procedural staging with saturation biopsies and standardized follow-up that also uses MRI imaging to ensure excellent detection of clinically significant cancer is highlighted by numerous studies [51, 52].

It is not possible to absolutely compare Oncological results between the various modalities: some of them are more extensively studied than others that are only in an experimental phase.

In terms of BCR, the range was 2–67.5%, 2,6–62%, 0–29%, 33–4.9% and 11,1% (only 1 study available) for HIFU, Cryotherapy, Brachytherapy, PDT and Partial Prostatectomy respectively (Table 2). For the other FT modalities, this data was not reported. However, these results should be treated with caution not only due to the different follow-up, but also due to the absence of data on number of patients lost at follow-up in many series and to the different definitions of BCR that have been used (Table 3). The most studied modalities were HIFU and Cryotherapy, with follow-up time up to 127 months. It was not possible to summarize the results in terms of presence of cancer in treated area and cancer in untreated area after re-biopsy, as the rate of clinically significant cancer in treated or untreated area was often underreported and the timing of re-biopsy is significantly heterogeneous among the papers. Salvage treatment rates, considering patients re-treated with focal or whole gland treatment, were 2.3–54%, 1.6–19.9%, 6.7–17%, 2–33.3%, 1–10.5%, 1.5–23.3% an 10% (only 1 report available) for HIFU, Cryotherapy, Brachytherapy, FLA, IRE, PDT and bRFA, respectively. On the other hand, the range of salvage therapy with Radical/Systemic treatments (Radio therapy, Radical Prostatectomy, ADT) were 3.3–91%, 1.3–44.4%, 3.8–16.7%, 0–16.7%, 2–16.2%, 8.3–66.7%, 20% (only 1 report available), 10–13%, 7,3–24% and 10% (only 1 report available) for HIFU, Cryotherapy, focal brachytherapy, FLA, IRE, PDT, bRFA, microwaves, Partial Prostatectomy, and PAE, respectively. Again, these results must be placed in a context of wide numerical variability in terms of studies, sample, and follow-up, and therefore are not comparable.

For Localized Prostate Cancer, the optimal outcome after RALP is Cancer Control along with the recovery of continence and erectile function, a so-called Trifecta, implemented as Pentafecta (adding no postoperative complications and negative surgical margins) [12, 13]. Predictably, it is not possible to translate the additional oncological outcome of the Pentafecta into the field of focal therapy, as this was designed to evaluate the surgical performance after exeresis of the whole prostate gland it is therefore illogical to argue on positive margins in FT, especially in the setting of our review, where whole-gland treatments were excluded. In Trifecta, successful Cancer Control after RALP is defined by achieving and sustaining PSA levels below the upper limit of detection of the assay (0.4 ng/mL before 1996 and 0.2 ng/mL afterward) [53], as well as by the lack of further therapeutic intervention. Subsequently, Trifecta was translated into the field of RT, although it should be noted that in this case it has been used the Phoenix BCR definition, since the definition of BCR mentioned in the Trifecta is not applicable to RT [54]. In the FT field, in 2009 Blana et al. proposed their own definition of BCR for HIFU, the "Stuttgart criteria", which was defined as the PSA Nadir plus 1.2 ng/mL [55]. On the other hand, Huber et al. proposed a definition of cancer control failure after HIFU, defined as nadir PSA of 1.0 ng/ml at 12 months and 1.5 ng/ml at 24–36 months [56]. According to our findings, among the overall 44 studies reporting rates of BCR, 3 papers published before 2008 used the ASTRO Criteria of 1997, 29 used the Phoenix criteria applied to FT, 4 used the Stuttgart criteria, 1 used the Huber criteria, 1 the AUA Criteria and notably 1 paper used a unique definition of Nadir + 0.5 ng/mL (Table 3). It must be underlined that there is no consensus on how to unequivocally report the BCR in FT field. Numerous consensus meetings exist in the literature whose aim was to standardize indications, follow up and outcomes of FT therapy [57–61]. Of these, three [59–61] stated that no definition of BCR can be recommended based on the current data, while two [57, 58] did not mention the BCR. On the other hand, regarding the second definition of Cancer Control intended as rate of salvage treatment, 86 studies reported the rate of patients undergoing further interventions (Salvage therapy). Furthermore, the question whether a focal re-treatment with the same or different energy can be considered salvage treatment remains unresolved. Several other oncological outcomes are reported by authors: metastases or PCa-specific mortality, OS, rates of cancer in treated or untread area. This leads to a difficult comparison a of FT with current gold standard therapies and of FT modalities among them, although nowadays some authors suggest that proving the exact efficacy of FT may be less important than re-confirming its safety, for men with intermediate-risk PCa [62]. Moreover, the absence of solid RCT in FT does not allow to perform a meta-analysis.

Comparing our work with previous reviews available on FT, Valerio et al. [63] included 37 studies, Hopstaken et al. [64] identified 72 studies, while in our study, a total of 124 paper were included. There are some substantial differences between these three reviews. First of all, our work focuses exclusively on the Oncological Outcomes of FT. Then, we identified two novel FT modality: microwaves and Partial prostatectomy, which were not included in previous works. Third, our review included larger series for HIFU, IRE, FLA, and PDT, and a longer median follow-up of 24 months. it should also be noted that more than 90 studies included patients with a GS = 7 (both GS 3 + 4 and GS 4 + 3) or Higher, highlighting the tendency to include patients with increasingly higher risk classes of PCa among candidates for FT. Moreover, we excluded whole gland treatments, focusing on partial gland ablation only. Similarly to previous works, one of the most important problems was the lack of heterogeneity not only in the disease characteristics of the included patients, but also in the ways and times of follow-up, making it impossible to perform a meta-analysis.

To our knowledge, this is the first Systematic Review on FT focusing on partial gland ablation and Oncological Outcomes results and definition, including 10 modalities. However, several limitations of our work deserve mention. First of all, the modalities described use different templates in the various studies: Hockey-stick template, hemi-ablation, ablation of a single ROI. In this setting, not only the template itself, but also the dimension of the ROI could greatly influence the oncological results. Second, as previously highlighted, there is a great heterogeneity on reporting outcomes and this makes it very difficult not only to compare the various studies available for each energy, but also to report all the myriad variables narratively and in tables, making this work also very complex to read. Third, some studies do not report lost-to-follow-up rates, suggesting the possible presence of missing data. Lastly, despite the very large number of studies retrieved thanks to our research strategy, we rescued only one RCT and we were therefore unable to perform a Meta-Analysis.

CONCLUSION

FT is a promising treatment in terms of Oncological Outcomes, for selected patients, willing to accept a strict follow up and significant re-treatment rate. There are currently 10 different modalities of FT. There is great heterogeneity in the outcomes reported in the literature. Further studies are needed to compare FT to standard of care and to implement consensual definition of BCR and therefore of Cancer Control.

DATA AVAILABILITY

The online version contains supplementary material, including the list of all articles retrieved and tables reporting information about these studies.

REFERENCES

1. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med. 2008;148:435–48.

2. Boorjian SA, Eastham JA, Graefen M, Guillonneau B, Karnes RJ, Moul JW, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. Eur Urol. 2012;61:664–75.
3. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368:436–45.
4. Ficarra V, Novara G, Rosen RC, Artibani W, Carroll PR, Costello A, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol. 2012;62:405–17.
5. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008;358:1250–61.
6. Schmidt-Hegemann NS, Zamboglou C, Mason M, Mottet N, Hinnen K, De Meerleer G, et al. ESTRO-ACROP recommendations for evidence-based use of androgen deprivation therapy in combination with external-beam radiotherapy in prostate cancer. Radiother Oncol. 2023;183:109544.
7. Bruinsma SM, Roobol MJ, Carroll PR, Klotz L, Pickles T, Moore CM, et al. Semantics in active surveillance for men with localized prostate cancer — results of a modified Delphi consensus procedure. Nat Rev Urol. 2017;14:312–22.
8. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med. 2016;375:1415–24.
9. Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, Part I: introduction, risk assessment, staging, and risk-based management. J Urol. 2022;208:10–8.
10. Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol. 2007;4:632–42.
11. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009;361:1704–6.
12. Bianco FJ, Scardino PT, Eastham JA. Radical prostatectomy: Long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology. 2005;66:83–94.
13. Patel VR, Sivaraman A, Coelho RF, Chauhan S, Palmer KJ, Orvieto MA, et al. Pentafecta: a new concept for reporting outcomes of robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2011;59:702–7.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
15. Azzouzi A-R, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, et al. Padeliporfin vascular- targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol. 2017;18:181–91.
16. Gill IS, Azzouzi AR, Emberton M, Coleman JA, Coeytaux E, Scherz A, et al. Randomized trial of partial gland ablation with vascular targeted phototherapy versus active surveillance for low risk prostate cancer: extended followup and analyses of effectiveness. J Urol. 2018;200:786–93.
17. Hamdy FC, Elliott D, le Conte S, Davies LC, Burns RM, Thomson C, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess. 2018;22:1–96.
18. Garcia-Barreras S, Sanchez-Salas R, Sivaraman A, Barret E, Secin F, Nunes-Silva I, et al. Compara- tive analysis of partial gland ablation and radical prostatectomy to treat low and intermediate risk prostate cancer: oncologic and functional outcomes. J Urol. 2018;199:140–6.
19. Scheltema MJ, Chang JI, Böhm M, van den Bos W, Blazevski A, Gielchinsky I, et al. Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World J Urol. 2018;36:1383–89.
20. Tourinho-Barbosa RR, Sanchez-Salas R, Claros OR, Collura-Merlier S, Bakavicius A, Carneiro A, et al. Focal therapy for localized prostate cancer with either HIFU or cryoa- blation: a single institution experience. J Urol. 2020;203:320–30.
21. Stabile A, Sanchez-Salas R, Tourinho-Barbosa R, Macek P, Pellegrino F, Gandaglia G, et al. Association between lesion location and oncologic outcomes after focal therapy for localized prostate cancer using either high intensity focused ultrasound or cryotherapy. J Urol. 2021;206:638–45.
22. Dias N, Rodriguez-Sanchez L, Colandrea G, Macek P, Cathelineau X. Medium-term oncological outcomes of intermediate-risk prostate cancer treated with HIFU or cryotherapy. A single center 10-year experience. Arch Ital Urol Androl. 2022;94:413–9.
23. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol. 2013;63:618–22. https://doi.org/10.1016/j.eururo.2012.11.057.
24. El Fegoun AB, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F, et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. Int Braz J Urol. 2011;37:213–9.
25. Reddy D, Peters M, Shah TT, van Son M, Tanaka MB, Huber PM, et al. Cancer control outcomes following focal therapy using high-intensity focused ultrasound in 1379 men with nonmetastatic prostate cancer: a multi-institute 15-year experience. Eur Urol. 2022;81:407–13.
26. Stabile A, Orczyk C, Giganti F, Moschini M, Allen C, Punwani S, et al. The role of percentage of prostate-specific antigen reduction after focal therapy using high-intensity focused ultrasound for primary localised prostate cancer. results from a large multi-institutional series. Eur Urol. 2020;78:155–60.
27. Abreu AL, Peretsman S, Iwata A, Shakir A, Iwata T, Brooks J, et al. High intensity focused ultrasound hemigland ablation for prostate cancer: initial outcomes of a United States series. J Urol. 2020;204:741–7.
28. Nahar B, Bhat A, Reis IM, Soodana-Prakash N, Becerra MF, Lopategui D, et al. Prospective evaluation of focal high intensity focused ultrasound for localized prostate cancer. J Urol. 2020;204:483–9.
29. Shoji S, Hiraiwa S, Uemura K, Nitta M, Hasegawa M, Kawamura Y, et al. Focal therapy with high-intensity focused ultrasound for the localized prostate cancer for Asian based on the localization with MRI-TRUS fusion image-guided transperineal biopsy and 12-cores transperineal systematic biopsy: prospective analysis of oncological and functional outcomes. Int J Clin Oncol. 2020;25:1844–53.
30. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. 2012;109:1648–54.
31. Marra G, Soeterik T, Oreggia D, Tourinho-Barbosa R, Moschini M, Filippini C, et al. Long-term outcomes of focal cryotherapy for low- to intermediate-risk prostate cancer: results and matched pair analysis with active surveillance. Eur Urol Focus. 2022;8:701–9.
32. Shah TT, Peters M, Eldred-Evans D, Miah S, Yap T, Faure-Walker NA, et al. Early-medium-term outcomes of primary focal cryotherapy to treat nonmetastatic clinically significant prostate cancer from a prospective multicentre registry. Eur Urol. 2019;76:98–105.
33. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The 'male lumpectomy': focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol Semin Orig Investig. 2008;26:500–5.
34. Oishi M, Gill IS, Tafuri A, Shakir A, Cacciamani GE, Iwata T, et al. Hemigland cryoablation of localized low, intermediate and high risk prostate cancer: oncologic and functional outcomes at 5 years. J Urol. 2019;202:1188–97.
35. Blazevski A, Amin A, Scheltema MJ, Balakrishnan A, Haynes A-M, Barreto D, et al. Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World J Urol. 2021;39:1107–14.
36. Scheltema MJ, Geboers B, Blazevski A, Doan P, Katelaris A, Agrawal S, et al. Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer. BJU Int. 2022;131:6–13. https://doi.org/10.1111/bju.15946.
37. Saito K, Matsuoka Y, Toda K, Yoshida S, Yokoyama M, Yoshimura R, et al. Medium-term oncological and functional outcomes of hemi-gland brachytherapy using iodine-125 seeds for intermediate-risk unilateral prostate cancer. Brachytherapy. 2021;20:842–8.
38. Ta M-H, Nunes-Silva I, Barret E, Renard-Penna R, Rozet F, Mombet A, et al. Focal brachytherapy for localized prostate cancer: midterm outcomes. Pract Radiat Oncol. 2021;11:e477–85.
39. Nguyen PL, Chen M-H, Zhang Y, Tempany CM, Cormack RA, Beard CJ, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol. 2012;188:1151–6.
40. Lepor H, Llukani E, Sperling D, Fütterer JJ. Complications, recovery, and early functional outcomes and oncologic control following in-bore focal laser ablation of prostate cancer. Eur Urol. 2015;68:924–6.
41. Azzouzi AR, Barret E, Bennet J, Moore C, Taneja S, Muir G, et al. TOOKAD® Soluble focal therapy: pooled analysis of three phase II studies assessing the minimally invasive ablation of localized prostate cancer. World J Urol. 2015;33:945–53.
42. Noweski A, Roosen A, Lebdai S, Barret E, Emberton M, Benzaghou F, et al. Medium-term follow-up of vascular-targeted photodynamic therapy of localized prostate cancer using TOOKAD soluble WST-11 (Phase II Trials). Eur Urol Focus. 2019;5:1022–8.
43. Barry Delongchamps N, Schull A, Anract J, Abecassis J-P, Zerbib M, Sibony M, et al. Feasibility and safety of targeted focal microwave ablation of the index tumor in patients with low to intermediate risk prostate cancer: Results of the FOSTINE trial. PLoS ONE. 2021;16:e0252040.
44. Oderda M, Marquis A, Calleris G, D'agate D, Faletti R, Gatti M, et al. Safety and feasibility of transperineal targeted microwave ablation for low- to intermediate-risk prostate cancer. Eur Urol Open Sci. 2022;46:3–7.
45. Chiu P.K., Chan C-H, Yee C-H, Lau S-Y, Teoh J.Y., Wong H-F, et al. Transperineal Targeted Microwave Ablation (TMA) of localized prostate cancer guided by MRI-Ultrasound fusion and organ-based tracking: a pilot study. Prostate Cancer Prostatic Dis. 2022. https://doi.org/10.1038/s41391-022-00577-8.
46. Villers A, Puech P, Flamand V, Haber G-P, Desai MM, Crouzet S, et al. Partial prostatectomy for anterior cancer: short-term oncologic and functional outcomes. Eur Urol. 2017;72:333–42.

47. Kaouk JH, Ferguson EL, Beksac AT, Zeinab MA, Kaviani A, Weight C, et al. Single-port robotic transvesical partial prostatectomy for localized prostate cancer: initial series and description of technique. Eur Urol. 2022;82:551–8.
48. Aydin AM, Gage K, Dhillon J, Cheriyan SK, Poch MA, Manley BJ, et al. Focal bipolar radiofrequency ablation for localized prostate cancer: Safety and feasibility. Int J Urol. 2020;27:882–9.
49. Orczyk C, Barratt D, Brew-Graves C, Peng Hu Y, Freeman A, McCartan N, et al. Prostate Radiofrequency Focal Ablation (ProRAFT) trial: a prospective development study evaluating a bipolar radio frequency device to treat prostate cancer. J Urol. 2021;205:1090–9.
50. Frandon J, Bey E, Hamard A, Mohammad H, Gonzalez S, Greffier J, et al. Early results of unilateral prostatic artery embolization as a focal therapy in patients with prostate cancer under active surveillance: cancer prostate embolisation, a pilot study. J Vasc Interv Radiol. 2021;32:247–55.
51. Lee AYM, Chen K, Tan YG, Lee HJ, Shutchaidat V, Fook-Chong S, et al. Reducing the number of systematic biopsy cores in the era of MRI targeted biopsy-implications on clinically-significant prostate cancer detection and relevance to focal therapy planning. Prostate Cancer Prostatic Dis. 2022;25:720–6. https://doi.org/10.1038/s41391-021-00485-3.
52. Ahn H, Hwang SI, Kim TM, Lee HJ, Choe G, Hong SK, et al. Diagnostic value of multiparametric MRI in detecting residual or recurrent prostate cancer after high-intensity focused ultrasound. Prostate Cancer Prostatic Dis. 2023;26:360–6. https://doi.org/10.1038/s41391-022-00531-8.
53. Toussi A, Stewart-Merrill SB, Boorjian SA, Psutka SP, Thompson RH, Frank I, et al. Standardizing the definition of biochemical recurrence after radical prostatectomy—what prostate specific antigen cut point best predicts a durable increase and subsequent systemic progression? J Urol. 2016;195:1754–9.
54. Jereczek-Fossa BA, Zerini D, Fodor C, Santoro L, Maucieri A, Gerardi MA, et al. Reporting combined outcomes with Trifecta and survival, continence, and potency (SCP) classification in 337 patients with prostate cancer treated with image-guided hypofractionated radiotherapy. BJU Int. 2014;114:E3–10.
55. Blana A, Brown SC, Chaussy C, Conti GN, Eastham JA, Ganzer R, et al. High-intensity focused ultrasound for prostate cancer: comparative definitions of biochemical failure. BJU Int. 2009;104:1058–62.
56. Huber PM, Afzal N, Arya M, Boxler S, Dudderidge T, Emberton M, et al. Prostate specific antigen criteria to diagnose failure of cancer control following focal therapy of nonmetastatic prostate cancer using high intensity focused ultrasound. J Urol. 2020;203:734–42.
57. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes-a report from a consensus meeting. Eur Urol. 2015;67:771–7.
58. Lebastchi AH, George AK, Polascik TJ, Coleman J, de la Rosette J, Turkbey B, et al. Standardized nomenclature and surveillance methodologies after focal therapy and partial gland ablation for localized prostate cancer: an international multidisciplinary consensus. Eur Urol. 2020;78:371–8.
59. Muller BG, van den Bos W, Brausi M, Cornud F, Gontero P, Kirkham A, et al. Role of multiparametric magnetic resonance imaging (MRI) in focal therapy for prostate cancer: a Delphi consensus project. BJU Int. 2014;114:698–707.
60. Postema AW, De Reijke TM, Ukimura O, Van den Bos W, Azzouzi AR, Barret E, et al. Standardization of definitions in focal therapy of prostate cancer: report from a Delphi consensus project. World J Urol. 2016;34:1373–82.
61. Van Den Bos W, Muller BG, Ahmed H, Bangma CH, Barret E, Crouzet S, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. Eur Urol. 2014;65:1078–83.
62. Marks LS. Prostate Cancer: a comparison of focal therapy and radical prostatectomy. Prostate Cancer Prostatic Dis. 2022;25:381–2. https://doi.org/10.1038/s41391-021-00334-3.
63. Valerio M, Cerantola Y, Eggener SE, Lepor H, Polascik TJ, Villers A, et al. New and established technology in focal ablation of the prostate: a systematic review [figure presented]. Eur Urol. 2017;71:17–34.
64. Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? Eur Urol. 2022;81:5–33.
65. Barkin J. High intensity focused ultrasound (HIFU). Can J Urol. 2011;18:5634–43.
66. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998;37:171–86.
67. Kimm SY, Tarin TV, Monette S, Srimathveeravalli G, Gerber D, Durack JC, et al. Nonthermal ablation by using intravascular oxygen radical generation with WST11: dynamic tissue effects and implications for focal therapy. Radiology. 2016;281:109–18.
68. Davalos RV, Mir LM, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng. 2005;33:223–31.
69. Lee T, Mendhiratta N, Sperling D, Lepor H. Focal laser ablation for localized prostate cancer: principles, clinical trials, and our initial experience. Rev Urol. 2014;16:55–66.
70. Cosset JM, Cathelineau X, Wakil G, Pierrat N, Quenzer O, Prapotnich D, et al. Focal brachytherapy for selected low-risk prostate cancers: a pilot study. Brachytherapy. 2013;12:331–7.
71. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur. J. Ultrasound. 2001;13:129–47.

AUTHOR CONTRIBUTIONS

RN and AA were responsible for interpreting data, editing and revise the tables, write the paper. DC, CHY, KZ, DP, PC and RC were responsible for interpreting data, editing summary tables, and editing the manuscript. DC and JYCT were responsible for designing the review protocol, coordinate the group and supervise the project. GRR, ED, GMP, GC, DF, CB, CG and VDS were responsible for collecting and reviewing journal articles, editing summary tables. SS, VG, CFN provided feedback on the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As this is a systematic review, institutional review board or patient consent were not required. As for all systematic reviews, the patients presented in this systematic review have been previously reported.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41391-023-00699-7.

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APPENDIX 1 – COMPLETE RESEARCH STRATEGY

Date: 21 February 2023
Search strategy for PubMed
(focal brachytherapy [title/abstract] OR Irreversible Electroporation [title/abstract] OR High-Intensity Focused Ultrasound [title/abstract] OR cryotherapy [title/abstract] OR microwave ablation [title/abstract] OR partial prostatectomy [title/abstract] OR focal laser therapy [title/abstract] OR photodynamic therapy [title/abstract] OR radiofrequency ablation [title/abstract]) AND ("prostate" [title/abstract] OR "prostatic" [title/abstract]) AND ("cancer" [title/abstract] OR "tumor" [title/abstract])
Search strategy for EMBASE
('focal brachytherapy' OR 'Irreversible Electroporation' OR 'High-Intensity Focused Ultrasound' OR 'cryotherapy' OR 'microwave ablation' OR 'partial prostatectomy' OR 'focal laser therapy' OR 'photodynamic therapy' OR 'radiofrequency ablation') AND ('prostate' OR 'prostatic') AND ('cancer' OR 'tumor')
Search strategy for Scopus
(focal brachytherapy OR Irreversible Electroporation OR High-Intensity Focused Ultrasound OR cryotherapy OR microwave ablation OR partial prostatectomy OR focal laser therapy OR photodynamic therapy OR radiofrequency ablation) AND (prostate OR prostatic) AND (cancer OR tumor)

APPENDIX 2 - COMPLETE LIST OF INCLUDED PAPERS, SORTED BY MODALITY ($N = 124$)

High Intensity Focused Ultrasound (HIFU) ($n = 40$)

1. Dellabella M, Branchi A, Di Rosa M, Pucci M, Gasparri L, Claudini R, et al. Oncological and functional outcome after partial prostate HIFU ablation with

focal-one®: a prospective single-center study. Prostate Cancer Prostatic Dis. 2021;24:1189–1197.
2. Annoot A, Olivier J, Valtille P, Deken V, Leroy X, Puech P, et al. Extra-target low-risk prostate cancer: implications for focal high-intensity focused ultrasound of clinically significant prostate cancer. World J Urol. 2019;37:261–268.
3. Rischmann P, Gelet A, Riche B, Villers A, Pasticier G, Bondil P, et al. Focal high intensity focused ultrasound of unilateral localized prostate cancer: a prospective multicentric hemiablation study of 111 patients. Eur Urol. 2017;71:267–273.
4. Glybochko P V, Amosov A V, Krupinov GE, Petrovskii N V, Lumpov IS. Hemiablation of localized prostate cancer by high-intensity focused ultrasound: a series of 35 cases. Oncology. 2019;97:44–48.
5. Ganzer R, Hadaschik B, Pahernik S, Koch D, Baumunk D, Kuru T, et al. Prospective multicenter phase II study on focal therapy (hemiablation) of the prostate with high intensity focused ultrasound. J Urol. 2018;199:983–989.
6. Tay KJ, Cheng CWS, Lau WKO, Khoo J, Thng CH, Kwek, JW. Focal therapy for prostate cancer with in-bore MR-guided focused ultrasound: two-year follow-up of a phase I trial-complications and functional outcomes. Radiology. 2017;285:620–628.
7. van Velthoven R, Aoun F, Marcelis Q, Albisinni S, Zanaty M, Lemort M, et al. A prospective clinical trial of HIFU hemiablation for clinically localized prostate cancer. Prostate Cancer Prostatic Dis. 2016;19:79–83.
8. Reddy D, Peters M, Shah TT, van Son M, Tanaka MB, Huber PM, et al. Cancer control outcomes following focal therapy using high-intensity focused ultrasound in 1379 men with nonmetastatic prostate cancer: a multi-institute 15-year experience. Eur Urol. 2022;81:407–413.
9. Abreu AL, Peretsman S, Iwata A, Shakir A, Iwata T, Brooks J, et al. High intensity focused ultrasound hemigland ablation for prostate cancer: initial outcomes of a United States Series. J Urol. 2020;204:741–747.
10. Dickinson L, Ahmed HU, Hindley RG, McCartan N, Freeman A, Allen C, et al. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol. 2017;**35**:30.e9–30.e15.
11. Feijoo ERC, Sivaraman A, Barret E, Sanchez-Salas R, Galiano M, Rozet F, et al. Focal high-intensity focused ultrasound targeted hemiablation for unilateral prostate cancer: a prospective evaluation of oncologic and functional outcomes. Eur Urol. 2016;69:214–220.
12. Hong SK, Lee H. Outcomes of partial gland ablation using high intensity focused ultrasound for prostate cancer. Urol Oncol. 2022;40:193.e1–193.e5.
13. Bass R, Fleshner N, Finelli A, Barkin J, Zhang L, Klotz L. Oncologic and functional outcomes of partial gland ablation with high intensity focused ultrasound for localized prostate cancer. J Urol. 2019;201:113–119.
14. Shoji S, Hiraiwa S, Uemura K, Nitta M, Hasegawa M, Kawamura Y, et al. Focal therapy with high-intensity focused ultrasound for the localized prostate cancer for Asian based on the localization with MRI-TRUS fusion image-guided transperineal biopsy and 12-cores transperineal systematic biopsy: prospective analysis of oncolo. Int J Clin Oncol. 2020;25:1844–1853.
15. Nahar B, Bhat A, Reis IM, Soodana-Prakash N, Becerra MF, Lopategui D, et al. Prospective evaluation of focal high intensity focused ultrasound for localized prostate cancer. J Urol. 2020;204:483–489.
16. Komura K, Inamoto T, Black PC, Fujisue Y, Katsuoka Y, Watsuji T, et al. Clinically significant urethral stricture and/or subclinical urethral stricture after high-intensity focused ultrasound correlates with disease-free survival in patients with localized prostate cancer. Urol Int. 2011;87:276–281.
17. Rosenhammer B, Niessen C, Rotzinger L, Reiss J, Schnabel MJ, Burger M, et al. Oncological outcome and value of postoperative magnetic resonance imaging after focal high-intensity focused ultrasound therapy for prostate cancer. Urol Int. 2019;103:270–278.
18. Rompré-Brodeur A, Marcq G, Tholomier C, Fugaru I, Loutochin O, Anidjar M, et al. Role of systematic control biopsies following partial gland ablation with high-intensity focused ultrasound for clinically significant prostate cancer. J Urol. 2021;206:1177–1183.
19. Huber PM, Afzal N, Arya M, Boxler S, Dudderidge T, Emberton M, et al. Focal HIFU therapy for anterior compared to posterior prostate cancer lesions. World J Urol. 2021;39:1115–1119.
20. von Hardenberg J, Westhoff N, Baumunk D, Hausmann D, Martini T, Marx A, et al. Prostate cancer treatment by the latest focal HIFU device with MRI/TRUS-fusion control biopsies: a prospective evaluation. Urol Oncol Semin Orig Investig. 2018;36:401.e1–401.e9.
21. Johnston MJ, Emara A, Noureldin M, Bott S, Hindley RG. Focal high-intensity focussed ultrasound partial gland ablation for the treatment of localized prostate cancer: a report of medium-term outcomes from a single-center in the United Kingdom. Urology. 2019;133:175–181.
22. Ghai S, Finelli A, Corr K, Chan R, Jokhu S, Li X, et al. MRI-guided focused ultrasound ablation for localized intermediate-risk prostate cancer: early results of a phase II trial. Radiology.2021;298:695–703.
23. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int. 2006;97:56–61.
24. Ganzer R, Rogenhofer S, Walter B, Lunz J-C, Schostak M, Wieland WF, et al. PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. Eur Urol. 2008;53:547–553.
25. Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, et al. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. Eur Urol. 2008;53:1194–1201.
26. Stabile A, Orczyk C, Hosking-Jervis F, Giganti F, Arya M, Hindley RG, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU Int. 2019;124:431–440.
27. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. 2008;38:192–199.
28. Westhoff N, Ernst R, Kowalewski KF, Schmidt L, Worst TS, Michel MS, et al. Treatment decision satisfaction and regret after focal HIFU for localized prostate cancer. World J Urol. 2021;39:1121–1129.
29. Misraï V, Rouprêt M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, et al. Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. *World J Urol*. 2008 Oct;26(5):481–5. https://doi.org/10.1007/s00345-008-0286-8. Epub 2008 Jun 26. PMID: 18581118.
30. Westhoff N, Ernst R, Kowalewski K-F, Derigs F, Neuberger M, Nörenberg D, et al. Medium-term Oncological Efficacy and Patient-reported Outcomes After Focal High-intensity Focused Ultrasound: The FOXPRO Trial. Eur Urol Focus. 2022. https://doi.org/10.1016/j.euf.2022.10.006.
31. Horiuchi A, Muto S, Horie S. Holmium laser enucleation of the prostate followed by high-intensity focused ultrasound treatment for patients with huge prostate adenoma and localized prostate cancer: 5-Year follow-up. Prostate Int. 2016;4:49–53.
32. Maestroni U, Dinale F, Minari R, Salsi P, Ziglioli F. High-intensity focused ultrasound for prostate cancer: long-term followup and complications rate. Adv Urol. 2012;2012:960835.
33. Van Velthoven R, Aoun F, Limani K, Narahari K, Lemort M, Peltier A. Primary Zonal High Intensity Focused Ultrasound for Prostate Cancer: Results of a Prospective Phase IIa Feasibility Study. Prostate Cancer. 2014;2014:756189.
34. Yee C-H, Chiu PK-F, Teoh JY-C, Ng C-F, Chan C-K, Hou S-M. High-intensity focused ultrasound (HIFU) focal therapy for localized prostate cancer with MRI-US fusion platform. Adv Urol. 2021;2021:7157973.
35. Ghai S, Finelli A, Corr K, Chan R, Jokhu S, Li X, et al. MRI-guided focused ultrasound ablation for localized intermediate-risk prostate cancer: early results of a phase II trial. Radiology. 2021;298(3):695-703.
36. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: A Prospective Development Study. Eur Urol. 2015;68:927–936.
37. Bacchetta F, Martins M, Regusci S, Jichlinski P, Meuwly JY, Lucca I, et al. The utility of intraoperative contrast-enhanced ultrasound in detecting residual disease after focal HIFU for localized prostate cancer. Urol Oncol. 2020;38(11):846 e1–e7.
38. Sumitomo M, Asakuma J, Yoshii H, Sato A, Horiguchi A, Ito K, et al. Anterior perirectal fat tissue thickness is a strong predictor of recurrence after high-intensity focused ultrasound for prostate cancer. Int J Urol. 2010;17(9):776–82.
39. El Fegoun AB, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F, et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. Int Braz J Urol. 2011;37(2):213–9; discussion 20-2.
40. Stabile A, Orczyk C, Giganti F, Moschini M, Allen C, Punwani S, et al. The Role of Percentage of Prostate-specific Antigen Reduction After Focal Therapy Using High-intensity Focused Ultrasound for Primary Localised Prostate Cancer. Results from a Large Multi-institutional Series. Eur Urol. 2020;78(2):155–60.

Cryotherapy (*n* = 24).

41. Tan WP, Chang A, Sze C, Polascik TJ. Oncological and functional outcomes of patients undergoing individualized partial gland cryoablation of the prostate: a single-institution experience. J Endourol. 2021;35:1290–1299.
42. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. 2012;109:1648–1654.
43. Bahn D, de Castro Abreu AL, Gill IS, Hung AJ, Silverman P, Gross ME, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol. 2012;62:55–63.
44. Tokuda B, Yamada K, Takahata A, Fujihara A, Iwata T, Ukimura O, et al. Time-course changes in multiparametric magnetic resonance imaging following focal cryotherapy for localized prostate cancer: Initial experience. Eur J Radiol. 2023;160:110714.
45. Marra G, Soeterik T, Oreggia D, Tourinho-Barbosa R, Moschini M, Filippini C, et al. Long-term outcomes of focal cryotherapy for low- to intermediate-risk prostate

cancer: results and matched pair analysis with active surveillance. Eur Urol Focus. 2022;8:701–709.
46. Baskin A, Charondo LB, Balakrishnan A, Cowan JE, Cooperberg MR, Carroll PR, et al. Medium term outcomes of focal cryoablation for intermediate and high risk prostate cancer: MRI and PSA are not predictive of residual or recurrent disease. Urol Oncol. 2022;40:451.e15–451.e20.
47. Kongnyuy M, Lipsky MJ, Islam S, Robins DJ, Hager S, Halpern DM et al. Predictors of biochemical recurrence after primary focal cryosurgery (hemiablation) for localized prostate cancer: a multi-institutional analytic comparison of Phoenix and Stuttgart criteria. Urol Oncol. 2017;35:530.e15–530.e19.
48. Shah TT, Peters M, Eldred-Evans D, Miah S, Yap T, Faure-Walker NA, et al. Early-medium-term outcomes of primary focal cryotherapy to treat nonmetastatic clinically significant prostate cancer from a prospective multicentre registry. Eur Urol. 2019;76:98–105.
49. Fernández-Pascual E, Manfredi C, Martín C, Martínez-Ballesteros C, Balmori C, Lledó-García E, et al. mpMRI-US fusion-guided targeted cryotherapy in patients with primary localized prostate cancer: a prospective analysis of oncological and functional outcomes. Cancers. 2022;14. https://doi.org/10.3390/cancers14122988.
50. Aker MN, Brisbane WG, Kwan L, Gonzalez S, Priester AM, Kinnaird A, et al. Cryotherapy for partial gland ablation of prostate cancer: Oncologic and safety outcomes. Cancer Med. 2023. https://doi.org/10.1002/cam4.5692.
51. Wysock JS, Becher E, Gogaj R, Velazquez N, Lepor H. Early oncological control following partial gland cryo-ablation: a prospective experience specifying reflex MRI guided biopsy of the ablation zone. Prostate Cancer Prostatic Dis. 2021;24:114–119.
52. Mercader C, Musquera M, Franco A, Alcaraz A, Ribal MJ. Primary cryotherapy for localized prostate cancer treatment. Aging Male 2021;23:1460–1466.
53. Basourakos SP, Al Hussein Al Awamlh B, Bianco FJ, et al. Feasibility of in-office MRI-targeted partial gland cryoablation for prostate cancer: an IDEAL stage 2A study. BMJ Surg Interv Health Technologies 2020;2:e000056. https://doi.org/10.1136/bmjsit-2020-000056.
54. Chuang R, Kinnaird A, Kwan L, Sisk A, Barsa D, Felker E, et al. Hemigland Cryoablation of Clinically Significant Prostate Cancer: Intermediate-Term Followup via Magnetic Resonance Imaging Guided Biopsy. J Urol 2020;204:941–949.
55. Gregg JR, Borregales LD, Choi H, Lozano M, McRae SE, Venkatesan AM, et al. Prospective trial of regional (hockey-stick) prostate cryoablation: oncologic and quality of life outcomes. World J Urol. 2021;39: 3259–3264.
56. Sze C, Tsivian E, Tay KJ, Schulman AA, Davis LG, Gupta RT, et al. Anterior gland focal cryoablation: Proof-of-concept primary prostate cancer treatment in select men with localized anterior cancers detected by multi-parametric magnetic resonance imaging. BMC Urol. 2019;19. https://doi.org/10.1186/s12894-019-0562-5.
57. Oishi M, Gill IS, Tafuri A, Shakir A, Cacciamani GE, Iwata T, et al. Hemigland Cryoablation of Localized Low, Intermediate and High Risk Prostate Cancer: Oncologic and Functional Outcomes at 5 Years. J Urol 2019;202:1188–1197.
58. Lian H, Zhuang J, Yang R, Qu F, Wang W, Lin T, et al. Focal cryoablation for unilateral low-intermediate-risk prostate cancer: 63-month mean follow-up results of 41 patients. Int Urol Nephrol 2016;48: 85–90.
59. Durand M, Barret E, Galiano M, Rozet F, Sanchez-Salas R, Ahallal Y, et al. Focal cryoablation: a treatment option for unilateral low-risk prostate cancer. BJU Int. 2014;113: 56–64.
60. Hale Z, Miyake M, Palacios DA, Rosser CJ. Focal cryosurgical ablation of the prostate: A single institute's perspective. BMC Urol 2013;13. https://doi.org/10.1186/1471-2490-13-2.
61. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The 'male lumpectomy': focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol Semin Orig Investig. 2008;26:500–505.
62. DiBlasio CJ, Derweesh IH, Malcolm JB, Maddox MM, Aleman MA, Wake RW. Contemporary analysis of erectile, voiding, and oncologic outcomes following primary targeted cryoablation of the prostate for clinically localized prostate cancer. Int Braz J Urol. 2008;34:443–450.
63. Lambert EH, Bolte K, Masson P, Katz AE. Focal Cryosurgery: Encouraging Health Outcomes for Unifocal Prostate Cancer. Urology. 2007;69:1117–1120.
64. Bahn DK, Silverman P, Lee F, Badalament R, Bahn ED, Rewcastle JC. Focal prostate cryoablation: Initial results show cancer control and potency preservation. J Endourol. 2006;20:688–692.

Irreversible Electroporation (IRE) ($n = 13$)

65. Guenther E, Klein N, Zapf S, Weil S, Schlosser C, Rubinsky B, et al. Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments. PLoS One. 2019;14(4):e0215093.
66. van den Bos W, Scheltema MJ, Siriwardana AR, Kalsbeek AMF, Thompson JE, Ting F, et al. Focal irreversible electroporation as primary treatment for localized prostate cancer. BJU Int. 2018;121:716–724.
67. Collettini F, Enders J, Stephan C, Fischer T, Baur ADJ, Penzkofer T, et al. Image-guided irreversible electroporation of localized prostate cancer: functional and oncologic outcomes. Radiology. 2019;292:250–257.
68. Ting F, Tran M, Böhm M, Siriwardana A, Van Leeuwen PJ, Haynes AM, et al. Focal irreversible electroporation for prostate cancer: functional outcomes and short-term oncological control. Prostate Cancer Prostatic Dis. 2016;19:46–52.
69. Murray KS, Ehdaie B, Musser J, Mashni J, Srimathveeravalli G, Durack JC, et al. Pilot study to assess safety and clinical outcomes of irreversible electroporation for partial gland ablation in men with prostate cancer. J Urol. 2016;196:883–890.
70. Blazevski A, Amin A, Scheltema MJ, Balakrishnan A, Haynes A-M, Barreto D, et al. Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World J Urol 2021;39:1107–1114.
71. Valerio M, Dickinson L, Ali A, Ramachadran N, Donaldson I, Mccartan N, et al. Nanoknife electroporation ablation trial: a prospective development study investigating focal irreversible electroporation for localized prostate cancer. J Urol. 2017;197(3 Pt 1):647–654.
72. Valerio M, Stricker PD, Ahmed HU, Dickinson L, Ponsky L, Shnier R, et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. Prostate Cancer Prostatic Dis. 2014;17:343–347.
73. Wang H, Xue W, Yan W, Yin L, Dong B, He B, et al. Extended focal ablation of localized prostate cancer with high-frequency irreversible electroporation: a nonrandomized controlled trial. JAMA Surg. 2022;157:693–700.
74. Scheltema MJ, Geboers B, Blazevski A, Doan P, Katelaris A, Agrawal S, et al. Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer. BJU Int. 2022. https://doi.org/10.1111/bju.15946.
75. Shin D, Yoon CE, Kwon HJ, Moon HW, Park YH, Cho HJ, et al. Irreversible electroporation for prostate cancer using PSMA PET-CT. Prostate Int. 2022. https://doi.org/10.1016/j.prnil.2022.08.004.
76. Enikeev D, Taratkin M, Morozov A, et al. Focal irreversible electropo- ration for localized prostate cancer management: prospective as- sessment of efficacy and safety. Minerva Urol Nefrol. 2020;72:644–5.
77. Giganti F, Stabile A, Giona S, et al. Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome. Magn Reson Imaging. 2019;58:143–7.

Focal Brachytherapy ($n = 11$)

78. Fischbach F, Hass P, Schindele D, Genseke P, Geisendorf L, Stehning C, et al. MRI targeted single fraction HDR Brachytherapy for localized prostate carcinoma: a feasibility study of focal radiation therapy (ProFocAL). Eur Radiol. 2020;30: 2072–2081.
79. Graff P, Portalez D, Lusque A, Brun T, Aziza R, Khalifa J, et al. IDEAL 2a Phase II Study of Ultrafocal Brachytherapy for Low- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2018;102:903–911.
80. Mahdavi SS, Spadinger IT, Salcudean SE, Kozlowski P, Chang SD, Ng T, et al. Focal application of low-dose-rate brachytherapy for prostate cancer: a pilot study. J Contemp Brachytherapy 2017;9:197–208.
81. Peters M, van Son MJ, Moerland MA, Kerkmeijer LGW, Eppinga WSC, Meijer RP, et al. MRI-guided ultrafocal HDR brachytherapy for localized prostate cancer: median 4-year results of a feasibility study. Int J Radiat Oncol Biol Phys. 2019;104:1045–1053.
82. Prada PJ, Cardenal J, García Blanco A, Andreescu J, Ferri M, Anchuelo J, et al. Focal high-dose-rate brachytherapy for localized prostate cancer: toxicity and preliminary biochemical results. Strahlentherapie und Onkol Organ der Dtsch Rontgengesellschaft [et al.] 2020;196:222–228.
83. Anderson E, Smyth LML, O'Sullivan R, Ryan A, Lawrentschuk N, Grummet J, et al. Focal low dose-rate brachytherapy for low to intermediate risk prostate cancer: preliminary experience at an Australian institution. Transl Androl Urol. 2021;10:3591–3603.
84. Cosset J-M, Cathelineau X, Wakil G, Pierrat N, Quenzer O, Prapotnich D, et al. Focal brachytherapy for selected low-risk prostate cancers: a pilot study. Brachytherapy 2013;12:331–337.
85. Hass P, Fischbach F, Pech M, Gawish A. Feasibility of MRI targeted single fraction HDR brachytherapy for localized prostate carcinoma: ProFocAL-study. J Cancer Res Clin Oncol. 2022. https://doi.org/10.1007/s00432-022-04491-3.
86. Nguyen PL, Chen M-H, Zhang Y, Tempany CM, Cormack RA, Beard CJ, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol. 2012;188:1151–1156.
87. Saito K, Matsuoka Y, Toda K, Yoshida S, Yokoyama M, Yoshimura R, et al. Medium-term oncological and functional outcomes of hemi-gland brachytherapy using iodine-125 seeds for intermediate-risk unilateral prostate cancer. Brachytherapy. 2021;**20**:842–848.
88. Ta M-H, Nunes-Silva I, Barret E, Renard-Penna R, Rozet F, Mombet A, et al. Focal brachytherapy for localized prostate cancer: midterm outcomes. Pract Radiat Oncol. 2021;11:e477–e485.

Focal Laser Ablation (FLA) ($n = 10$)

89. Chao B, Lepor H. 5-Year outcomes following focal laser ablation of prostate cancer. Urology. 2021;155:124–129.

90. Natarajan S, Raman S, Priester AM, Garritano J, Margolis DJA, Lieu P, et al. Focal laser ablation of prostate cancer: phase I clinical trial. J Urol. 2016;196:68–75.
91. Meneghetti I, Giardino D, Morganti R, Marino V, Menchini Fabris F, Bartoletti R et al. A single-operator experience using EchoLaser SoracteLiteTM for focal laser ablation of prostate cancer: one more arrow in the quiver for the conservative management of the disease. Arch Ital di Urol Androl organo Uff [di] Soc Ital di Ecogr Urol e Nefrol. 2022;94:406c412.
92. Walser E, Nance A, Ynalvez L, Yong S, Aoughsten JS, Eyzaguirre EJ, et al. Focal laser ablation of prostate cancer: results in 120 patients with low- to intermediate-risk disease. J Vasc Interv Radiol. 2019;30:401–409.e2.
93. Al-Hakeem Y, Raz O, Gacs Z, Maclean F, Varol C. Magnetic resonance image-guided focal laser ablation in clinically localized prostate cancer: safety and efficacy. ANZ J Surg. 2019;89:1610–1614.
94. Oto A, Sethi I, Karczmar G, McNichols R, Ivancevic MK, Stadler WM, et al. MR imaging-guided focal laser ablation for prostate cancer: phase I trial. Radiology. 2013;267:932–940.
95. Lepor H, Llukani E, Sperling D, Fütterer JJ. Complications, Recovery, and Early Functional Outcomes and Oncologic Control Following In-bore Focal Laser Ablation of Prostate Cancer. Eur Urol. 2015;68:924–926.
96. Mehralivand S, George AK, Hoang AN, Rais-Bahrami S, Rastinehad AR, Lebastchi AH, et al. MRI-guided focal laser ablation of prostate cancer: a prospective single-arm, single-center trial with 3 years of follow-up. Diagn Interv Radiol. 2021;27:394–400.
97. Barqawi A, Krughoff K, Li H, Patel NU. Initial experience of targeted focal interstitial laser ablation of prostate cancer with MRI guidance. Curr Urol. 2015;8:199–207.
98. Natarajan S, Jones TA, Priester AM, et al. Focal laser ablation of prostate cancer: feasibility of magnetic resonance imaging-ultra- sound fusion for guidance. J Urol. 2017;198:839–47.

PhotoDynamic therapy (PDT) (*n* = 8)

99. Taneja SS, Bennett J, Coleman J, Grubb R, Andriole G, Reiter RE, et al. Final results of a phase I/II multicenter trial of WST11 vascular targeted photodynamic therapy for hemi-ablation of the prostate in men with unilateral low risk prostate cancer performed in the United States. J Urol. 2016;196:1096–1104.
100. Lebdai S, Bigot P, Leroux P-A, Berthelot L-P, Maulaz P, Azzouzi A-R. Vascular targeted photodynamic therapy with padeliporfin for low risk prostate cancer treatment: midterm oncologic outcomes. J Urol. 2017;198:335–344.
101. Moore CM, Azzouzi A-R, Barret E, Villers A, Muir GH, Barber NJ, et al. Determination of optimal drug dose and light dose index to achieve minimally invasive focal ablation of localised prostate cancer using WST11-vascular-targeted photody-namic (VTP) therapy. BJU Int. 2015;116:888–896.
102. Moore CM, Nathan TR, Lees WR, Mosse CA, Freeman A, Emberton M, et al. Photodynamic therapy using meso tetra hydroxy phenyl chlorin (mTHPC) in early prostate cancer. Lasers Surg Med. 2006;38:356–363.
103. Flegar L, Baunacke M, Buerk BT, Proschmann R, Zacharis A, Propping S, et al. Decision regret and quality of life after focal therapy with vascular-targeted photodynamic therapy (TOOKAD®) for localized prostate cancer. Urol Int. 2022;106:903–908.
104. Azzouzi AR, Barret E, Bennet J, Moore C, Taneja S, Muir G, et al. TOOKAD® Soluble focal therapy: pooled analysis of three phase II studies assessing the minimally invasive ablation of localized prostate cancer. World J Urol. 2015;33:945–953.
105. Noweski A, Roosen A, Lebdai S, Barret E, Emberton M, Benzaghou F, et al. Medium-term follow-up of vascular-targeted photodynamic therapy of localized prostate cancer using TOOKAD soluble WST-11 (Phase II Trials). Eur Urol Focus. 2019;5:1022–1028.
106. Rastinehad AR, Anastos H, Wajswol E, et al. Gold nanoshell-local- ized photothermal ablation of prostate tumors in a clinical pilot device study. Proc Natl Acad Sci. 2019;116:18590–6.

Microwave ablation (*n* = 3)

107. Oderda M, Marquis A, Calleris G, D'Agate D, Faletti R, Gatti M, et al. Safety and feasibility of transperineal targeted microwave ablation for low- to intermediate-risk prostate cancer. Eur Urol open Sci. 2022;46:3–7.
108. Chiu PK-F, Chan C-H, Yee C-H, Lau S-Y, Teoh JY-C, Wong H-F, et al. Transperineal Targeted Microwave Ablation (TMA) of localized prostate cancer guided by MRI-Ultrasound fusion and organ-based tracking: a pilot study. Prostate Cancer Prostatic Dis. 2022. https://doi.org/10.1038/s41391-022-00577-8.
109. Barry Delongchamps N, Schull A, Anract J, Abecassis J-P, Zerbib M, Sibony M, et al. Feasibility and safety of targeted focal microwave ablation of the index tumor in patients with low to intermediate risk prostate cancer: Results of the FOSTINE trial. PLoS ONE. 2021;16:e0252040.

Partial Prostatectomy (*n* = 3)

110. Kaouk JH, Ferguson EL, Beksac AT, Zeinab MA, Kaviani A, Weight C, et al. Single-port robotic transvesical partial prostatectomy for localized prostate cancer: initial series and description of technique. Eur Urol. 2022;82:551–558.
111. Villers A, Puech P, Flamand V, Haber G-P, Desai MM, Crouzet S, et al. Partial prostatectomy for anterior cancer: short-term oncologic and functional outcomes. Eur Urol. 2017;72:333–342.
112. Sood A, Jeong W, Keeley J, Abdollah F, Hassan O, Gupta N, et al. Subtotal surgical therapy for localized prostate cancer: a single-center precision prostatectomy experience in 25 patients, and SEER-registry data analysis. Transl Androl Urol. 2021;10:3155–3166.

bipolar Radio Frequency Ablation (bRFA) (*n* = 2)

113. Aydin AM, Gage K, Dhillon J, Cheriyan SK, Poch MA, Manley BJ, et al. Focal bipolar radiofrequency ablation for localized prostate cancer: Safety and feasibility. Int J Urol Off J Japanese Urol Assoc. 2020;27:882–889.
114. Orczyk C, Barratt D, Brew-Graves C, et al. Prostate Radiofrequency Focal Ablation (ProRAFT) trial: a prospective development study evaluating a bipolar radio frequency device to treat prostate cancer. J Urol 2021;205:1090–9.

Prostatic artery embolization (PAE) (*n* = 1)

115. Frandon J, Bey E, Hamard A, et al. Early results of unilateral prostatic artery embolization as a focal therapy in patients with prostate cancer under active surveillance: cancer prostate embolisation, a pilot study. J Vasc Interv Radiol. 2021;32:247–55.

Comparative studies (*n* = 9)

116. Azzouzi A-R, Vincendeau S, Barret E, et al. Padeliporfin vascular- targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomized controlled trial. Lancet Oncol. 2017;18:181– 91.
117. Gill IS, Azzouzi AR, Emberton M, et al. Randomized trial of partial gland ablation with vascular targeted phototherapy versus active surveillance for low risk prostate cancer: extended followup and analyses of effectiveness. J Urol. 2018;200:786–93.
118. Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess. 2018;22:1–96.
119. Garcia-Barreras S, Sanchez-Salas R, Sivaraman A, et al. Compara- tive analysis of partial gland ablation and radical prostatectomy to treat low and intermediate risk prostate cancer: oncologic and functional outcomes. J Urol. 2018;199:140–6.
120. Scheltema MJ, Chang JI, Böhm M, van den Bos W, Blazevski A, Gielchinsky I, Kalsbeek AMF, van Leeuwen PJ, Nguyen TV, de Reijke TM, Siriwardana AR, Thompson JE, de la Rosette JJ, Stricker PD. Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World J Urol. 2018 Sep;36(9):1383–1389. https://doi.org/10.1007/s00345-018-2281-z. Epub 2018 Mar 28. PMID: 29594551; PMCID: PMC6105143.
121. Tourinho-Barbosa RR, Sanchez-Salas R, Claros OR, et al. Focal therapy for localized prostate cancer with either HIFU or cryoa- blation: a single institution experience. J Urol. 2020;203:320–30.
122. Stabile A, Sanchez-Salas R, Tourinho-Barbosa R, Macek P, Pellegrino F, Gandaglia G, Moschini M, Cathala N, Mombet A, Montorsi F, Briganti A, Cathelineau X. Association between Lesion Location and Oncologic Outcomes after Focal Therapy for Localized Prostate Cancer Using Either High Intensity Focused Ultrasound or Cryotherapy. J Urol. 2021;206(3):638–645. https://doi.org/10.1097/JU.0000000000001787. Epub 2021 Apr 23. PMID: 33890485.
123. Dias N, Rodriguez-Sanchez L, Colandrea G, Macek P, Cathelineau X. Medium-term oncological outcomes of intermediate-risk prostate cancer treated with HIFU or cryotherapy. A single center 10-year experience. Arch Ital Urol Androl. 2022;94(4):413–419. https://doi.org/10.4081/aiua.2022.4.413. PMID: 36576465.
124. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, Macek P, Durand M, Prapotnich D, Rozet F, Cathelineau X. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol. 2013 Apr;63(4):618–22. https://doi.org/10.1016/j.eururo.2012.11.057. Epub 2012 Dec 13. PMID: 23265382.