REVIEW ARTICLE

New kids on the block: MRI guided transrectal focused US, TULSA, focal laser ablation, histotripsy – a comprehensive review

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INTRODUCTION: Prostate cancer (PCa) management poses challenges due to treatment-related morbidities associated with conventional therapies. Focal therapy (FT) is emerging as a promising alternative for intermediate-risk PCa, aiming to selectively target localized cancerous lesions while preserving healthy tissue. This review explores emerging FT modalities for PCa treatment, focusing on transrectal MRI-guided focused ultrasound surgery (MRgFUS), transurethral ultrasound ablation (TULSA), focal laser ablation (FLA), and histotripsy.

METHODS: A comprehensive literature search was conducted to identify studies and clinical trials related to FT. Relevant articles were selected and data were synthesized to provide insights into the efficacy and feasibility of MRgFUS, TULSA, FLA, and histotripsy for FT.

RESULTS: MRgFUS utilizes transrectal high-intensity focused ultrasound under MRI guidance to selectively ablate cancerous tissue, demonstrating positive outcomes in oncologic control and preservation of urinary and sexual function. TULSA employs transurethral delivery of high-intensity ultrasound energy under MRI guidance, showing promising results for whole gland treatment. FLA benefits from precise ablation, indicating effectiveness in tumor destruction while preserving quality-of-life. Histotripsy, a mechanical ablation method, exhibits promise by inducing tissue fractionation through bubble activity, offering advantages such as tissue selectivity and real-time treatment monitoring.

CONCLUSION: Emerging FT modalities present promising alternatives for the management of localized PCa, offering personalized treatment. Further research and clinical trials are warranted to establish the long-term efficacy of these techniques in PCa management.

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INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men globally, with its management dependent on precise disease grading, staging, and risk assessment utilizing TNM staging, Gleason score, and prostate-specific antigen (PSA) levels [1–31].

Conventional treatments for localized PCa, including radical prostatectomy (RP) and pelvic radiation therapy, offer disease control but are often associated with enduring urinary and sexual dysfunction, affecting over half of the treated patients [1, 2]. In contrast, while active surveillance is recommended for low-risk PCa and spares patients of treatment-related morbidities, its applicability in patients with intermediate-risk PCa remains contentious due to concerns regarding disease progression, particularly in men with magnetic resonance imaging (MRI) visible disease [3–5].

Advancements in disease localization techniques, particularly MRI, have facilitated the emergence of focal therapy (FT) as a promising treatment modality for PCa [6–8]. Targeted ablation of the clinically significant (cs) index lesion, often predictive of disease progression, while sparing adjacent healthy tissue, aims to minimize treatment-related morbidities [9]. By selectively treating only the cancerous areas that are likely to cause harm, there is an attempt to reduce the risk of side effects commonly associated with more aggressive treatments, such as urinary incontinence and sexual dysfunction. In 2022, the American Urological Association/American Society for Radiation Oncology guidelines were updated to state that minimally invasive FT lacks high quality

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data compared to existing conventional treatments for PCa but may be considered for intermediate-risk PCa in the appropriately counseled patient with clinical trial or prospective registry enrolment prioritized [10].

Guided by various imaging modalities, FT adopts a personalized approach tailored to individual patient characteristics. While ultrasound (US)-guided FT has undergone extensive investigation, more recently, there has been a growing interest in exploring and studying innovative MRI-guided techniques [6, 7, 11]. Since multiparametric MRI (mpMRI) is considered the standard of care for the detection of csPCa [6], recent studies have focused on MRI-guided FT. MRI-guidance allows better delineation of tumor in all 3 planes, enabling better targeting and planning. In addition, real-time thermal monitoring (MR-thermometry) allows instant real-time intra-procedure thermal feedback and provides an opportunity for optimization of ablation temperatures. However, since MRI may underestimate the histological tumor volume, targeted FT requires treatment beyond the visible tumor, ideally with a margin of 9-10 mm [12, 13]. MRI-guidance for FT, utilizing energy sources such as high-frequency focal ultrasound (HIFU), and interstitial laser thermal therapy (FLA) have been studied over the last few years.

In addition to developments in imaging, innovative energy sources such as histotripsy, a non-invasive non-thermal high-intensity ultrasound technique, have also been studied for FT. Histotripsy delivers short (microsecond to milliseconds duration) very-intense HIFU bursts (10-100 fold more intense than thermal exposures) to illicit bubble activity at the focus. Interactions between bubbles and ultrasound waves produce precise non-thermal mechanical ablation of targeted tissue [14]. Histotripsy is under development as a future FT of PCa [15, 16]. This review delves specifically into examining these newer techniques for FT for PCa and provides a comprehensive analysis of these emerging techniques in PCa management.

TRANSRECTAL MRI-GUIDED FOCUSED ULTRASOUND SURGERY (MRGFUS)

Transrectal MRI-guided focused ultrasound surgery (MRgFUS) has emerged as a promising modality for treating localized PCa in recent years. The ExAblate 2100 prostate device (Insightec Ltd, Haifa, Israel) is a non-invasive transrectal MRgFUS system [17]. Like other thermal HIFU devices, it utilizes the conversion of mechanical energy of sonication to thermal energy, raising the temperature to achieve tissue coagulation and allows for sharp ablation margins between the target zone and surrounding normal tissue [17–19] The phased-array transducer is made of approximately 1000 elements and operates within the range 0.8–3.5 MHz. The ultrasound beam can be electronically steered to the desired location in the gland planned for treatment.

The procedure is performed under general anesthesia or sedation, with the patient positioned in lithotomy on a modified MRI table. Following placement of a Foley catheter for continuous bladder drainage, the ExAblate endorectal probe is positioned in the rectum [17–20]. The endorectal balloon is then filled and circulated with degassed water at 14 °C for rectal and device cooling for protection. Initial imaging is obtained to ensure no air bubbles are present in the endorectal balloon, as air can disrupt ultrasound wave transmission. T2-weighted (T2WI) and diffusion-weighted (DWI) images are acquired for tumor localization and rectum, prostate and tumor contouring, including 10 mm margins when possible [17, 19]. The software then generates the treatment plan, specifying energy level and number of sonications. Subtherapeutic sonications are initially delivered for verification, followed by treatment sonications. Macrosonications are delivered on each axial slice covering the tumor and margins. Nominal sonication spots are delivered where required based on the MR-thermography feedback during treatment. Updated anatomical MRI between sonications allows intraoperative treatment plan modification. Post-ablation, dynamic contrast-enhanced (DCE) MRI confirms coverage and assesses the de-vascularized non-perfused volume (NPV) to confirm ablation [19] (Fig. 1).

Over the past decade, various phase I and II clinical trials have demonstrated the safety and efficacy of MRgFUS FT as a treatment option in men with low and intermediate risk PCa yielding positive quality-of-life outcomes and oncologic responses. The primary findings of these trials are outlined in Table 1.

Initially, Napoli et al. conducted a proof-of-principle study, enrolling five patients with localized PCa, who underwent MRgFUS ablation followed by open radical prostatectomy [17]. No adverse surgical complications related to the MRgFUS procedure were noted. Histopathological analysis revealed extensive coagulative necrosis within the treatment zone, indicating the feasibility of MRgFUS ablation for localized PCa.

Subsequently, Tay et al. investigated MRgFUS focal ablation in 14 patients with low-risk PCa [21]. Follow-up assessments included monitoring of PSA levels, Expanded Prostate Cancer Index Composite (EPIC) questionnaire, mpMRI imaging, and biopsy. The procedure demonstrated good tolerance, with self-limiting hematuria being the most common early adverse effect. Functional outcomes related to sexual activity and urinary symptoms normalized in 3 months and thereafter. Although PSA levels decreased significantly by 38.8% at 3 months, some patients experienced an increase at 6 months, with biopsy revealing cancer outside the treatment area in 6 participants, one with Grade Group (GG) 2 PCa. At 2 years, template transperineal biopsy revealed two men with ≥GG2 disease.

In 2018, Ghai et al. reported a phase I study involving eight patients (10 lesions) with PCa [<GG3 PCa] [18]. Results indicated the feasibility and safety of MRgFUS therapy with favorable short-term oncologic outcomes. No adverse events were reported during the perioperative period, and functional outcomes, as assessed by International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF)-15 scores, remained largely unchanged post-treatment. At 6 months, one participant had persistent ≥ GG2 disease at the treatment site.

More recently, Ehdaie et al. conducted a multicenter phase II study involving 101 patients with unilateral intermediate-risk PCa (79 with GG2 and 22 with GG3 PCa) [22]. At the 6-month assessment, a significant decrease in PSA levels was observed, with most patients (96/101) showing no evidence of csPCa on biopsy. At 24 months, 88% (78/89) of participants did not harbor csPCa (≥GG2) at the treatment site on biopsy. There was a slight decline in IIEF-15 scores (difference of -3.5) at 2 years.

Additionally, a single-center phase II trial by Ghai et al. evaluated 2-year oncological and functional outcomes in 44 patients with unifocal csPCa (36 with GG2 and 8 GG3 PCa) [23, 24]. Median procedure and sonication times were 256 and 125 min respectively. The authors reported that men with larger ablation volumes (>15cc) had a greater decline in IIEF-15 scores during the early period following treatment. The majority of patients exhibited favorable outcomes, with 39/43 men (91%) exhibiting no residual csPCa at the treatment site over the 2-year period on biopsy. There were 3 additional men with de novo csPCa outside the treatment area. No significant change was noted in the median IIEF-15 and IPSS scores between baseline and 24 months, and no participant reported pad use. Overall, these studies collectively suggest that MRgFUS FT is a promising treatment option for PCa, offering favorable safety profiles and very encouraging oncological responses.

Advantages of MRgFUS FT for PCa include its minimally invasive approach, precise targeting enabled by MRI guidance, and real-time temperature feedback during treatment to ensure ablative temperatures (>65 °C) are reached [17, 25]. Additionally, post-treatment contrast-enhanced images enable immediate assessment of the NPV and coverage of the ablated area. While MRgFUS

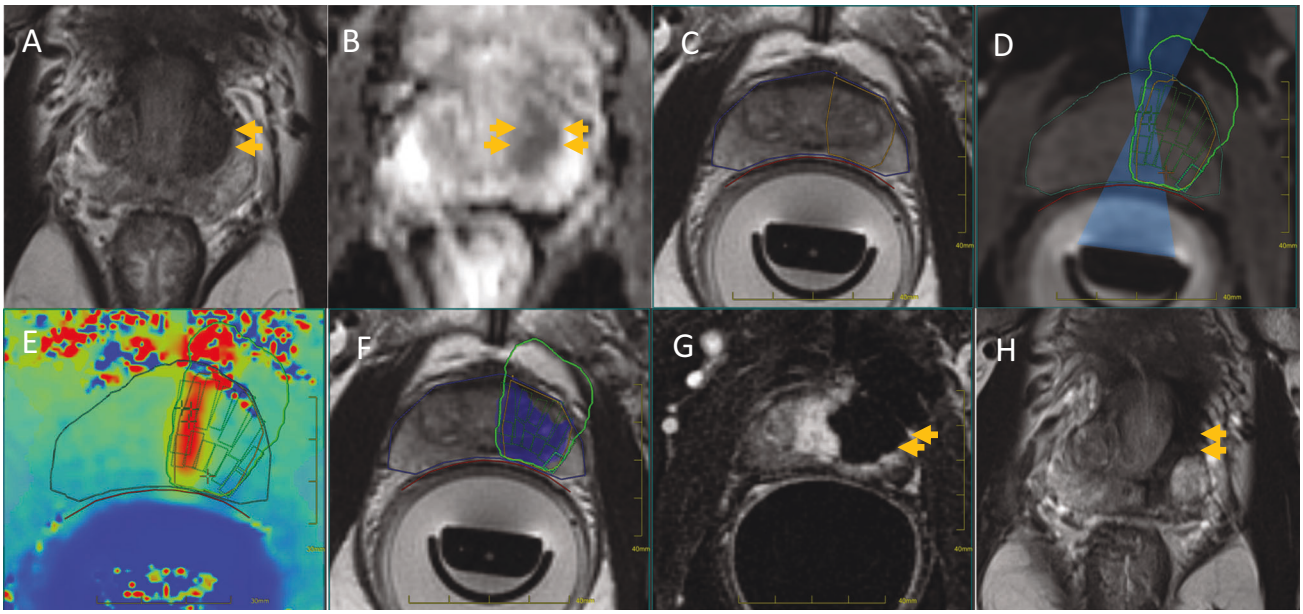

Fig. 1 Imaging findings of a 67-year-old patient with biopsy-proven Gleason 7 (3 + 4) prostate cancer treated by transrectal MRgFUS. **A** Pre-treatment axial T2-weighted fast spin–echo MRI (repetition time (TR)/echo time (TE), 3820/97) and **B** apparent diffusion coefficient (ADC) map image, acquired on a 3T Siemens Skyra Fit scanner, showing the tumor in the left mid gland transition zone (arrows). **C** Intraoperative MRI obtained on a 1.5T GE Excite Twinspeed scanner showing the contoured rectal wall (red line), prostate margin (blue outline) and region of interest (orange outline). **D** Intraoperative MRI showing a focused ultrasound beam path (blue) overlaid on the treatment plan. The rectangular boxes within the region of interest illustrate each sonication spot. **E** MRI thermography image during treatment showing heat deposition color coded in red overlaid on the sonication spot. **F** Accumulated thermal dose map image at end of treatment depicting the predicted area of thermal damage color coded in blue. **G** Axial gadovist-enhanced MRI obtained immediately post-treatment showing the de-vascularized ablated volume (arrows). **H** T2-weighted fast spin–echo MRI (TR/TE, 3820/97) obtained 24 months following the ablation on the same scanner, showing involution and volume loss at the treated area (arrow). Findings from a targeted biopsy of the treatment zone and the rest of the gland at 24 months were negative.

procedure times are longer than for US-guided HIFU, the overall safety profile and oncologic outcomes suggest MRgFUS as a favorable modality for focal PCa treatment [23, 26, 27]. It offers personalized treatment with the potential to enhance patient outcomes and quality-of-life, compared to existing FT literature.

Despite its advantages, MRgFUS has some limitations, similar to other transrectal HIFU devices. The transrectal MRgFUS approach may limit access to lesions in the anterior gland [28]. The Phase II studies described above did not include tumors >4–6 cm from the rectal wall. Additionally, the procedure requires access to MRI and expertise, leading to additional costs.

TRANSURETHRAL ULTRASOUND ABLATION (TULSA)

TULSA, or transurethral ultrasound ablation (TULSA-PRO, Profound Medical Inc, Toronto, Canada), is a minimally invasive procedure developed in 2012 for the treatment of PCa [29]. Using a transurethral approach, TULSA delivers ablative therapy directly to the prostate under MRI guidance for precise localization and MR thermometry for real-time monitoring [30]. The TULSA-PRO device, featuring rectal and urethral cooling, uses a linear array of 10 US transducers emitting high-intensity energy directionally into the prostate, intending consistent ablation while concurrently protecting the urethra and anterior rectal wall [30]. During the procedure, the US applicator is positioned within the prostatic urethra with the first US element placed 3 mm from the apical margin to provide safety for the apical sphincter [29]. Targeting temperatures of ≥55 °C, TULSA achieves acute thermal coagulation [29]. Immediately post-treatment, contrast-enhanced MRI assesses the NPV to confirm ablation (Fig. 2).

The literature on TULSA showcases encouraging results in safety and efficacy for treating PCa in select patients (Table 2). In a proof-of-principle treat-and-resect investigation, Chopra et al. assessed its feasibility in 8 individuals with ≤GG3. They demonstrated a mean spatial targeting accuracy of $-1.0\,\text{mm} \pm 2.6\,\text{mm}$, with no evidence of thermal effects on surrounding structures [30].

Subsequently, Chin et al. led a multi-center phase I investigation assessing whole-gland TULSA in 30 patients with low- to intermediate-risk PCa (24 GG1, 6 GG2) [29]. There were no rectal injuries or fistulae. At 12 months follow-up, there were no significant differences in mean functional outcomes, as assessed by the IPSS and IIEF-15 scores and erections sufficient for penetration were maintained in 85%. Median PSA decreased from 5.8 ng/ml at baseline to 0.8 ng/ml at 12 months. Of the 29 patients who completed a follow-up biopsy, 9 were positive for csPCa (≥GG2), of whom 2 underwent salvage prostatectomy at 12 months. In a 3-year follow-up of the initial phase I population, Nair et al. in 2021 reported that 32% (7 of 22) had recurrent PCa [31]. Of these 7 men, 4 underwent salvage prostatectomies. Pathology confirmed the location of the residual disease was congruent with the untreated peripheral zone safety region [31].

A pivotal multi-center evaluation of TULSA by Klotz et al. was reported on 115 men with low- to intermediate-risk PCa [43 GG1, 69 GG2, 3 GG3], undergoing whole gland evaluation [32]. Median procedure and ablation times were 243 and 51 minutes respectively, similar to those reported for the MRgFUS procedures. Twelve Grade 3 adverse events (UTI, urethral stricture, urinary retention, urethral calculus and urinoma) were recorded in 9 participants, all resolved by 12-months. No rectal injury was reported. Erections were maintained or regained at 12 months in 75% (69 of 92) of potent men at baseline. Three participants had moderate urinary incontinence at 12 months and <1% of men were incontinent to a >1 pad/day level. Primary efficacy endpoint of PSA reduction of ≥75% was achieved in 96% (110 of 115) of patients with decrease in median PSA from 6.3 ng/ml to 0.34 ng/ml. There was a concurrent 91% median prostate volume reduction from 37 cc at baseline to 2.8

Table 1. Key findings of major PCa MRgFUS studies.

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
Napoli et al. [17]	2013	$N = 5$	Proof of principle [treat and resect] study [single center]	-Unifocal, biopsy-proven PCa on mpMRI GG1: 3 (60%) GG2: 2 (40%)	Radical prostatectomy in 7–14 days (mean 9 days)	-No technical difficulties related to MRgFUS ablation during surgery	n/a	n/a	-Extensive coagulative necrosis at ablation site -No residual viable tumor in the ablation area or margins
Tay et al. [21]	2017	$N = 14$	Phase I Safety and efficacy study [single center]	- Age 50–75 years -GG1 -≤ cT2a -Index tumor ≤10cc -Maximum of two positive zones on biopsy or MR-identifiable tumors or a combination of the two	2 years	7 Clavien-Dindo grade 1–2 complications -1/7 acute urinary retention -1/7 epididymo-orchitis -5/7 self-limiting hematuria	Median decrease by 2.9 ng/mL at 6 months	No significant change in urinary symptom and sexual function scores at 2 years	At 6 months: -6 patients with ≥GG1 [1 with ≥GG2] At 24 months: -8/12 patients in-field/adjacent recurrence [3 with ≥GG2]
Ghai et al. [18]	2018	$N = 8$ (10 lesions)	Phase I safety and efficacy study [single center]	PSA ≤ 10 ng/mL -≤cT2a -≤GG3 GG1: 6 (60%) GG2: 2 (20%) GG3: 2 (20%)	6 months	Not reported	Mean decrease by 1.66 ng/mL at 6 months	Quality of life parameters stable between baseline and 6 months in 6/8 patients	At 6 months: -3/10 sites GG1 disease -1/10 site GG4 disease
Ehdaie et al. [22]	2022	$N = 101$	Phase II safety, functional and oncological outcomes [multi-center]	-Age >50 years -Unilateral, organ-confined, visible on mpMRI -GG2 or GG3 -stage ≤ T2 -PSA ≤ 20 ng/mL	2 years	-1 patient with urinary tract infection	Mean decrease by 2.6 ng/mL at 24 months	-IIEF-15 score decreased [-3.5] at 24 months -No significant change in IPSS scores	At 24 months: -78/89 (88%) free of csPCa (≥GG2) at the treated site -59/98 (60%) in the entire gland
Ghai et al. [24]	2024	$N = 44$	Phase II safety, functional and oncological outcomes [single center]	-Age ≥50 years -Unifocal, organ-confined, <20 mm max length, -GG2 or GG3 -PSA ≤ 20 ng/mL -Life expectancy >10 years	2 years	-1 patient with persistent pelvic pain	Median decrease by 3.7 ng/ml at 24 months	-No significant decline in IIEF-15 and IPSS scores	At 24 months: -39/43 (91%) free of csPCa (≥GG2) at the treated area -36/43 (84%) in entire gland

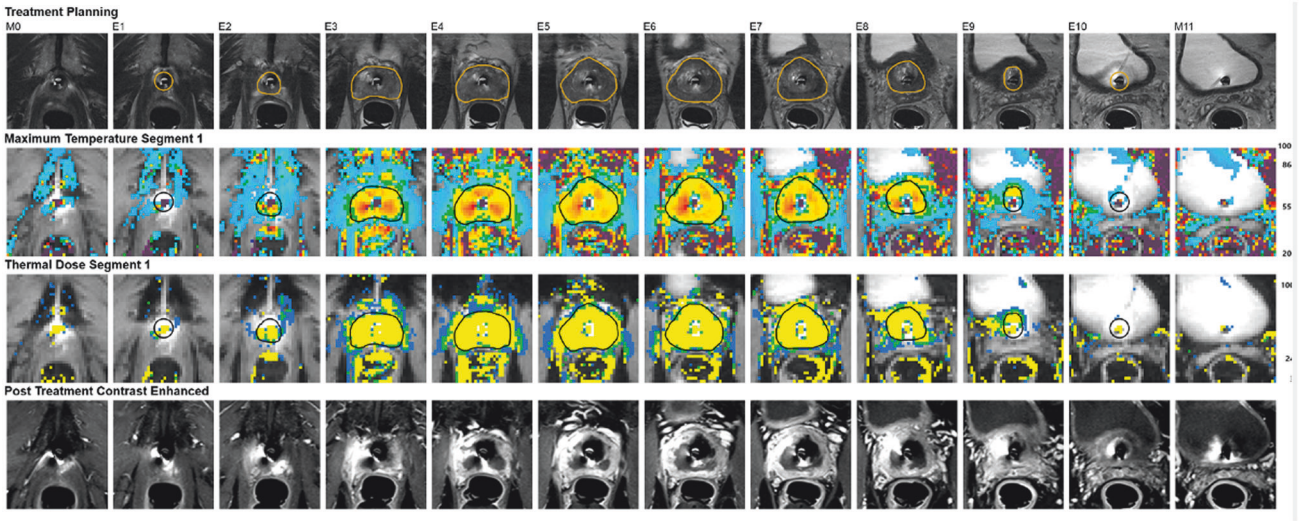

Fig. 2 A 69 year-old man with PSA 6.4 ng/ml and biopsy-proven GG2 prostate cancer in a PIRADS 4 lesion at the left mid-gland and GG1 cancer bilaterally was treated with whole gland TULSA. Treatment was circumferential and primarily using elements E2-E8 for this small (35cc) prostate. The Thermal Dose images show good distribution of ablation energy throughout the gland, while urethral sparing is most evident on the Maximum Temperature images. Red indicates the hottest temperatures, and yellow through red indicates that ablative temperatures have been reached. A 1-year post-treatment biopsy was negative and the patient's PSA has fluctuated between 0.2 ng/ml and 0.6 ng/ml over 3 years post-treatment, with most recent PSA at 0.4 ng/ml.

cc at 12 months [32]. At 12 months follow-up, 65% (72 of 111) of patients had no evidence of cancer and 79% (54 of 68) with ≥GG2 disease at baseline were free of csPCa. Amongst the men with residual disease, 8 sought salvage treatment at 12 months (4 prostatectomy and 4 radiation therapy). The multivariate predictors of persistent csPCa at 12 months were intraprostatic calcifications at screening, suboptimal MRI thermal coverage of target volume, and PI-RADS ≥ 3 lesions on MRI ($p < 0.05$) [32].

While these multi-center studies assessed whole gland / sub-total ablation with the TULSA-PRO device, there have been a few recent treat-and-resect studies assessing sectoral FT. Ramsay et al. assessed safety and feasibility of sectoral ablation extending to the capsule in 5 patients with ≤GG2 PCa. Whole mount histology demonstrated an average target accuracy −1.5 mm ±2.8 mm [33]. In another trial by Anttinen et al., 6 patients (≤GG4) underwent lesion-targeted FT with the TULSA device, followed by robot-assisted-laparoscopic-prostatectomy at 3 weeks [34]. On histo-pathology, no viable tumor was noted in the ablation zones, but 4 of 6 patients had residual cancer outside of the planned ablation volume, within the pre-planned 3 mm safety margin, near the neurovascular bundle [34].

Anttinen et al. further conducted a phase I investigation of salvage TULSA in the treatment of radiorecurrent PCa in 11 patients [35]. At 12 months, there were no urethral strictures, rectal injuries, or fistulas. The median EPIC-26 irritative/obstructive domain decreased by 20% and 91% (10 of 11) men were free of any PCa in the targeted ablation zone [35].

Overall, the current literature suggests TULSA holds promise as a safe and effective treatment option for low to intermediate risk PCa, with encouraging early oncologic and quality-of-life outcomes.

The transurethral approach of TULSA is amenable to treating anterior lesions, which may lie beyond the reach of transrectal approaches [30]. Similar to other MRI-guided FT, MR thermometry for real-time monitoring of ablation temperatures further enhances treatment precision and safety [6]. One aspect unique to TULSA is that the measured temperatures are also used as a quantitative input to a feedback control algorithm that dynamically modulates the US intensity and frequency of each treatment element and the device rotation rate to ensure the target volume reaches therapeutic temperatures [29].

While TULSA offers a non-invasive transurethral approach, inserting a rigid US applicator into the prostatic urethra may lead to discomfort and potential complications, such as urethral injury or stricture [32]. Similar to other intra-procedural MRI guidance techniques, it adds complexity and time to the procedure, potentially increasing overall treatment costs and resource utilization. Notably, challenges related to intraprostatic calcifications may affect treatment efficacy and increase the risk of residual and recurrent disease [32]. It is recommended that patients with coarse calcifications in the beam path be excluded from TULSA treatment [32].

FOCAL LASER ABLATION (FLA)

Focal Laser Ablation (FLA) is an interstitial procedure to treat localized PCa by inserting laser fibers into the prostate gland under image guidance, typically using transperineal or transrectal approaches [36, 37]. Once positioned, the laser emits beams of electromagnetic radiation, typically in the infrared spectrum (700–1064 nm), directly into the targeted tissue. The laser's energy rapidly elevates the prostate tissue's temperature, inducing protein denaturation and coagulative necrosis, leading to tissue destruction [38]. The diode laser fibers ablate a cylindrical zone with ablation diameters of <15 mm, and thereby multiple applicators are required to cover the planned ablation volume including margins beyond the MRI visible tumor (Fig. 3).

FLA has garnered increasing attention as a FT option for localized PCa, with numerous recent studies shedding light on its efficacy, safety profile, and potential as an alternative to radical treatments in selected patients (Table 3).

Although, FLA has been predominantly evaluated under MRI guidance, some studies have assessed its feasibility under US / MRI- Transrectal (TRUS) fusion guidance, and with the new high-resolution micro-US. MRI guidance allows definition of the tumor in all 3 planes in addition to MRI thermometry. On the other hand, ultrasound guidance enables shorter treatment durations and requires fewer resources compared to MRI guidance, resulting in reduced costs.

An initial Phase 1 feasibility and proof-of-principle study by Lindner et al. from the University of Toronto, validated laser energy as an ablative modality using imaging and histopathology

Table 2. Key findings of major PCa TULSA studies.

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
Chopra et al. [30]	2012	$N = 8$	Proof of principle [treat and resect] study [single center]	-mean age = 60 yr -GS ≤ 7 -PSA < 15 ng/mL	Radical prostatectomy same day	Not reported	n/a	n/a	-Mean spatial targeting accuracy was -1.0 mm ± 2.6 mm -No evidence of thermal effects on surrounding structures
Chin et al. [29]	2016	$N = 30$	Phase I safety and efficacy study [whole gland treatment] [multi center]	-Treatment-naïve men aged ≥65 yr with biopsy-proven organ confined PCa -PSA ≤ 10 ng/mL -GS 3 + 3 or 3 + 4 GS6 (3 + 3): 24 (80%) GS7 (3 + 4): 6 (20%)	12 months	-No rectal injury or fistula, -No G4 or higher adverse events -1 epididymitis, resolved with IV antibiotics	-Median PSA decreased by 87% from 5.8 ng/mL at baseline, to 0.8 ng/mL at 1 month, and was stable at 0.8 ng/mL at 12 months	-Median IPSS values returned to baseline by 3 months -Median IIEF-15 values returned to baseline by 12 months	At 12 months: -16/29 (55%) patients had positive biopsy for any residual disease -9/29 (31%) patients had clinically significant disease -20/29 (69%) patients had no clinically significant disease
Klotz et al. [32]	2021	$N = 115$	Phase II safety and efficacy study [whole gland treatment] [multi-center]	-45–80 years old -T2b or less -GG 1-2 -PSA < 15 ng/mL -minimum 10 core biopsy -no previous treatment GG1: 43 (37%) GG2: 69 (60%) GG3: 3 (3%)	12 months	-12 grade 3 adverse events occurred in 9 patients, all resolved by 12 months -no grade 4 events, rectal injuries, severe incontinence, or sever erectile dysfunction	-median PSA decreased from 6.3 ng/mL at baseline to nadir of 0.34 ng/mL -at 12 months, median PSA was stable at 0.5 ng/mL	-Of the 92 patients who were potent at baseline, 69 (75%) maintained or regained potency by 12 months -At 12 months, less than 1% of patients were incontinent per EPIC-50	At 12 months, patients free of PCa: -13/17 (76%) patients with baseline low volume GG1 -16/26 (14%) patients with baseline high volume GG1 -43/68 (63%) patients with baseline GG ≥ 2 -overall, 72/111 (65%) patients had no evidence of cancer
Ramsay et al. [33]	2017	$N = 5$	Proof of principle [treat and resect] study [sectoral ablation] [single center]	-T1 or T2a PCa -GS ≤ 7 -PSA < 15 ng/mL	Radical prostatectomy same day	Not reported	n/a	n/a	-Averaged temperature control accuracy -1.6 ± 4.8 °C -Spatial target accuracy -1.5 mm ± 2.8 mm -Average treatment accuracy -0.4 ± 1.7 mm

Table 2. continued

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
Anttinen et al. [35]	2020	$N = 6$ (8 MRI-visible, MRI-targeted biopsy confirmed lesions, PI-RADS ≥ 3)	Phase I safety and efficacy [treat and resect] study [sectoral ablation] [single center]	-Median age 70 yrs -Median PSA = 8.9 ng/mL GS 6 (3 + 3): 1 (17%) GS 7 (3 + 4): 2 (33%) GS 7 (4 + 3): 2 (33%) GS 8 (4 + 4): 1 (17%)	3 weeks	No treatment related complications	-not analyzed by authors	-No difference in quality of life outcomes (IPSS, IIEF-5, UCLA-PCI-UFI, ICIQ-SF, and EPIC26-BD) between baseline and 3 weeks post-TULSA	At 3 weeks: -Target ablations were successful in all patients, with target treatment volumes of 7-19 mL -At prostatectomy, histopathology demonstrated no viable malignancy within the ablated targets -4/6 (67%) patients had residual cancer outside of the planned ablation volume, inside the pre-planned 3 mm safety margin near the NVB at the prostate capsule
Anttinen et al. [35]	2020	$N = 11$	Phase I safety and efficacy study [Salvage treatment] [single center]	-localized, histopathologically verified, radiorecurrent PCa -median age 69 years -9 patients received external beam RT -1 patient received high dose rate brachytherapy -1 patient received external beam RT and second-line salvage high dose rate brachytherapy	12 months	-1 grade 3 adverse events -3 grade 2 adverse event, related to urinary retention and infection -at 12 months, 10 patients were free of catheterization; 1 patient who received prior salvage brachytherapy remained on intermittent catheterization -no urethral strictures, rectal injuries, or post-TULSA fistulas	-Median PSA decreased from 7.6 ng/mL at baseline to nadir of 0.2 ng/mL and was 0.23 ng/mL at 12 months	-All patients had severe erectile dysfunction (per IIEF-5) at the time of study enrollment -Reduction in EPIC-26 irritative/obstructive domain scores from median 94 at baseline to 75 at 12 months	At 12 months: 10/11 (91%) patients were free of PCa in the targeted ablation zone, confirmed on imaging and biopsy -2 out of field recurrence detected on PSMA-1007 PET-CT -1/11 (9%) in field recurrence detected on PSMA-1007 PET-CT, located at the periphery of the ablated region

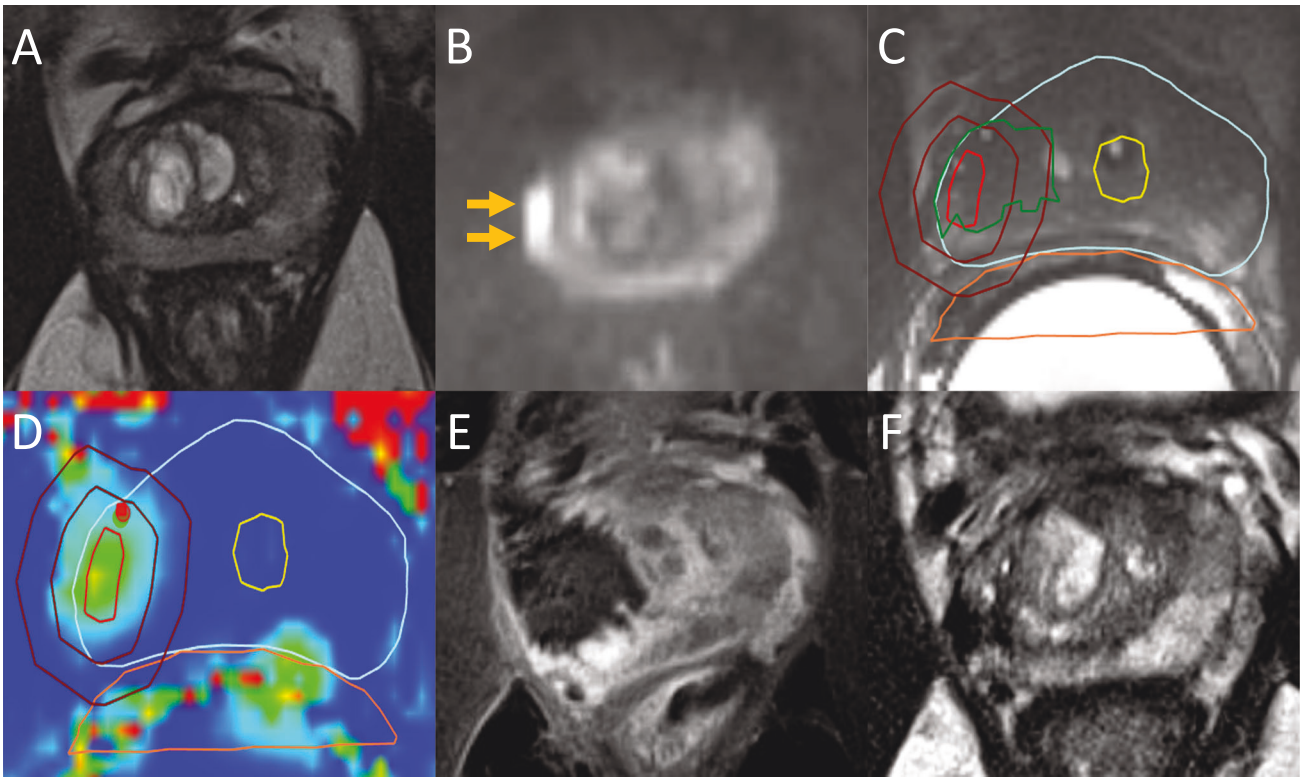

Fig. 3 Imaging findings of a 59-year-old patient with biopsy-proven Gleason 7 (3 + 4) prostate cancer treated by transperineal MRgFLA. **A** Pre-treatment axial T2-weighted fast spin–echo MRI (repetition time (TR)/echo time (TE), 7990/97) and **B** Corresponding diffusion weighted Image (DWI) image, *b* 1600 s/mm^{2,} acquired on a 3T Siemens Skyra Fit scanner, showing the tumor in the right mid gland peripheral zone (arrows). **C** Intraoperative MRI obtained on a 1.5T GE Excite Twinspeed scanner showing the contoured rectal wall (orange line), prostate margin (blue outline) and region of interest (red outline) with 5 mm and 10 mm margins (maroon outline). **D** MRI thermography image during treatment showing heat deposition color coded in green overlaid on the contoured region of interest. **E** Axial gadovist-enhanced MRI obtained immediately post-treatment showing the de-vascularized ablated volume (arrows). **F** T2-weighted fast spin–echo MRI (TR/TE, 7990/97) obtained 6 months following the ablation on the same scanner, showing involution and volume loss at the treated area (arrow). Findings from a targeted biopsy of the treatment zone at 6 months were negative.

correlation [39, 40]. Twelve men with low-risk PCa underwent FLA with water-cooled 980 nm diode laser fibers (Visualase Inc., Houston, Texas) using a prototype MRI-TRUS fusion device, and four of these men underwent radical prostatectomy 1 week following FLA. The ablation volume measured on MR images was, on average, 1.1 times larger than the ablation volumes calculated using vital stain histopathology images (range 0.96–1.29). The same group also published the first study establishing the feasibility of FT under MRI guidance. Two patients with low-risk PCa were treated with outpatient MRI-guided FLA and MRI thermometry monitoring. Accumulated thermal damage was calculated in real time, and immediate post-contrast images confirmed the devascularization of the target [41].

Subsequently, Phase 1 and Phase II studies assessing in-bore transperineal FLA utilizing Visualase were reported by Oto et al. and Eggener et al. from University of Chicago [37, 42]. Nine men with low-risk MRI visible PCa (≤GG2) were successfully treated in the Phase 1 study. 7/9 (78%) men had no residual PCa at the treatment site on follow-up biopsy, and there was no significant change from baseline in the average Sexual Health Inventory for Men (SHIM) and IPSS scores. In their Phase II study, 27 men [23 GG1, 3 GG2 and 1 GG3 PCa] with MRI-visible stage T1c-T2a disease and PSA < 15 ng/ml were treated by transperineal MRI-guided FLA and followed for 12 months. Persistent disease at the treatment site was detected in 3 (11%) men on biopsy. No significant change in IPSS and SHIM scores were noted over the 12-month period.

In 2015, Lepor et al. reported 3-month early results from 25 consecutive men with MRI-visible localized disease (11 GG1, 13 GG2, 1 GG3 PCa) who underwent in-bore MRI-guided FLA for PCa with Visualase using MRI-thermometry temperature monitoring [43]. The study found no significant differences in SHIM scores between baseline and the 3-month mark, and none of the participants required pads. Mean PSA levels decreased by 2.3 ng/ml (44.2%) between baseline and 3-months. 26/28 sites subjected to target biopsy (96%) showed no evidence of PCa. While early results of this study were very promising, longer-term follow-up was lacking to establish the durability of oncologic control.

Al-Hakeem et al. evaluated oncological and functional outcomes in 49 patients (53 lesions) treated with FLA for low- and intermediate-risk PCa (13 GG1, 29 GG2, 7GG3) [44]. The procedure was performed in-bore either transperineally or transrectally based on the location of the tumor. All men underwent per protocol biopsy at 6 months and then as indicated based on PSA or mpMRI. At 18 months post-treatment, 39 patients (79.6%) experienced treatment success per the Donaldson criteria, with no cancer or only insignificant cancer in the ablated area [44]. No significant complications were noted. IPSS scores remained unchanged. SHIM scores dropped in the first year after treatment but were not different from baseline at 18 months. PSA levels remained significantly lower at 18 months vs. baseline.

In another study of 120 patients with low- to intermediate-risk PCa (37 GG1, 56 GG2, 27 GG3) treated by transrectal MRI-guided FLA using Visualase, 17% of patients required additional oncological treatment after 1 year, with no significant change in their quality-of-life or urologic function [45]. However, only men with suspicious post-treatment MRI or PSA elevation underwent a biopsy. With further refined techniques, including hemi-ablations with larger margins, this clinically significant residual tumor rate at

Table 3. Key findings of major PCa FLA studies.

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
MRI-guided FLA (MRgFLA)									
Raz et al. [41]	2010	$N = 2$	Proof of principle [treat and resect] study [single center]	Pt 1: cT1c PCa, PSA 4.79 ng/mL, GS 6 (3 + 3) Pt 2: cT1c PCa, PSA 2.74 ng/mL, GS 6 (3 + 3)	1 month	-No complications reported at 1 month follow up	n/a	-Not assessed	No viable tumor was found in whole mount histopathologic examination of the ablated area
Oto et al. [37]	2013	$N = 9$	Phase I safety and efficacy study [single center]	-GS ≤ 7 or ≤3 cores limited to one sextant obtained on US-guided biopsy and a concordant lesion at MRI	6 months	-1 perineal abrasion, self-resolved -1 focal paresthesia of the glans	No significant difference in PSA at 1, 3, and 6 months post-treatment ($p = 0.8$)	-no significant difference in SHIM or IPSS score between baseline to 6 months follow up	At 6 months: -7/9 (78%) patients had no cancer in the ablation zone -2/9 (22%) patients had GS3 cancer in the ablation zone
Al-Hakeem et al. [44]	2019	$N = 49$ (53 lesions)	Phase II safety, functional and oncological outcomes [single center]	-Aged 50–75 yrs -PSA ≤ 15 ng/mL T1c-T2a -1 or 2 lesions (PI-RADS ≥ 3) on MRI -GS 6 (> 3 mm) or GS 7 on targeted biopsy GS 6 (3 + 3): 13 (26.5%) GS 7 (3 + 4): 29 (59.2%) GS 7 (4 + 3): 7 (14%)	18 months	-14 self-limiting hematuria -13 self-limiting hematospermia -No urinary tract infection or fever	Significant decrease in PSA at 18 months ($p < 0.05$)	-No significant difference in IPSS scores at 18 months follow up SHIM scores reduced from baseline at 1 month ($p = 0.001$) and returned to baseline at 18 months ($p = 0.097$)	-Treatment was successful in 39 patients (79.6%) and 44 of 53 lesions (81.1%) -Persistent cancer (GS ≥ 7 or GS 6 > 3 mm) in ablated areas was seen in 10 patients (20.4%); all 10 patients had evidence of incomplete ablation
Lepor et al. [43]	2015	$N = 25$	Phase II safety, functional and oncological outcomes [single center]	-T1c and T2a disease -PSA < 10 ng/mL -GS < 8 GS ≤ 6 (3 + 3): 11 (44%) GS 7 (3 + 4): 13 (52%) GS 7 (4 + 3): 1 (4%)	3 months	No complications reported	Significant decrease in PSA between baseline to 3 mo at 2.3 ng/mL (44.2%)	-No significant differences between baseline and 3 mo mean AUASS or SHIM scores -No men required pads at any time following FLA	At 3 months: -of the 28 sites subjected to follow up biopsy, 26 (96%) showed no evidence of residual PCa -1 site showed cancer with GS 7 (3 + 4) disease
Eggener et al. [42]	2016	$N = 27$	Phase II study safety, functional, and oncological outcomes [single center]	-T1c-T2a -PSA < 15 ng/mL -GS ≤ 7 or <25% of biopsy cores and no evidence of metastasis GS 6 (3 + 3): 23 (85%) GS 7 (3 + 4): 3 (11%) GS 7 (4 + 3): 1 (4%)	12 months	-4 hematuria -3 perineal ecchymosis -2 acute urinary retention -1 palpable perineal lump	No significant decrease in PSA from baseline to 12 months in men with and without residual prostate cancer in the ablation zone	-No significant change in median IPSS score from baseline to 12 months ($p > 0.05$) -SHIM was lower at 1 month ($p = 0.03$), and no significant difference at 12 months ($p = 0.38$)	At 12 months: 10 (37%) patients with cancer on systematic core-biopsy -3 (11%) patients with cancer in the ablation zone -8 (30%) patients with cancer in and outside the ablation zone -in one patient, cancer was in and out of the ablation zone
Chao et al. [46]	2021	$N = 36$	Phase II safety, functional and oncological outcomes [single center]	-T1c or T2a disease -PSA < 10 ng/mL -GS < 8 -Concordance between MRI lesion and site(s) of biopsy proven PCa GS ≤ 6: 16 (47%) GS 7 (3 + 4): 16 (47%) GS 7 (4 + 3): 2 (6%)	2 years	Not reported	No significant difference in PSA from baseline to 2 years in patients with negative MRI	-No significant difference in median SHIM or AUASS score between baseline to 1 year ($p = 0.153$, $P = 0.674$)	At 2 years: -8 patients had MRIs suspicious for cancer, all confirmed on biopsy 4 (50%) within 3–6 months of ablation 2 (25%) within 12 months of ablation 2 (25%) within 2 years of ablation -24 patients had MRI with negative findings 9 (64%) had positive biopsy

Table 3. continued

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
Walser et al. [45]	2019	$N = 120$	Phase II safety, functional and oncological outcomes [single center]	-T1c-T2b -PSA < 15 ng/mL -PSA density <0.15 ng/mL/ cm^3 -GS ≤ 7 -No metastases GS 6 (3 + 3): 37 (30.8%) GS 7 (3 + 4): 56 (46.7%) GS 7 (4 + 3): 27 (22.5%)	24 months	-1 urinary tract infection -2 rectourethral fistulas, resolved with continuous catheterization -9 hematuria	Median PSA decreased significantly from baseline at 6.05 to 3.25 ng/mL at 12 months ($p < 0.001$) and 3.9 ng/mL at 24 months ($p < 0.001$)	-No significant change in median IPSS or SHIM score between baseline to 24 months	At 24 months: 44 (36.4%) patients had positive MR imaging or persistent PSA after ablation -4 (9%) patients GS ≤ 6 -18 (41%) patients GS ≥ 7 -22 (50%) patients had benign biopsy results
Mehralivand et al. [47]	2021	$N = 15$	Phase II safety, functional, and oncological outcomes [single center]	-T1c or T2a -1 or 2 visible lesions on mpMRI -Gleason score ≤7 -PSA < 15 ng/mL or PSA density <0.15 (if PSA > 15 ng/mL) -no metastases GS 6 (3 + 3): 7 (46.7%) GS 7 (3 + 4): 8 (53.3%)	36 months	-4 hematuria -1 urinary urgency -1 post-operative fever without evidence of bacterial infection or sepsis No serious complications, and all grade 1 and 2 complications self-resolved	Mean PSA significantly decreased from baseline to 36 months ($p < 0.001$)	-No significant change in mean IPSS ($p = 0.46$) and QoL scores ($p = 0.441$) -Significant decrease in mean SHIM scores in 7 of 15 patients compared to baseline ($p = 0.01$)	At 36 months: -of the 12 (80%) patients who underwent a follow up biopsy, 8 (53.3%) were cancer free in treatment area -7 (46.7%) of 15 patients had residual cancer in, adjacent, or in close proximity to the treatment area -4 (26.7%) of 15 patients underwent salvage therapy (2 repeat FLA, 2 radical prostatectomy)
Magee et al. [48]	2021	$N = 3$	Phase I safety and efficacy study [Salvage treatment] [single center]	Previously failed HIFU for PCa -GG2	6 months	No complications reported	-PSA trended downwards at 6 months follow up for 2 patients -PSA trended upwards at 6 months follow up for 1 patient	-All 3 patients had initial worsening of IPSS scores at 30 days, which returned to baseline at 6 months -2 patients did not recover from the initial erectile dysfunction per IIEF scores -1 patient had a return of sexual function to baseline per IIEF scores	At 6 months: Pt 1: all 5 biopsy cores from ablation area were negative Pt 2: all 7 biopsy cores from ablation area were negative Pt 3: all 5 cores from ablation area were negative
Ultrasound (US)-guided FLA									
Lindner et al. [40]	2009	$N = 12$	Phase I safety and efficacy study [single center]	-T1c-T2a -PSA < 10 ng/ml -GS ≤ 6 -< 30% of cores taken positive for cancer and <50% of 1 core taken up by cancer	6 months	-no perioperative complications -2 perineal discomfort, self-resolved -2 hematuria, self-resolved	Not analyzed	-No significant decrease in IIEF-5 scores at 1, 3 or 6 months -No significant change in urinary symptoms, assessed by IPSS	At 6 months: -6/12 (50%) had negative biopsies -2/12 (17%) had no tumor in the ablated region, positive for tumor in the contralateral site of targeted area -4/12 (33%) had residual tumor in previously treated area

Table 3. continued

Author	Year	Number of patients	Study objective	Inclusion criteria	Study duration	Complications	PSA	Functional outcomes	Oncologic outcomes
Natarajan et al. [49]	2016	$N = 8$	Phase I safety and efficacy study [single center]	-Aged 58-72 years -T2b or less PCa -GS ≤ 7 GS 6: 1 (12.5%) GS 7: 7 (87.5%)	6 months	-23 grade 1 events, resolved spontaneously -7 grade 2 events, resolved spontaneously	Median PSA decreased significantly at 6 months ($p < 0.01$)	-No statistically significant change in IPSS and SHIM between baseline to 6 months follow up	At 6 months: -Biopsies at follow up revealed no evidence of safety concerns or adverse tissue changes -5 patients had no cancer in the treated region -3 patients had PCa found in the treated area (GS 3 + 4, GS 3 + 4, GS 6)
van Riel et al. [50]	2022	$N = 12$	Phase I safety and efficacy study [single center]	- ≥40 yr of age -Histopathologically confirmed, organ-confined PCa -Prostate volume ≥40 ml -Patients scheduled for robot-assisted radical prostatectomy	4 weeks	-No treatment-related complications -No serious grade ≥3 adverse events	Not analyzed	-No significant difference in EPIC sexual function domain at 4 weeks compared to baseline -No significant difference in IIEF-15 score between baseline to 4 weeks -No significant change in IPSS at 1 & 4 weeks compared to baseline	N/A

1-year follow-up post-FLA decreased to 6.8% of patients [45]. Moreover, it was identified that the tumor size was the only predictor for a positive post-ablation MRI risk, suggesting its significance in aiding future patient selection.

Chao and Lepor's prospective investigation assessed 5-year failure-free survival (FFS) following transrectal FLA with Visualase and found that 83% patients (25 of 30) exhibited 5-year FFS [46]. Notably, 10 patients (40%) developed in-field recurrence, with 9 patients undergoing further salvage therapy with partial ablation with FLA, Cryoablation, or HIFU [46]. Additionally, Mehralivand et al. reported oncological and functional outcomes in 15 patients treated with transperineal FLA using Visualase over a 3-year follow-up [47]. No severe or persistent post-procedural complications were reported [47]. 47% (7 of 15 patients had PCa recurrence at follow-up. More recently, Magee et al. demonstrated the feasibility of salvage MRI-guided FLA for HIFU recurrences utilizing non-water cooled 1063 nm laser fibers [Clinical Laserthermia System (CLS) Inc, Lund, Sweden] [48].

Following the initial Phase I FLA study for localized PCa by Lindner et al. utilizing a prototype MRI-TRUS guidance for guidance in 2010, Natarajan et al. confirmed the feasibility of performing FLA under MRI-TRUS guidance using Visualase in 11 men [40, 49]. More recently, van Riel et al. demonstrated safety and feasibility of transperineal FLA using the Echolaser system (Calenzano, Italy) in 12 men prior to radical prostatectomy [50]. Ablation zone volumes on MRI and contrast enhanced US (CEUS) showed good correlation with histology (Pearson r = 0.94 [95% CI]). On-going studies are also exploring FLA under micro-US guidance [51]. With studies reporting real-time visualization of MRI lesions with micro-US, it may obviate the need for MRI-TRUS fusion [52, 53].

FLA offers several advantages over traditional treatments for localized PCa. Its real-time MRI imaging guidance ensures precise real-time targeting of lesions, minimizing damage to surrounding healthy tissue [38]. Moreover, due to the absorption rate and low vascularity, prostate tissue is well-suited for FLA and allows for finely controlled ablation [36, 54]. Similar to other focal therapies for PCa, studies have highlighted the preservation of urinary and sexual function in patients post-FLA, highlighting its potential to maintain quality-of-life compared to more invasive radical therapies [38]. Numerous studies have previously found that FLA or secondary whole-gland therapies remain viable options for post-FLA treatment.

One limitation of FLA is that within the current literature, most investigations for FLA for PCa treatment are small, non-randomized studies with relatively short-term follow-up periods [55]. Notably, there are currently numerous active phase II clinical trials assessing in-bore FLA for treating PCa including at the Princess Margaret Hospital, Toronto; Radboud University Medical Center, Nijmegan; and Mayo clinic, Rochester [56–58].

HISTOTRIPSY

Histotripsy is a non-invasive pulsed HIFU technique that produces non-thermal mechanical ablation of tissue through delivery of short bursts (microseconds to milliseconds-long) of high-amplitude HIFU waves containing shock fronts [14, 59]. These bursts induce bubble activity at the focal point, and interactions between bubbles and ultrasound waves breaks tissue into subcellular components. Compared to thermal HIFU ablation, histotripsy employs pulses with higher intensity (10-100 fold greater) delivered at a lower duty factor (≤1%) [14, 60, 61].

There are two primary methods of initiating bubble activity in histotripsy: 'cavitation cloud' histotripsy and 'boiling' histotripsy. Cavitation cloud histotripsy can be performed using shock scattering or intrinsic cavitation techniques using pulses ≤20 microseconds in duration at pulse repetition frequencies up to several hundred pulses per second. Conversely, boiling histotripsy

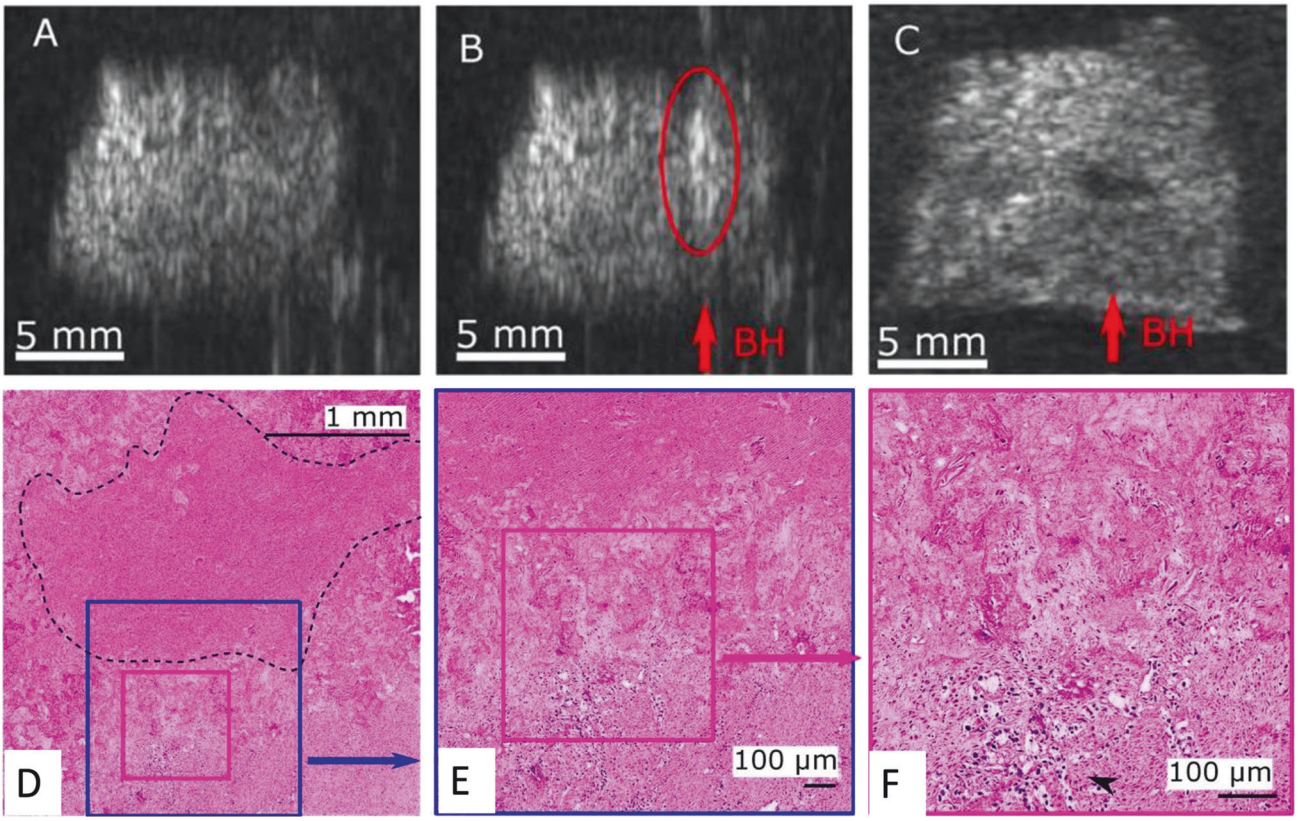

Fig. 4 Ex vivo human prostate cancer tissue treated with boiling histotripsy. B-mode ultrasound appearance of tissue (**A**) pre-treatment, (**B**) during treatment demonstrating hyperechoic bubbles at the focus (within red oval), and (**C**) after treatment demonstrating a hypoechoic cavity consistent with histotripsy induced mechanical fractionation. Red arrow indicates the direction of BH sonications. Histologic appearance of H&E stained human prostate tissue from a rapid autopsy with Gleason $5+5=10$ prostate cancer treated with boiling hisotripsy at low power (**D**), medium power (**E**), and high power (**F**). Histotripsy induced cellular fractionation is seen on lower power within the dashed boundary. At higher power sharp demarcation between treated (top half of panels **E** and **D**) and untreated tissue (bottom half of panels **E** and **D**) is seen with a boundary of ~100 μm. Untreated prostate cancer cells (black arrowhead) are present outside the treatment zone. Figure adapted from Rosnitskiy PB, et al. *Ultrasonics* 2023; **133**: 107029 with permission.

uses pulses of 1–10 milliseconds duration with pulse repetition frequencies up to 10 pulses per second [14]. Both techniques rely on nonlinear propagation of sound waves, leading to the formation of shock waves at the focal point to create bubbles. With cavitation-based techniques the high peak negative pressure of the shocks result in dense cavitation bubble clouds that produce tissue fractionation [14, 62]. In boiling histotripsy, extremely rapid shock induced heating generates a vapor bubble (i.e., boiling) at the focus. As long as pulse duration is just longer than time to boil, and duty factor is low (≤1%), boiling histotripsy produces identical tissue fractionation without thermal effects [61, 63].

Histotripsy techniques offer advantages over thermal ablation, such as tissue selectivity, where cells are more sensitive to damage than extracellular structures (e.g., blood vessels and ducts) [64]. Additionally, histotripsy is not affected by heat sink effects or increased perfusion, addressing challenges faced by thermal ablation methods [65, 66]. Further, owing to the appearance of hyperechoic bubbles at the focus, and subsequent production of a hypoechoic cavity with treatment (from mechanical loss of tissue scatters), histotripsy enables ultrasound imaging based real-time treatment monitoring and feedback that is not possible with thermal techniques [59–61].

Histotripsy technology for prostate ablation has been tested in several preclinical animal studies [67–72]. The feasibility of prostate histotripsy was demonstrated in canine subjects using a 750 kHz transducer with a pulse repetition frequency (PRF) of 100–500 Hz (duty cycle <0.4%) [68]. It was noted that the dense peri-urethral tissue required a greater number of pulses for tissue fractionation [68, 71]. A pilot ex vivo study using boiling histotripsy showed subcellular tissue fractionation in both human PCa and benign prostate parenchyma, thereby establishing that human PCa tissue can be mechanically ablated using the boiling histotripsy method [15] [Fig. 4].

Existing pre-clinical data for prostate histotripsy is encouraging and suggests that with further refinement it could be assessed in clinical trials as a novel PCa FT technique.

CONCLUSION

In conclusion, emerging FT techniques, including MRgFUS, TULSA, and FLA, represent innovative approaches for treating localized PCa while minimizing treatment-related side effects (Table 4). Clinical trials have demonstrated the safety and efficacy of these modalities, offering promising outcomes in oncological control and preservation of quality-of-life. Ablation of smaller volumes is associated with reduced functional decline and the precision of MRI allows for better targeting in all planes and thereby minimizes unnecessary treatment of surrounding healthy tissue [23, 26, 27]. While still in development, histotripsy offers advantages such as tissue selectivity, lack of heat sink effects and improved real-time treatment monitoring.

Different FT technologies have proven efficacy in managing localized prostate cancer. The collective body of evidence underscores the evolving landscape of FT in PCa management.

Beyond the clinical evidence, discussed for newer technologies in this review, factors such as tumor location and characteristics play a key role. Local infrastructure and expertise are also crucial in selecting a platform for focal treatment. We advocate for a tailored

Table 4. Summary of focal therapies.

	Mechanism of action	Treatment approach	Indications/ contraindications	Strengths/ limitations	Important studies	Stage of modality
Transrectal MRI-guided focused ultrasound surgery (MRgFUS)	• Non-invasive technique • Uses mechanical energy of focused ultrasound waves to generate precise thermal energy. • Raises tissue temperature to >55 °C with resultant coagulative necrosis and precise tissue ablation margins.	• Performed under MRI guidance to monitor ablation in real-time • Transrectal approach • Patient under general anesthesia or deep sedation, in low lithotomy position on a modified MRI table. • Foley or suprapubic catheter for continuous bladder drainage • Endorectal treatment probe and balloon filled with degassed water for rectal and device cooling	Indications: Localized intermediate-risk prostate cancer suitable for focal therapy Contraindications: Any contraindication to MRI; Tumors >4–6 cm from the rectal wall; Calcifications adjacent to rectum or in the treatment beam path	Strengths: Precise targeting with MRI guidance; real-time temperature feedback; immediate post-treatment assessment with contrast-enhanced MRI Limitations: Limited access to anterior gland lesions; Calcifications in beam path may impede treatment; procedural length and additional costs compared to US-guided HIFU	Ehdaie et al. [22] Ghai et al. [24]	Phase II studies completed; FDA approval
Transurethral ultrasound ablation (TULSA)	• Minimally invasive procedure • Delivers high-intensity directional ultrasound energy to produce ablative temperatures • Raises tissue temperature to >55 °C with resultant coagulative necrosis and precise tissue ablation margins.	• Performed under MRI guidance to monitor ablation in real-time • Transurethral approach • Patient under general anesthesia or deep sedation • Ultrasound applicator is inserted into the prostatic urethra; rectal and urethral cooling to protect surrounding tissues	Indications: Intermediate-risk prostate cancer; subtotal gland ablation Contraindications: Any contraindication to MRI; Urethral stricture or inability to place the urethral device	Strengths: MRI guidance enhances precision and safety; Real-time thermometry and feedback control for consistent ablation; immediate post-treatment assessment with contrast-enhanced MRI; Able to treat anterior lesions Limitations: Risk of urethral injury or stricture due to rigid applicator; potential for residual cancer in the presence of calcifications in beam path; increased procedure time, complexity, and cost due to MRI guidance	Klotz et al. [32] Chin et al. [29]	Phase II studies completed; FDA approval
Focal laser ablation (FLA)						
MRI-guided FLA	• Requires interstitial placement of diode lasers • Delivers electromagnetic radiation (700–1064 nm) in the form of coherent light, typically in the near- infrared spectrum • Heat from the laser induces protein denaturation and coagulative necrosis	• MRI-guided for real-time lesion targeting and temperature monitoring • Transperineal or transrectal approach	Indications: localized, intermediate-risk prostate cancer Contraindications: large tumors may limit use	Strengths: Precise targeting with MRI guidance; real-time temperature feedback for precise control of ablation temperatures; minimizes damage to surrounding tissue Limitations: Forms cylindrical ablation zones with diameters <15 mm, requiring multiple applicators for adequate coverage; Increased procedure time, cost, and complexity due to MRI guidance	Eggener et al. [42] Walser et al. [45]	Phase II with FDA approval for soft tissue ablation

Table 4. continued

	Mechanism of action	Treatment approach	Indications/ contraindications	Strengths/ limitations	Important studies	Stage of modality
Ultrasound-guided FLA	• Requires interstitial placement of diode lasers • Delivers electromagnetic radiation (700–1064 nm) in the form of coherent light, typically in the near- infrared spectrum • Heat from the laser induces protein denaturation and coagulative necrosis	• Guided by ultrasound or MRI-TRUS fusion for lesion localization • Transperineal or transrectal approach	Indications: Localized, intermediate-risk prostate cancer Contraindications: large tumors may limit use	Strengths: Shorter procedure times compared to MRI guidance; reduces resource utilization and costs; easier to perform and more widely accessible given ultrasound-guidance Limitations: Forms cylindrical ablation zones with diameters <15 mm, requiring multiple applicators for adequate coverage; Less precise than MRI-guided techniques as relies on cognitive or software fusion for targeting	Van Riel et al. [50]	Phase I safety and efficacy study
Histotripsy	• Non-invasive pulsed High-Intensity Focused Ultrasound (HIFU) to induce non-thermal mechanical ablation of tissue • Shock waves lead to bubble activity at the focal point, breaking tissue into subcellular components Employs two methods: • Cavitation cloud histotripsy: High peak negative pressure, dense cavitation bubble clouds • Boiling histotripsy: Shock-induced heating generates vapor bubbles at the focal point	• Transrectal approach via ultrasound imaging. • Non-invasive; does not require transperineal or transurethral access • Enables real-time ultrasound monitoring for treatment feedback	Indications: Potential for treating localized prostate cancer; Applicable in both benign and malignant prostate tissue Contraindications: Not yet validated for large tumors; requires further research in clinical trials to establish safe guidelines	Strengths: non-thermal energy source mitigates heat-sink effects or tissue perfusion challenges; tissue selectivity to spare extracellular structures and minimize damage to surrounding structures; real-time ultrasound-based monitoring Limitations: Primarily at the preclinical stage with limited human trials	Schade et al. [72] Rosnitskiy et al. [15]	Preclinical stage

'a la carte' approach, choosing the most appropriate technology based on the tumor's specific features (size, location, distance from rectum, presence or calcification etc), local expertise and technology availability.

Despite the advantages, challenges such as limited long-term data and logistical complexities remain. Future research endeavors, including randomized controlled trials such as FARP (Focal Prostate Ablation versus Radical Prostatectomy) and ENFORCE (Effectiveness of Focal therapy in Men with PCa) with long-term follow-up and advancements in technology, are crucial to facilitate the integration of these novel therapies into clinical practice [73, 74]. As the field continues to advance, personalized approaches tailored to individual patient characteristics and preferences will likely play a pivotal role in optimizing treatment strategies for localized PCa, ultimately enhancing patient care and prognosis.

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AUTHOR CONTRIBUTIONS

SG conceived the study, and TN and SG wrote the initial manuscript draft and prepared the manuscript revisions. CP, JF, GS, RS, FC, SE, JF, AG, AV, and JR provided expert feedback and revisions on the manuscript content.

COMPETING INTERESTS

SG served as Principal Investigator for Phase I and Phase II studies assessing MRgFUS sponsored by Insightec Ltd. GS currently serves as a consultant to EDAP Technomed Inc., an advisor to Immunity Bio, owns intellectual property licensed to Petal Surgical, and his work has been funded by the NIH (NIH R01DK119310 and R01CA258581) and American Cancer Society (RSG2117101). SE previously served as a member of the medical advisory board for Profound Medical approximately from the years 2016-2020. All other co-authors declare no potential competing interests.

ADDITIONAL INFORMATION

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