Review Article

A narrative clinical trials review in the realm of focal therapy for localized prostate cancer

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Background and Objective: The role of focal therapy in the treatment of localized prostate cancer is evolving. However, despite accumulating evidence, current guidelines and regulatory bodies refrain from endorsing focal therapy outside of clinical trials. Our goal was the to review the focal therapy realm for ongoing clinical trials and high impact recently published trials.

Methods: Our comprehensive investigation includes an exhaustive review of ClinicalTrials.gov and PubMed databases, identifying and analyzing clinical trials with diverse modalities of focal therapy. In this review, we focused on critical ongoing and recently concluded clinical trials (2-15-2023) in the focal therapy realm.

Key Content and Findings: We identified several trials on focal therapy at various stages of progression and various trial design. The trials study all different modalities of focal therapy including high-intensity focused ultrasound (HIFU), cryoablation, irreversible electroporation (IRE), focal laser ablation (FLA), transurethral ultrasound ablation (TULSA)-PRO®, and Water Vapor ablation. The trials focus both on oncological outcomes and quality of life outcomes. Novel clinical trials study the additive impact of androgen deprivation therapy (ADT) to different focal therapy modalities.

Conclusions: The exploration of focal therapy in prostate cancer holds promise for achieving oncological control while minimizing the impact on patients' quality of life. Continued research and trial results will play a pivotal role in delineating focal therapy's optimal role in the broader prostate cancer treatment spectrum.

Keywords: Prostate cancer; localized prostate cancer; focal therapy; prostate ablation

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Introduction

Focal therapy presents an opportunity for targeted intervention in localized prostate cancer, circumventing the necessity for radical therapeutic approaches. Conventional treatments for prostate cancer have historically centered on radical prostatectomy (RP), radical radiation therapy (comprising external beam or brachytherapy), and active surveillance (AS). Focal therapy, operationally defined as the "guided ablation of an image-defined, biopsy-confirmed, cancerous lesion with a safety margin surrounding the targeted lesion", predominantly employs multiparametric magnetic resonance imaging (mpMRI) as the primary imaging modality (1). A diverse array of modalities currently exists for focal therapy, exhibiting improved side effect profiles and promising efficacy in cancer control. Modalities encompassing high-intensity focused ultrasound (HIFU), cryotherapy, laser ablation, irreversible electroporation (IRE), transurethral ultrasound ablation (TULSA),

microwave ablation, photodynamic therapy (PDT), robotic partial prostatectomy, bipolar radiofrequency ablation, and prostatic artery embolization constitute the spectrum of focal therapy options (1,2). Notwithstanding the accumulating evidence on focal therapy efficacy over the last decade (3,4), extant guidelines by the American Urological Association (AUA) (5), and the National Comprehensive Cancer Network (NCCN) (6) currently refrain from endorsing the utilization of focal therapy for localized prostate cancer, except within the context of clinical trials. Furthermore, the United States Food and Drug Administration (FDA) does not currently endorse focal therapy for cancer treatment and defines it strictly as a tissue ablative therapy.

Several protracted trials have supplied compelling evidence suggesting that conventional treatment strategies do not surpass AS/monitoring in terms of survival advantage and are associated with increased side effects. The PROTECT trial, encompassing 1,643 men with prostate cancer randomized to active monitoring, RP, or radical radiotherapy, reported recent follow-up data after a median period of 15 years, revealing no significant disparity in prostate cancer-specific death among the three groups. Notably, a high survival rate (~97%) from prostate cancer death was observed across all treatment paradigms, irrespective of initial tumor grade, stage, or prostate-specific antigen (PSA) level, which did not impact treatment outcomes. While the radical treatments' arms exhibited diminished metastases, clinical progression, and reduced utilization of androgen deprivation therapy (ADT), these effects did not translate into a discernible difference in mortality (7). The PIVOT trial concurred in a study involving 731 men randomized to RP or AS, finding no disparity in prostate cancer or all-cause mortality between the two groups. However, surgery was associated with more pronounced incidences of incontinence and erectile dysfunction (ED) during the median follow-up period of 12.7 years (8,9). Furthermore, a study incorporating nearly 700,000 men diagnosed with prostate cancer across Sweden and the United States revealed that patients were more likely to succumb to causes other than prostate cancer (10). This data underscores the imperative to reassess priorities in prostate cancer treatment and advocates against hasty recourse to radical interventions. The potential of focal therapy modalities as viable options for treating prostate cancer without compromising the quality of life necessitates further exploration, emphasizing the imperative role of clinical trials in addressing these critical questions.

This narrative review provides a concise overview of significant ongoing and recently completed trials focused on focal therapy. It grants readers a glimpse into the dynamic realm of ongoing research in focal therapy, fostering a better comprehension of the practical applications and efficacy of this therapeutic modality. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2406/rc).

Methods

Our investigation encompassed an exhaustive review of ClinicalTrials.gov and PubMed databases to identify ongoing or recently concluded clinical trials about diverse modalities of focal therapy for the management of localized prostate cancer. The search strategy employed involved the utilization of multiple permutations of pertinent terms, including, but not limited to "prostate cancer", "ablative treatment for prostate cancer", "focal therapy for prostate cancer", "high-intensity focused ultrasound (HIFU)", "irreversible electroporation (IRE)", "cryoablation", "focal laser ablation", "microwave ablation", "water vapor ablation", and "transurethral ultrasound ablation of the prostate (TULSA)". Emphasis was directed towards ongoing trials delineating the oncological and quality of life outcomes associated with focal therapy. Additionally, scrutiny was applied to trials, making comparisons between diverse focal therapy modalities and established treatments for prostate cancer. *Table 1* summarizes the search strategy.

Results

We identified several trials on focal therapy for localized prostate cancer at various stages of progression—some are ongoing, others are poised to commence patient recruitment, and a subset has concluded patient recruitment but awaits the publication of their findings. *Tables 2,3* summarize recent and ongoing trials along with the primary and secondary endpoints. These trials are described below based on the primary energy modality being evaluated.

More than one energy modality trials

The CHRONOS (NCT04049747) (11) trial represents a prospective, multicenter therapeutic phase 2 randomized controlled trial (RCT) conducted across multiple sites in the United Kingdom. Constituting two parallel RCTs,

Table 1 The search strategy summary

Items	Specification
Date of search	December 1st, 2023
Databases and other sources searched	ClinicalTrials.gov, PubMed
Search terms used	"Prostate cancer", "ablative treatment for prostate cancer", "focal therapy for prostate cancer", "high-intensity focused ultrasound (HIFU)", "irreversible electroporation (IRE)", "cryoablation", "focal laser ablation", "microwave ablation", "water vapor ablation", and "transurethral ultrasound ablation of the prostate (TULSA)"
Timeframe	2015–2023 (for published trials), and ongoing clinical trials
Inclusion criteria	Feasibility trials, phase 2–3 clinical trials, English language
Selection process	A.L. and V.V. conducted the selection process; consensus was obtained by the authors

Table 2 Trials characteristics and primary endpoints

Trial name	Trial ID	Study type	Study groups	Primary endpoint measure	Primary endpoint timeline (months)
Ongoing trials					
CHRONOS	NCT04049747	–	–	–	–
CHRONOS-A	–	RCT	FT (HIFU/Cryo) *vs.* RT (RadT, BT, RP)	PFS	60
CHRONOS-B	–	RCT	FT (HIFU/Cryo) *vs.* FT + neoadjuvant finasteride or bicalutamide	FFS	60
HIFUSA	NCT03531099	RCT	HIFU *vs.* AS	Conversion to RT	48
FOCALE	NCT03568188	Single arm	HIFU	Controlled disease (% positive biopsies in treated lobe)	12
ENHANCE	NCT03845751	Single arm	HIFU + short-course ADT (leuprolide acetate)	Treatment failure	12
EMERHIT	NCT05710861	RCT	HIFU *vs.* RP	Cost/utility ratio	24
MD Anderson	NCT05454488	Single arm	Cryo	Negative in-field recurrence	6
CAPTAIN	NCT05027477	RCT	TULSA *vs.* RP	(I) Efficacy (free from treatment failure)	(I) 36
				(II) Safety (urinary continence and erectile potency)	(II) 12
PRIS	NCT05513443	RCT	–	–	–
PRIS 1	–	–	IRE *vs.* RP	Urinary continence	12
PRIS 2	–	–	IRE *vs.* RadT	Irritative urinary symptoms	12
PRESERVE	NCT04972097	Single arm	IRE	(I) Efficacy (negative in-field biopsy)	12
				(II) Safety (AE)	
Mayo	NCT02600156	Single arm	FLA	(I) Efficacy (success rate)	36
				(II) Safety (treatment AE)	

Table 2 (*continued*)

Table 2 (*continued*)

Trial name	Trial ID	Study type	Study groups	Primary endpoint measure	Primary endpoint timeline (months)
San Diego	NCT05826470	Single arm	FLA	Safety (treatment AE)	12
Avenda Health FLA	NCT06047509	Single arm	FLA	Safety (AE)	12
VAPOR 2	NCT05683691	Single arm	WVA	(I) Efficacy (freedom from systemic disease, systemic therapy, salvage therapy, Gleason GG ≥2)	(I) 36
				(II) Safety (urinary incontinence)	(II) 12
ATLANTA	NCT03763253	RCT	SOC *vs.* SOC + FT (HIFU/Cryo) *vs.* SOC + RT (RP/RadT)	(I) Efficacy (biopsy findings)	(I) 6
				(II) Safety (AE)	(II) 24–48
				(III) PFS	(III) 24–48
Cincinnati	NCT05790213	Single arm	FT + ADT + HT (apalutamide)	(I) Efficacy (CSPC in ablated/nonablated tissue)	(I) 6
				(II) Safety (AE)	(II) 12
Completed trials					
PART	ISRCTN99760303	RCT	HIFU *vs.* RP	Feasibility of future RCT	–
TACT	NCT02766543	Single arm	TULSA whole gland	(I) Efficacy (PSA nadir ≤25% of baseline)	12
				(II) Safety (treatment AE)	
De La Rosette	NCT01835977	RCT	Focal IRE *vs.* extended IRE	Patient experience	60
VAPOR 1	NCT04087980	Single arm	WVA	AE	6

RCT, randomized controlled trial; FT, focal therapy; HIFU, high-intensity focused ultrasound; Cryo, cryoablation; RT, radical therapy; RadT, radiation therapy; BT, brachytherapy; RP, radical prostatectomy; PFS, progression-free survival; FFS, failure-free survival; AS, active surveillance; ADT, androgen deprivation therapy; TULSA, transurethral ultrasound ablation; IRE, irreversible electroporation; AE, adverse event; FLA, focal laser ablation; WVA, water vapor ablation; GG, grade group; SOC, standard-of-care; HT, hormone therapy; CSPC, clinically significant prostate cancer; PSA, prostate-specific antigen.

CHRONOS-A and CHRONOS-B, each CHRONOS trial will undergo an initial pilot phase. The primary objective of this phase is to establish the feasibility of the trial design, optimizing the enrollment, randomization, and retention processes of eligible men into either CHRONOS-A or CHRONOS-B based on their eligibility and preference. In its full-scale phase 2 trial, CHRONOS-A will undertake a non-inferiority head-to-head RCT comparing focal therapy alone to radical therapy encompassing radiotherapy, brachytherapy, or prostatectomy. The planned recruitment is set at 1,190 patients, with the study aiming to ascertain whether focal therapy alone is non-inferior to radical therapy concerning progression-free survival (PFS) at the 5-year in men with clinically significant non-metastatic prostate cancer. PFS is operationally defined as the duration from randomization to salvage whole gland or systematic therapy, prostate cancer metastases, or prostate cancer-specific mortality.

Meanwhile, CHRONOS-B is structured as a multi-arm, multi-stage RCT, allowing patients to select focal therapy, acknowledging the current scarcity of RCTs in focal therapy. The overarching objective is to assess whether the addition of neoadjuvant and adjuvant agents to focal therapy, in comparison to focal therapy alone, enhances failure-free survival at the 5-year juncture in men with clinically significant non-metastatic prostate cancer. Failure-free survival, in this context, is delineated as the interval from randomization to subsequent focal therapy session or salvage whole gland or systemic therapy, prostate cancer metastases, or prostate cancer-specific mortality. Initially,

Table 3 Trial secondary endpoints

Secondary endpoint	Ongoing trials															Completed trials			
	CHRONOS (A and B)	HIFUSA	FOCALE	ENHANCE	EMERHIT	MD Anderson	CAPTAIN	PRIS (1 and 2)	PRESERVE	Mayo	San Diego	Avenda Health	VAPOR 2	ATLANTA	Cincinnati	PART	TACT	De La Rosette	VAPOR 1
Additional therapy needed		x	x	x		x			x						x				
Pos/neg biopsy findings		x	x			x			x		x				x		x	x	x
Clinically significant cancer detection		x	x								x								
GS/Gleason GG/cancer evolution		x	x			x								x					
New foci development		x	x																
Metastasis		x	x												x				
Extracapsular extension		x	x																
PSA trend	x			x		x			x					x	x		x	x	x
Testosterone trend				x											x				
Treatment failure							x	x											
Imaging findings (including prostate volume)	x					x	x		x	x	x			x			x	x	x
OS		x	x		x		x								x				
RFS		x	x																
PCSS		x	x				x												
Salvage-free survival							x												
Metastasis-free survival							x												
Quality of life	x	x	x	x	x	x	x	x	x					x	x		x		
SAE/AE/treatment toxicity	x	x	x	x		x	x	x											x
Symptom and side effect profile	x	x	x	x	x		x	x	x		x		x	x	x		x		x
Economic/financial considerations	x				x	x													
Other	[1]		[2]				[3]									[4]	[5]		

The "x" means positive (that the study checked this secondary end-point). [1], MRI predictive value; [2], anti-tumoral immunity induction, circulating tumor cell number reduction, non-coding RNA prostate cancer gene 3 level reduction; [3], penile rehab, penile length, blood loss, transfusion volume, hospital stay duration; [4], qualitative recruitment investigation; [5], targeting accuracy. GS, Gleason score; GG, grade group; PSA, prostate-specific antigen; OS, overall survival; RFS, recurrence-free survival; PCSS, prostate cancer-specific survival; SAE, serious adverse event; AE, adverse event.

CHRONOS-B will allocate equal randomization between a focal therapy alone arm, a 12-week course of neoadjuvant finasteride followed by focal treatment, or a 12-week course of neoadjuvant bicalutamide followed by focal therapy. The potential incorporation of additional arms in the future is contingent upon the findings of future research or clinical results. CHRONOS-B is statistically powered to assess the superiority of neoadjuvant agents in conjunction with focal therapy and aims to recruit 1,260 patients.

Secondary outcomes of the CHRONOS trial encompass adverse events, health economics, and functional outcomes, gauged through validated questionnaires. The focal therapies offered within the ambit of the CHRONOS trial include HIFU and cryotherapy, with the choice of focal therapy modality being determined collaboratively by the physician and the patient, taking into consideration technical factors.

The ongoing ATLANTA trial (additional treatments to the local tumor for metastatic prostate cancer: assessment of a novel treatment algorithm; NCT03763253) is a phase 2 RCT with three unblinded treatment arms, aiming to recruit 399 patients across multiple sites in England and scheduled for completion in January 2027. The study includes patients diagnosed within 6 months of recruitment (proven histologically) with metastatic prostate cancer (any T, any N, M1+), irrespective of grade, stage, or PSA level, who exhibit a performance status of 0–2 and are deemed fit to undergo standard-of-care treatment for metastatic disease, as well as both minimally invasive therapy and radical treatment (radiation or RP). The study's hypothesis posits that local tumor treatment, either in radical therapy or minimally invasive ablative therapy (focal therapy), combined with metastatic-directed treatment, will lead to improved survival compared to standard-of-care approaches. The trial comprises three arms: the first adheres to the standard-of-care as determined by the treating physician/team (ADT, chemotherapy, abiraterone, enzalutamide), with radiotherapy defined as palliative/cytoreductive in high-volume metastases or mirroring the STAMPEDE (12) local radiotherapy arm in low-volume metastases. The second arm involves focal therapy (cryotherapy or HIFU) to the primary tumor in addition to standard-of-care, with metastases-directed therapy declared before randomization. The third arm includes radical treatment (radiotherapy or RP) in addition to standard-of-care, and once again, metastases-directed therapy is declared before randomization. Follow-up will extend until progression or up to 4 years, whichever occurs first. Primary outcomes encompass the proportion of patients with complete pathological response, measured on post-standard-of-care prostate biopsy (an internal pilot), safety, and PFS at 2–4 years. PFS is calculated as a composite outcome of biochemical recurrence, local progression, lymph node progression, new sites of bone metastases, or progression or development of new distant metastases, defined as lymph nodes outside the pelvis, bone or organ involvement, or skeletal-related events.

Another phase 2, single-arm trial is currently investigating the combination of focal prostate ablation therapy with ADT and novel hormonal therapy for the treatment of intermediate-risk prostate cancer (NCT05790213). Conducted at the University of Cincinnati Medical Center, the study aims to enroll 57 patients and is slated to conclude in April 2028. Eligible participants include those with newly diagnosed localized intermediate-risk prostate cancer [Gleason grade group (GG) 2–3] exhibiting PSA levels <20 ng/mL, clinical stage no higher than T2c, and no extracapsular extension (ECE) or seminal vesicle (SV) involvement. Patients aged 18 years and above, with good performance status and a life expectancy exceeding 10 years, are included. The treatment protocol comprises Apalutamide at 240 mg orally daily for a total of 6 months, ADT treatment for 6 months, and focal therapy to be completed within 8–12 weeks of initiating Apalutamide. Primary outcomes include the proportion of men with clinically significant prostate cancer (Gleason GG 2 and above) in the ablated and unablated zones at 6 months post-focal therapy, as defined by mpMRI and mpMRI-targeted prostate biopsy. Another primary outcome involves monitoring adverse events within 12 months of focal therapy.

HIFU trials

HIFU is progressively substantiated in the scientific literature as a particularly promising modality. HIFU employs ultrasonic waves to induce tissue destruction through thermal, mechanical, and cavitation effects, resulting in coagulative necrosis (13).

The PART trial (14), conducted by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) from January 2015 to November 2017, represents a feasibility study that employed randomization to assess the comparative efficacy of RP—encompassing open, laparoscopic, or robotic-assisted procedures—and HIFU as a partial gland ablation treatment for

intermediate-risk, clinically localized prostate cancer. The primary objectives were to evaluate the feasibility of conducting a RCT comparing HIFU *vs.* RP by recruiting and randomizing 80 patients. Additionally, the study aimed to elucidate recruitment challenges, inform optimal recruitment strategies for a definitive RCT, collect data on quality of life, and explore data capture methods and their feasibility to inform power calculations and health economic evaluations for a larger-scale trial. This prospective, non-blinded, multicenter feasibility trial was conducted across England's five National Health Service (NHS) referral centers.

The study population comprised men with unilateral intermediate-risk prostate cancer or unilateral intermediate-risk and small contralateral low-risk prostate cancer. By May 2017, 82 patients had been randomized, with 41 each allocated to RP and HIFU arms. While the trial was not powered to assess the clinical effectiveness of HIFU treatment compared to RP, the health-related quality of life outcomes aligned with prior observational studies, suggesting that, in the short to medium term, patients treated with HIFU experienced superior health-related quality of life outcomes compared to those undergoing RP. This successful feasibility trial sets the stage for a comprehensive and definitive RCT comparing RP and partial prostate ablation.

The HIFUSA trial (NCT03531099) is a phase 3, multicenter RCT aimed at assessing the efficacy and tolerability of HIFU therapy compared to AS in patients with low-risk prostate cancer. This ongoing trial, conducted across multiple sites in France, targets the challenging landscape of managing psychologically burdensome AS. The study includes patients aged 50–80 years with a life expectancy of more than 5 years, diagnosed with Gleason GG 1 localized prostate cancer (T1c or T2a). The primary endpoint is the proportion of patients requiring radical treatment within 48 months, with specific criteria for seeking radical treatment defined. Secondary endpoints encompass additional treatment needs, positive biopsy rates, clinically significant cancer rates, metastases, extracapsular extension, overall survival (OS), recurrence-free survival (RFS), prostate cancer-specific survival (PCSS), and quality of life measures.

The FOCALE trial (NCT03568188) is a phase 2, multicenter, prospective cohort study assessing the efficacy of HIFU therapy in patients with localized intermediate-risk prostate cancer. Also conducted in multiple sites across France, this trial aims to recruit 170 patients and focuses on determining the success rate of HIFU using the Focal-One machine in GG2, clinical stage T1c or T2a, intermediate-risk prostate cancer patients. The primary endpoint is the percentage of positive biopsies in the treated lobe at 12 months. Secondary outcomes include the need for additional therapy, rates of positive biopsies, clinically significant cancer rates, Gleason grade evolution, the appearance of another focus, extracapsular extension or metastases, OS, PCSS, and RFS, as well as quality of life assessments.

The ENHANCE trial (NCT03845751) is a single-arm, phase 2 prospective feasibility trial assessing HIFU hemi-ablation and short-term ADT combination to enhance prostate cancer control for intermediate-risk localized prostate cancer. Recruiting 20 patients in Paris, France, the study includes individuals aged 40 years and above with a life expectancy of 10 years and above, featuring localized (T1c–T2b), GG2, and intermediate-risk prostate cancer. Primary endpoint: treatment failures determined by prostate biopsy at 12 months. Secondary outcomes cover urinary and sexual functions, toxicity, additional treatment, quality of life, PSA, and testosterone variation at different times.

The EMERHIT trial (NCT05710861) is a randomized medical economic trial comparing Focal HIFU to total prostatectomy in treatment naïve patients with favorable intermediate-risk prostate cancer. Enrolling patients across multiple sites in France, the trial aims to evaluate the cost/utility ratio expressed as the differential cost per quality-adjusted life year (QALY) in favor of HIFU compared to RP at 24 months. Secondary endpoints include cost differentials, real production costs, survival outcomes, and measures of urinary and sexual function and quality of life measures.

Focal cryoablation trials

Focal cryotherapy involves the targeted transperineal placement of small-diameter needles, undergoing freeze/thaw cycles with helium and argon gases.

MD Anderson Cancer Center in Houston, Texas, is currently enrolling 30 patients for an evidenced focal cryotherapy protocol designed for the focal ablation of intermediate-risk prostate cancer (NCT05454488). The primary objective of this study is to investigate the efficacy of cryotherapy as a focal therapy in controlling prostate cancer. Eligible patients include those histologically confirmed with GG 2–3 prostate cancer (with additional

GG 1 allowed up to 6 mm), clinical stage T1c–T2b, a visible tumor on mpMRI, absence of ECE or SV invasion, and the lesion being anatomically suitable for cryotherapy treatment based on the treating physician's discretion. Additionally, patients should have PSA ≤15 ng/mL.

The study's primary endpoint is to assess the effectiveness of cryotherapy ablation by measuring negative in-field recurrence at 6 months post-ablation. Secondary endpoints include evaluating the quality of life following the procedure using validated questionnaires [Expanded Prostate Cancer Index Composite (EPIC)26, AUA Symptoms Score, Sexual Health Inventory for Men (SHIM)], PSA kinetics, rate of out-of-field recurrence at 6 months, post-procedural mpMRI findings, rate of progression and re-intervention over 5 years, describing the financial toxicity associated with focal cryotherapy, detailing the incidence and severity of complications within 30 days, and describing imaging findings on positron emission tomography (PET) prostate-specific membrane antigen (PSMA) and MRI conducted in a subset of men following the procedure and before the 6-month biopsy.

TULSA-PRO® trials

The transurethral TULSA device consists of a rigid ultrasound applicator which incorporates a linear array of 10 ultrasound transducers that emit directional energy to the prostate, which results in a continuous region of thermal ablation to the prostate capsule. The procedure is done within the MRI machine (15).

The TACT trial (15), a single-arm investigation encompassing 115 men diagnosed with favorable to intermediate prostate cancer across 13 centers in the United States, Canada, and Europe, was conducted to evaluate the safety and efficacy of whole gland ablation utilizing TULSA-PRO® while sparing the urethra and apical sphincter. Among the participants, 63% presented with GG 2 prostate cancer, and 67% exhibited intermediate-risk disease according to the NCCN guidelines. The trial's mandated primary endpoint, a PSA reduction of ≥75%, was achieved in 96% of cases, with a median PSA reduction of 95% and a nadir of 0.34 ng/mL. Notably, pretreatment GG 2 patients exhibited a freedom rate of 79% from GG 2 on the 12-month biopsy, and among those with available biopsy data, 65% showed no evidence of cancer. Median prostate volume decreased from 37 to 3 mL. Erectile function was either maintained or regained in 75% of cases.

The subsequent venture in the TULSA field is the CAPTAIN trial (NCT05027477), a phase 3, multicentered RCT comparing RP and the TULSA-PRO® procedure over a 10-year follow-up period. Enrolling 201 patients across various sites in the United States, Canada, and Finland, the study will randomly assign 67 patients to RP and 134 to the TULSA procedure. Eligible participants include men aged 40–80 years and diagnosed with favorable and unfavorable intermediate-risk prostate cancer (GG 2–3), exhibiting a maximal stage of cT2cN0M0 and presenting with PSA ≤20 ng/dL. The primary endpoints encompass the proportion of patients maintaining both urinary continence and erectile potency at 12 months and the proportion of patients free from treatment failure at 36 months. Secondary endpoints include biochemical failure, histological failure, mpMRI endpoint failure, salvage-free survival, metastases-free survival, PCSS, OS, surgical complications, penile rehabilitation, change in penile length, International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), EPIC, quality of life (EQ-5D-5L) scores, blood loss, transfusion rate, and inpatient hospital stay.

IRE trials

IRE uses microseconds electrical pulses to generate pores in the cell membrane and leads to cell destruction as the cell cannot maintain homeostasis (16).

In February 2023, De La Rosette *et al.* (17) published the outcomes of a multicenter, randomized, single-blind, two-arm intervention study investigating adverse events and quality of life after IRE for the ablation of localized low-intermediate risk prostate cancer. The study involved 51 patients subjected to focal IRE and 55 to extended IRE, with a median follow-up of 30 months. At the 3-month mark, rates of adverse events and ED were comparable between focal and extended ablation groups (21.7% and 23.5%, respectively). Quality-of-life measures, including pain, IIEF, IPSS, and EPIC scores, displayed no significant intergroup differences. The study also reported early oncological outcomes at 6 months, revealing clinically significant prostate cancer (Gleason GG 2 and above) in 18.7% and 13% of patients in the focal and extended ablation groups, respectively, with no significant disparity.

The Prostate Cancer IRE Study (PRIS trial, NCT05513443) (18) is an ongoing randomized controlled open-label trial comparing focal IRE therapy to conventional radical treatment for localized prostate cancer. Enrolling 184 patients across four sites in Stockholm,

Sweden, the trial comprises PRIS1 and PRIS2 studies. PRIS1 randomizes patients for focal treatment with IRE or RP, while PRIS2 randomizes patients for focal therapy with IRE or radiation therapy. The PRIS study targets patients diagnosed with GG 2–3 prostate cancer from a single mpMRI visible lesion without any Gleason grade 4 in systematic biopsy outside the target, clinical stage T1c–T2c, unifocal disease, and PSA ≤20 ng/mL. Extraprostatic extension (EPE) lower than 1.5 mL in volume is allowed. PRIS1's primary endpoint is urinary incontinence at 12 months, while PRIS2's primary endpoint is irritative urinary symptoms at 12 months. The secondary endpoints cover ED, voiding function, bowel function, quality of life at 12 months, adverse events at 3 months, and treatment failure during a follow-up of up to 24 months.

The PRESERVE trial (NCT04972097) is a pivotal single-arm study assessing the NanoKnife system's efficacy for ablating prostate tissue in an intermediate-risk prostate cancer population. The trial recently concluded enrollment with 121 patients across multiple United States sites, aged >50 years, diagnosed with GG 2–3, stage T1c–T2c, with no evidence of EPE or SV invasion by mpMRI and PSA ≤15 ng/mL. Primary endpoints include the rate of negative in-field biopsy and the incidence of adverse events at 12 months, while secondary endpoints include negative out of field biopsy at 12 months (defined by the Delphi consensus criteria), urinary and erectile function, quality of life at 12 months, PSA kinetics, change in mpMRI prostate volume, evaluation of prostate tissue by mpMRI at 3–10 days and 12 months post-treatment, and the need for secondary or adjuvant treatment at 12 months. The results of the trial are pending.

Focal laser ablation (FLA) trials

FLA is an MRI-guided technique that uses low powered laser fiber to deliver thermal energy to the target tissue (in which the temperature exceeds 60 ℃) (16).

A prospective study is currently underway at Mayo Clinic, Rochester, Minnesota (NCT02600156) to assess the safety and efficacy of MRI-guided FLA in managing low to intermediate risk prostate cancer. The trial, enrolling 20 participants aged 45 years and above, focuses on those with GG 2–3 or intermediate risk Gleason 6, clinical stage T1c–T2a, PSA ≤20 ng/mL, 1–3 suspicious lesions on mpMRI, and no radiographic indication for extracapsular extension. Over 3 years, primary endpoints include the success rate and incidence of treatment adverse events, while secondary endpoints encompass short and mid-term ablative success.

In San Diego, California, a researcher-initiated investigation (NCT05826470) is recruiting 15 subjects to explore the safety and efficacy of transperineal FLA for localized prostate cancer using high-frequency micro-ultrasound imaging. Employing the TRANBERG® device, eligible candidates, aged 40–85 years, present with GG 1–2, clinical stage T2b or less, low, or favorable risk prostate cancer, and PSA <20 ng/mL. The MRI suspicious lesion should be unilateral, with cumulative lesion volumes not comprising more than 50% of the lobe. The lesion distances from the outer perimeter of the energy emitting zone of the diffuser to adjacent vital structures (bladder wall, rectal wall, neurovascular bundle, and urethra) must be ≥8 mm. The primary endpoint, evaluated over 12 months, focuses on safety and tolerability, with secondary endpoints addressing FLA efficacy, clinical outcomes at 12 months (urinary incontinence and sexual function), volumetric changes in prostate lesions, and cancer control in treated areas assessed via mpMRI and prostate biopsy. The study aims to determine the presence of clinically significant prostate cancer in the ablation zone, evaluate the imaging capabilities of high-frequency micro-ultrasound, compare ablation sizes using post-procedural MRI and measure treatment duration.

The Avenda Health Focal Laser Ablation Trial (NCT06047509) is an open-label feasibility/pilot study aimed at evaluating the safety and efficacy of Avenda Health's FocalPoint System for FLA, coupled with the Unfold-AI Software designed to enhance the diagnostic process and assist in laser delivery, particularly in conjunction with mpMRI and biopsy findings. Conducted at University of California Los Angeles (UCLA)/Jonsson Comprehensive Cancer Center, the trial commenced recruitment in September 2023 and is anticipated to conclude by October 2025. Targeting a cohort of 20 individuals, the inclusion criteria specify ages between 40 and 85 years, Gleason 7 stage ≤ T2b cancer, prostate volumes ranging from 20 to 80 cc, histologically confirmed adenocarcinoma from MRI/US fusion targeted biopsy within 6 months of treatment, and an MRI within 9 months of treatment indicating a lesion with PIRADSv2 > grade 3. The primary study endpoint is safety, gauged by adverse events up to 12 months post-treatment, defined by the absence of any grade 3 or higher adverse events. The trial plans comprehensive follow-up until 1-year post-treatment/retreatment, with a provision for long-term follow-up extending up to 10 years.

Water vapor ablation trial

The VAPOR 2 trial (NCT05683691) is an ongoing prospective, multicenter, single-arm study designed to evaluate the safety and efficacy of the transurethral Vanquish water vapor ablation device from Francis Medical in patients diagnosed with Gleason GG2 localized intermediate-risk prostate cancer. With recruitment initiated in May 2023, the trial aims to enroll 400 individuals across 30 clinical sites in the United States, anticipating completion in April 2029. Inclusion criteria comprise an age of 50 or older, a life expectancy of at least 10 years, a prostate volume ranging from 20 to 80 cc, PSA levels not exceeding 15 ng/mL, clinical stage not exceeding T2c, and the presence of a lesion with greatest diameter of less than 15 mm. The primary effectiveness endpoint, assessed at 36 months, is determined by the absence of systemic disease, avoidance of systemic therapy, absence of salvage therapy, and no progression to Gleason GG ≥2. Additionally, VAPOR 2 establishes a primary safety endpoint at 12 months, measured by the proportion of subjects free from new or worsening urinary incontinence based on pad use. Secondary outcomes include evaluating the proportion of subjects free from impotence at the 36-month mark.

Discussion

Focal therapy in prostate cancer marks a pivotal evolution in treatment strategies, offering a targeted alternative to traditional radical interventions. This shift is driven by the desire to address prostate cancer with precision while mitigating the potential morbidities associated with procedures like RP and radiation therapy. The historical emphasis on these treatments, including AS, has paved the way for a diverse array of focal therapy modalities.

The operational definition of focal therapy, underscores the commitment to tailored interventions guided by advances in imaging, particularly mpMRI (1). This definition reflects a paradigm that seeks to balance therapeutic efficacy with the preservation of patients' quality of life. The reviewed trials collectively enrich our understanding of focal therapy's nuances, offering insights into its efficacy, safety, and impact on patient outcomes in diverse clinical contexts.

While radical interventions demonstrate reduced metastases and clinical progression, these benefits often do not translate into discernible differences in mortality (7,8). The ongoing clinical trials such as CHRONOS (11), with its dual-arm approach comparing focal therapy alone to radical therapy and exploring the integration of neoadjuvant/adjuvant agents, exemplifies the commitment to refining treatment paradigms. The consideration of patient-reported outcomes, health economics, and functional outcomes in these trials reflects a comprehensive evaluation of the holistic impact of focal therapy. Clinical trials in the field of focal therapy are increasingly prevalent, delving into novel modalities and fine-tuning follow-up protocols. The ongoing research endeavors and the outcomes from these trials are poised to be instrumental in defining the optimal position of focal therapy within the expansive landscape of prostate cancer treatment. Furthermore, these findings are anticipated to enhance the global acceptance of focal therapy, fostering its broader integration and application in prostate cancer care.

Conclusions

Focal therapy offers a targeted approach to prostate cancer treatment, balancing efficacy with preserving genitourinary function and quality of life. Ongoing clinical trials are refining treatment paradigms and assessing holistic outcomes, shaping the broader acceptance and integration of focal therapy into clinical practice.

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Footnote

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