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Established focal therapy—HIFU, IRE, or cryotherapy—where are we now?—a systematic review and meta-analysis

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INTRODUCTION: Focal Therapy (FT) is a treatment option for the treatment of limited volume clinically significant prostate cancer (csPCa). We aim to systematically review outcomes of established FT modalities to assess the contemporary baseline and identify gaps in evidence that will aid in further trial and study design.

METHODS: We conducted a systematic review and meta-analysis of all primary studies reporting outcomes of FT using cryotherapy, high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE). We described patient inclusion criteria, selection tools, treatment parameters, and surveillance protocols, and pooled overall survival (OS), cancer-specific survival (CSS), metastasis-free survival (MFS), biochemical progression (BP), biopsy, secondary treatment, sexual, and urinary function outcomes. Composite failure was defined as salvage whole gland ablation, radical treatment, hormonal therapy or transition to watchful waiting.

SYNTHESIS: We identified 49 unique cohorts of men undergoing FT between 2008 and 2024 (21 cryotherapy, 20 HIFU, and 8 IRE). Median follow-up ranged from 6 to 63 months. Pooled OS was 98.0%, CSS 99.3%, and MFS 98.5%. Pooled BP was 9.4%/year. Biopsy was mandated post-FT within 24 months in 36/49 (73.5%) cohorts, with pooled csPCa (GG ≥ 2) rates of 22.2% overall, 8.9% infield, and 12.3% outfield. The pooled rate of secondary FT was 5.0%, radical treatment 10.5%, and composite failure 14.1%. Of 35 studies reporting sexual function, 45.7% reported a low, 48.6% moderate, and 5.7% severe impact. For 34 cohorts reporting urinary function, 97.1% reported a low impact. No differences were noted between cryotherapy, HIFU, or IRE in any of the outcomes.

CONCLUSION: FT with cryotherapy, HIFU, and IRE is associated with good short-intermediate term oncological and functional outcomes. However, outcome reporting is heterogeneous and often incomplete. Long-term follow-up and standardized reporting are required to better define and report FT outcomes.

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INTRODUCTION

Radical therapy with surgery or radiation is the gold standard for treatment of localized prostate cancer (PCa) [1]. However, it is associated with significant treatment-related sexual, urinary, and bowel morbidity [2]. Focal therapy (FT), where only the area of cancer within the prostate is targeted for destruction, could potentially spare the adjacent critical anatomical structures responsible for sexual, urinary, and bowel function from damage, and thus preserve quality of life. Though it was first proposed in the 2000s, physician adoption of FT was limited prior to the late 2010s.

The majority of prostate cancers are multifocal. However, it is now recognized that not every prostate cancer lesion may need to be treated with the understanding that intermediate- and high-grade (Gleason score ≥3 + 4) prostate cancers are the ones that tend to progress and are clinically significant (csPCa), whereas low-grade cancers have low cancer-specific mortality and metastasis and can be safely monitored on active surveillance [3, 4]. Furthermore, when small, low-grade cancer foci are discounted, the proportion of unifocal csPCa increases substantially [5]. The key to successful FT is thus the accurate identification of such unifocal csPCa lesions within the prostate.

Over the last decade, multiparametric magnetic resonance imaging (mpMRI) has emerged as a key imaging tool of the prostate, being able to detect and locate csPCa lesions [6]. The advent of mpMRI-fusion biopsy has allowed physicians merge mpMRI data with accessible office prostate biopsies [7]. These capabilities have significantly increased the feasibility and interest in FT.

There are now multiple new ablative energy sources and delivery methods being developed for FT. This has resulted in efforts being focused on many early-phase studies rather than definitive trials [8]. Despite more than a decade of investigation, majority of FT reports are those of single-arm cohorts.

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Furthermore, comparison between FT modalities have also been hampered by different trial designs with varying use of pre- and post-treatment imaging and biopsy since these have been developing practices over the last decade.

Among the multiple FT modalities now available, cryotherapy, high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) have the longest history of use. A review of these "established" modalities will help us to identify gaps in evidence that will aid in further trial and study design. In this report, we aim to systematically review oncological and functional outcomes of established focal therapy modalities with a view to assess the contemporary baseline and identify gaps in evidence that will aid in further trial and study design.

METHODS

Study selection

This systematic review and meta-analysis was registered on PROSPERO (CRD42024554177) and performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [9].

An electronic literature search was conducted on PubMed, Embase, and Scopus from inception to May 29, 2024, without language restrictions. Bibliographies of each included study were screened, and a search on Google Scholar using the first and last author of each included study was conducted to ensure inclusion of all relevant studies. Abstracts and full texts were reviewed by two independent investigators, with conflicts resolved by a third investigator.

Studies describing either cryotherapy, HIFU, or IRE outcomes with either re-biopsy or progression results were included. Case reports, reviews, conference abstracts, and studies reporting <20 patients were excluded. Duplicate publications were removed. Where a cohort was reported more than once, the latest report was used. We included only cohorts reporting ablation of half the gland or less in this review of focal therapy (Fig. 1A). A standardized data collection template with predefined data fields including study characteristics, patient demographics, and outcomes was used for data extraction by two independent investigators. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) detailed in Supplementary Table 1 [10].

Outcome measures

Outcomes extracted included: D'Amico/National Comprehensive Cancer Network (NCCN)/Cancer of the Prostate Risk Assessment (CAPRA) risk groups, Gleason scores and International Society of Urological Pathology (ISUP) grade groups (GG), pre-treatment mpMRI use, pre-treatment targeted/systematic biopsy use, target lesion location, ablation modality, ablation pattern, follow-up MRI use, follow-up biopsy use, follow-up biopsy outcomes, biochemical progression, secondary treatments, overall survival (OS), cancer-specific survival(CSS), metastasis-free survival (MFS), and sexual and urinary functional outcomes.

Due to the varying criteria used to assess functional outcome, we defined the treatment impact of FT on sexual and urinary function arbitrarily by comparison to baseline regardless of the individual measure used. Where function was reduced by <10% compared to baseline, this was classified as low impact. Where function was reduced by 10–30% compared to baseline, this was classified as moderate impact. Where function was reduced by >30% compared to baseline, this was classified as severe impact.

Statistical analysis

Meta-analysis of proportions was carried out for several outcomes. The primary outcome in this study was cancer detection post-FT. This was analyzed in the form of 6 post-FT biopsy outcomes: any cancer, any clinically significant (GG ≥ 2) cancer, in-field cancer, infield clinically significant cancer, outfield cancer, and outfield clinically significant cancer. Secondary outcomes included biochemical progression, treatment failure, acute urinary retention, and urinary tract infection. Outcomes were reported for each of cryotherapy, HIFU, and IRE, and only if >3 studies reporting the outcome in question were available.

For primary outcomes, respective outcome numbers and biopsied patients per study were pooled for each outcome. Random-effects meta-analysis of proportions was conducted and forest plots were generated, with stratification according to time of biopsy if possible. For secondary outcomes, given the short to medium-term follow-up in all studies, the lack of Kaplan-Meier curves in most studies for accounting of time-varying status, as well as low overall event rates, OS, CSS, and MFS were synthesized as proportions for meta-analysis. To account for the significant variation of follow-up time for biochemical progression between studies, and given that this was the significant oncological outcome measure for studies not using mandatory repeat biopsy as part of the protocol given the medium-term follow-up, we assumed that biochemical progression occurred linearly and averaged it over the follow-up time for the purpose of data synthesis, effectively generating an estimate of average biochemical progression rate per year. Forest plots for all outcomes were displayed alongside 95% confidence intervals (95%CI). Heterogeneity was considered low, moderate, or considerable for I^2 values < 40%, 40–75%, and >75%, respectively. Funnel plot symmetry was visually assessed for publication bias.

Synthesis

We reviewed 56 original articles on the topic of cryotherapy, HIFU, or IRE FT after excluding systematic reviews, meta-analyses, and editorials (Fig. 1B). After applying our exclusion criteria, we identified a total of 49 unique cohorts for analysis (Table 1). Focal cryotherapy comprised 21/49 (42.9%) cohorts [11–31]. Focal HIFU comprised 20/49 (40.8%) of the cohorts [23, 32–50]. Focal IRE comprised 8/49 (16.3%) of the cohorts [51–58].

Evolution of patient inclusion criteria and selection tools over time

The patient inclusion criteria for FT among studies was highly heterogeneous, including a range of low-, intermediate-, and high-risk patients, as well as a large range of GGs. In all, only 29/49 (59.2%) of cohorts reported D'Amico/NCCN/CAPRA risk stratification, while 48/49 (98.0%) of cohorts reported ISUP GG compositions of their patients. Earlier cohorts were more likely to report the risk strata compositions of their cohorts. In the 2018–2012 time period, 4/4 (100%) of cohorts reported risk stratification; from 2013 to 2016, 7/7 (100%); from 2017 to 2020, 8/13 (61.5%); and from 2021 to 2024, 10/25 (40.0%).

Over time, we observed a gradual increase in the proportion of GG2-5 patients in the reported cohorts, whereas earlier cohorts generally included a higher proportion of GG1 patients, reflecting a change in the patient selection criteria for FT to target patients with clinically significant prostate cancer (Fig. 1C). In the 2008–2012 time period, 4 studies reported that the proportion of their cohort having csPCa ranged from 35.0 to 42.5%; from 2013 to 2016, 7 studies reported 0.0–57.2%; from 2017 to 2020, 13 studies 16.0–74.3%; and, from 2021 to 2024, 25 studies 66.3–85.3%.

A total of 38/49 (77.6%) of cohorts reported the use of mpMRI in the pre-diagnostic workup before FT. Later cohorts were more likely to utilize mpMRI compared to earlier cohorts. In the 2008–2012 time period, 0/4 (0%) studies reported utilizing mpMRI; from 2013 to 2016, 4/7 (57.1%); from 2017 to 2020, 12/13 (92.3%); and, from 2021 to 2024, 22/25 (88.0%) studies reported utilizing mpMRI. 27/49 (55.1%) of cohorts reported utilizing targeted biopsies while 26/49 (53.1%) cohorts reported using some form of systematic biopsy (12-core or mapping biopsy).

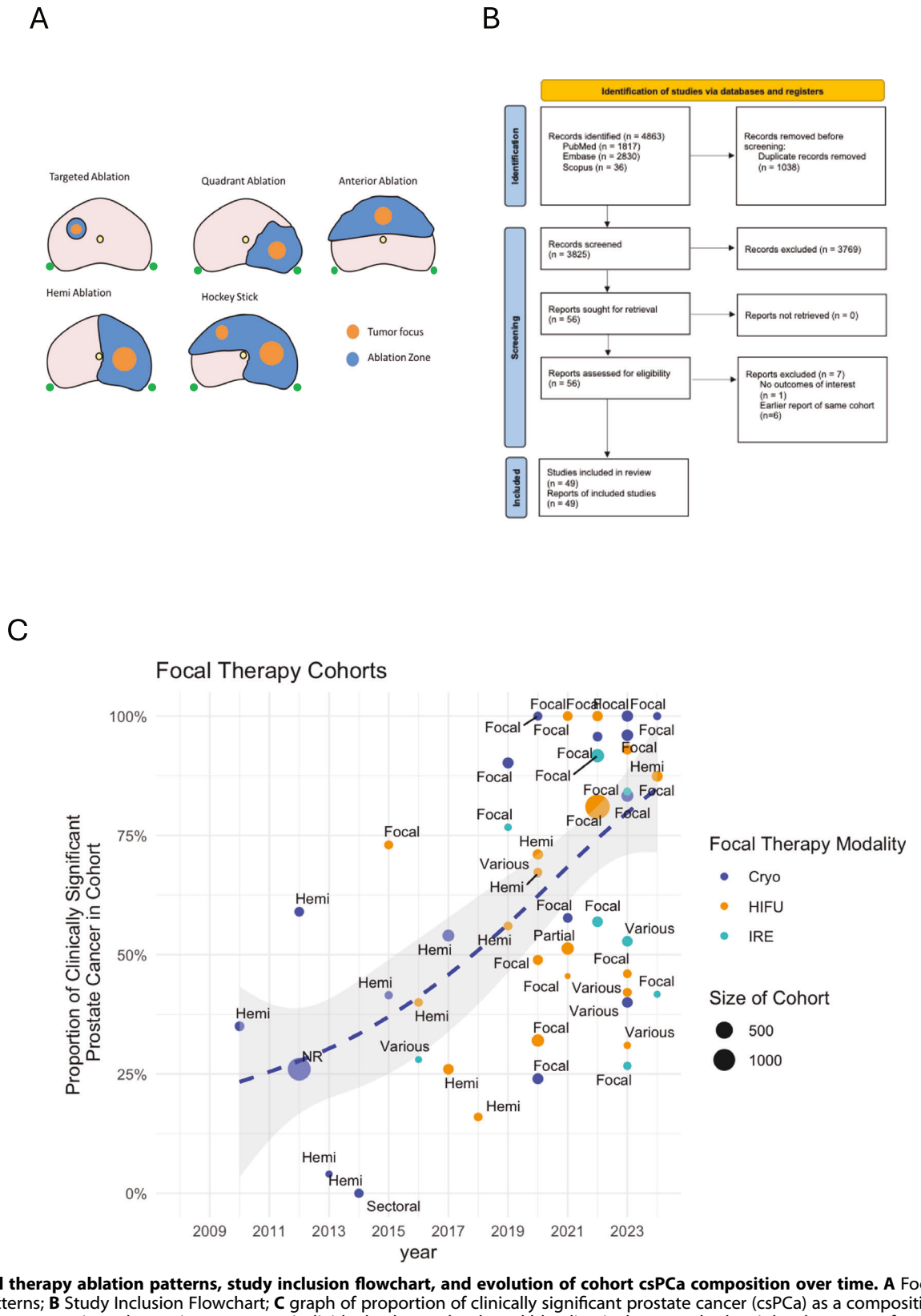


Fig. 1 Focal therapy ablation patterns, study inclusion flowchart, and evolution of cohort csPCa composition over time. A Focal therapy ablation patterns; **B** Study Inclusion Flowchart; **C** graph of proportion of clinically significant prostate cancer (csPCa) as a composition of focal therapy cohorts over time; data points represent individual cohorts; the dotted blue line is the smoothed weighted average of proportion of csPCa over time.

Table 1. Characteristics of included cohorts.

First author	Year	Number of participants	Institution	Pre-diagnostic workup	Declared inclusion criteria	NCCN risk group (%)			GG ≥ 2 (%)	Ablation pattern	Anterior tumors (%)	Follow-up protocol	Median follow-up (months)
						Low	Intermediate	High					
Focal cryotherapy													
Onik	2008	48	Florida	TRUS Biopsy (restaging TMB after 2001)	Unilateral cancer	48	38	14	NR	Hemi-ablation	NR	3 monthly PSA for 2 years then 6 monthly, routine biopsy at 12 months	54
Truesdale	2010	77	Winthrop	TRUS Biopsy	Unilateral cancer	57	40	3	35	Hemi-ablation	NR	3, 6-month serum PSA and 6 monthly after, 12-core TRUS if BCR (Phoenix)/positive DRE.	24
Bahn	2012	73	USC	TRUS biopsy	Unilateral, Gleason 7 or less	33	67	0	59	Hemi-ablation	NR	3–6 monthly PSA, 6–12-month TRUS then yearly	44.4
Ward	2012	1160	COLD	NR	NR	47	41	12	26	NR	NR	NR	21.1
Hale	2013	26	MD Anderson	Staging TMB	Low–intermediate risk	88.5	11.5	0	4	Hemi-ablation	NR	3 monthly PSA for 2 years then 6 monthly, Triggered TRUS bx if PSA/DRE abnormal	19.1
Barqawi	2014	62	USC	TMB	40–85 yrs. cT1-T2b; Gleason 3 + 4 or less; Less than 50% positive core, After TTMB, <20% total prostate, index lesion < 5cc, 4 or less zones involved	100	0	0	0	Sectoral ablation	NR	PSA at 3, 6, 12, 18, 24 months	28
Durand	2014	48	IM	12 core staging TRUS biopsy + mpMRI	PSA < 10, Positive cores <33%, %core <50, Unilateral, Gleason 6 or less	100	0	0	0	Hemi-ablation	NR	3 monthly for 1st year then 6 monthly PSA, 12 core TRUS mandatory at 12 months	13.2
Lian	2015	41	Nanjing University	Minimum 12 core biopsy	Unilateral cancer, PSA < 20, 1–2 cores, <50% involvement, Gleason 6–7, cT2b or less	56	44	0	41.5	Hemi-ablation	NR	3 monthly for 1st year then 6 monthly PSA, 12-core TRUS biopsy at 6-12 months then yearly/triggered	63
Kongnyuy	2017	163	Winthrop and Columbia	NR	Unilateral localized disease	52	41	7	54	Hemi-ablation	NR	PSA checks: year 1—every 3 months. Then every 6 months	36.6
Shah	2019	122	UK multicenter	TRUS, TMB + mpMRI	GGG: 2 or 3 or high volume GGG1 (3 + 3)	0	71	29	90.2	Focal ablation	80	mpMRI at 12 months; Biopsy after BCR	27.8
Basourakos	2020	55	NYP-Weill Cornell	MRI/TRUS fusion Target and 12-core Systematic Biopsy	GGG > 2	NR	NR	NR	100	Focal ablation	NR	mpMRI and targeted and systematic biopsy at 6 months	6
Boissier	2020	26	Barcelona	Systematic and Targeted biopsy	Low-intermediate risk	15	85	0	67	Hemi-ablation	NR	Biopsy after BCR	47
Tourinho-Barbosa	2020	119	IM	Systematic and targeted Transperineal biopsy	Low or intermediate-risk PCa	66	34	0	24	Focal ablation	NR	mpMRI at 1 and 12 months; systematic core biopsy at 12 months	45
Tan	2021	71	Duke	mpMRI + targeted and systematic biopsy	Low-intermediate PCa	NR	NR	NR	57.7	Focal ablation	40	mpMRI at 3–6 months, 12–24 months, and 5 years	28
Baskin	2022	75	UCSF	NR	Unilateral GG > 2	1.3	82.7	16	95.7	Focal ablation	NR	MRI and control biopsy at 12 months	20
Aker	2023	143	UCLA	mpMRI + Targeted biopsy	Unilateral csPCa–GG2 or more; PSA < 20 ng/ml;	NR	NR	NR	96	Focal ablation	66	MRI and MRI-guided biopsy at baseline; 6 and 18 months.	
Wysock	2023	132	NYU	Systematic and targeted biopsy	Unilateral GG < 4	NR	NR	NR	100	Focal ablation	22	mpMRI and targeted + ipsilateral systematic biopsy at 6,24, and 60 months	6

Table 1. continued

First author	Year	Number of participants	Institution	Pre-diagnostic workup	Declared inclusion criteria	NCCN risk group (%)			GG ≥ 2 (%)	Ablation pattern	Anterior tumors (%)	Follow-up protocol	Median follow-up (months)
						Low	Intermediate	High					
Tan	2023	28	SGH	mpMRI + Targeted biopsy and systematic saturation biopsy	GG ≥ 2, PSA < 20 ng/ml, Lesion volume < 3 ml (single) or 1.5 ml (dual)	0	85.7	14.3	100	Focal ablation	NR	mpMRI + Targeted biopsy of the treated zone and new targets/ systematic saturation biopsy 12–18 months	18
Khan	2023	163	Fremont	TRUS or TMB	Retrospective: Organ-confined, any GG, for men whom sexual and urinary function preservation was a major goal	16.5	70.5	14.1	83.3	Focal	NR	3-monthly PSA for the first year then 6-monthly thereafter	39
Selvagio	2023	110	University of Foggia, Italy	18-core TRUS biopsy	Low-intermediate risk, elderly patients > 70 years	49.1	38.2	12.7	40	Various	NR	PSA follow-up in clinic, for cause biopsy with biochemical progression	36
Siddana	2024	36	University of Cincinnati	TRUS- or TP- MRI fusion biopsy	Retrospective: Patients who underwent "true focal" therapy				100	Focal	NR	PSA 3 monthly for the first year then 6-monthly, mandatory 6–9th month MRI + targeted + 12-core systematic biopsy then MRI at 24 months and 2-yearly thereafter	29.1
Focal HIFU													
Ahmed	2015	56	UCL	mpMRI + TRUS biopsy or TMB	PIRADS 4/5 with concordant biopsy findings; Gleason ≤ 4 + 3; PSA ≤ 20; Stage ≤ t3a	12.5	83.9	3.6	73	Focal ablation	NR	Clinical review and PSA at 1, 3, 6, 9, 12 months. Mandatory targeted biopsy of treated area at 6 months. Contrast-MRI at 2 weeks and mpMRI at 6 months.	12
Van Velthoven	2016	50	Joules Bordet Institute, Belgium	mpMRI + targeted biopsy	Concordant biopsy with mpMRI; Stage ≤ T2; PSA < 15; Prostate volume < 40 ml; Life expectancy ≥ 5 yr	48	52	0	40	Hemi-ablation	NR	Clinical review and PSA at 1, 3, and 6 months then 6 monthly. TRUS biopsy if PSA recurrence (Phoenix)	39.5
Rischmann	2017	111	France multicenter	mpMRI + targeted biopsy	Unilateral cancer, Gleason score ≤ 3 + 4	NR	NR	NR	26	Hemi-ablation	NR	Clinical review and PSA at 1, 3, 6, 12, and 6-monthly thereafter. mpMRI at 6–12 months and targeted biopsy of suspicious areas	30.4
Ganzer	2018	51	AUO multicenter	TRUS biopsy 12-core + mpMRI	unilateral disease; Stage T1c–T2a, Positive biopsies < 30; Gleason score ≤ 3 + 4, max core length 5 mm; PSA < 10	NR	NR	NR	16	Hemi-ablation	NR	Clinical review, PSA, and TRUS 3 monthly. Mandatory mpMRI 12-core TRUS biopsy at 12 months	17.4
Annoot	2019	55	Lille	mpMRI + targeted biopsy	Clinical stage < cT2; Unilateral cancer; <GG 3 + 4	NR	NR	NR	56	Hemi-ablation	NR	mpMRI and systematic and targeted biopsy at 12 months	33
Tourinho-Barbosa	2020	119	IM	Systematic and targeted Transperineal biopsy	Low or intermediate-risk PCa	54	46	0	32	Focal ablation	NR	mpMRI at 1 and 12 months; systematic core biopsy at 12 months	45
Abreu	2020	100	USC	mpMRI + systematic + targeted biopsy	Unilateral cancer; <cT2; <GG 4	28	67	5	71	Hemi-ablation	NR	mpMRI and 12 core systematic and target biopsy at 6–12 months	20

Table 1. continued

First author	Year	Number of participants	Institution	Pre-diagnostic workup	Declared inclusion criteria	NCCN risk group (%)			GG ≥ 2 (%)	Ablation pattern	Anterior tumors (%)	Follow-up protocol	Median follow-up (months)
						Low	Intermediate	High					
Nahar	2020	52	University of Miami	mpMRI + systematic + targeted biopsy	Organ unilateral localized PCa; any ISUP	NR	NR	NR	67.3	Various	NR	mpMRI and fusion biopsy at 6 and 12 months	12
Shoji	2020	90	Tokai	mpMRI + systematic + targeted biopsy	PSA < 20 ng/ml; unilateral PCa	34.4	48.9	16.7	48.9	Focal ablation	NR	mpMRI at 2 weeks and 6 months; 6 months: systematic and targeted biopsy	21
Dellabaella	2021	189	IRCCS-INRCA	mpMRI + Transrectal MRI-targeted + systematic biopsy	stage cT ≤ 2, GG ≤ 3	NR	NR	NR	51.3	Partial ablation	20.7	mpMRI and biopsy at 12 months	29
Rompré-Brodeur	2021	77	McGill	mpMRI + Transrectal MRI-targeted + systematic biopsy	GGG ≥ 2, PSA ≤ 15 ng/ml	NR	NR	NR	100	Focal ablation	NR	mpMRI and biopsy at 12 months	17
Ghai	2021	44	Toronto	mpMRI + MRI-targeted + systematic biopsy	PSA level of 20 ng/mL or less; GG 2 or GG 3	NR	NR	NR	100	Focal ablation	20.4	mpMRI and biopsy at 5 months	24
Yee	2021	20	CUHK	mpMRI + MRI-targeted/ systematic biopsy	stage ≤ T2; PSA ≤ 20 ng/ml; GG < 5	NR	NR	NR	45.5	Focal ablation	18.2	mpMRI and biopsy at 6 months	
Reddy	2022	1379	HEAT	mpMRI + Transrectal/ transperineal, systematic biopsy	Gleason score 6–9, stage cT3b or less	6.1	65	28	81	Focal ablation	NR	mpMRI at 6–12 months; TMB for cause	32
Ehdaie	2022	101	MSKCC-led multicenter	mpMRI + MRI-targeted + systematic biopsy	Men aged 50 years and older with unilateral, organ-confined, intermediate-risk prostate adenocarcinoma (psa ≤ 20 ng/mL; grade group 2 or 3; ≤T2) visible on MRI and confirmed on combined MRI-targeted and systematic biopsy, and with no previous treatment for prostate cancer	0	100	0	100	Focal ablation	NR	mpMRI and biopsy at 6 and 24 months	26
Westhoff	2023	50	Mannheim	mpMRI	Unilateral disease; PSA < 10 ng/ml; GG < 2	70	30	0	46	Focal ablation	18	mpMRI and biopsy at 12 months	42
Duwe	2023	29	Johannes-Gutenberg University	mpMRI + MRI-targeted + systematic biopsy	PSA ≤ 15, stage ≤ cT2, prostate volume ≤ 90 ml	NR	NR	NR	31	Various	NR	mpMRI and biopsy at 12 and 24 months	23
Mala	2023	57	Charité University Medicine Berlin	mpMRI + MRI-targeted + systematic biopsy	PSA ≤ 15, GG ≤ 2	NR	NR	NR	42.1	Various	NR	mpMRI and for-cause biopsy	27.5
Kaufman	2023	91	Zurich	mpMRI + MRI-targeted + systematic saturation biopsy	PSA ≤ 15, GG ≤ 3, stage ≤ cT2, up to 2 lesions	NR	NR	NR	93	Hemi-ablation	24	mpMRI and biopsy at 6, 12, and 36 months	36
Ladjevardi	2024	119	FAAST	mpMRI + MRI-targeted + systematic biopsy	PSA ≤ 20, GG ≤ 3, stage ≤ cT2, single csPCa lesion	NR	NR	NR	87.4	Focal ablation	18.5	mpMRI and biopsy at 12 and 36 months or for-cause	12
Focal IRE													
Murray	2016	25	MSKCC	mpMRI + targeted + systematic 12 core biopsy	Maximum Gleason 3 + 4	72	28	0	28	Various	NR	PSA every 3–6 months. mpMRI at 4–6 weeks post-treatment. 12-core TRUS biopsy at 6 months	10.9
Collectini	2019	30	Charité–Universitätsmedizin Berlin	mpMRI + Fusion or TRUS systematic	PSA ≤ 15; GG ≤ 2; stage ≤ T2c; MRI lesion size ≤ 20 mm	13.3	86.7	0	76.7	Focal ablation	30	mpMRI at 6 and 12 months; target in-bore biopsy (cause)	20

Table 1. continued

First author	Year	Number of participants	Institution	Pre-diagnostic workup	Declared inclusion criteria	NCCN risk group (%)			GG ≥ 2 (%)	Ablation pattern	Anterior tumors (%)	Follow-up protocol	Median follow-up (months)
						Low	Intermediate	High					
Wang	2022	109	Shanghai multicenter	mpMRI + Transperineal cognitive + systematic biopsy	PSA < 20; <T2c; Gleason score of 7 or less	24.8	75.2	0	56.9	Focal ablation	NR	mpMRI at 1 and 6 months; fusion targeted and systematic biopsy at 6 months	
Scheltema	2022	229	St Vincents	mpMRI + MRI-targeted + systematic biopsy	Stage < T2b, max Gleason score 8	7.4	86	6.6	91.7	Focal ablation	NR	mpMRI at 6 months and Transperineal biopsy at 12 months.	60
Gielchinsky	2023	38	Israel	mpMRI + MRI-targeted + TTMB	ISUP ≤ 3	NR	NR	NR	84.2	Focal ablation	NR	PSA, mpMRI at 6 months, then mpMRI + targeted bx + TTMB at 12 months, then yearly mpMRI with for-cause biopsy	NR
Minana	2023	41	CUN Prostate Center, Spain	mpMRI + MRI-targeted + systematic biopsy	MRI concordant biopsy, lesion >5 mm from critical structures	NR	NR	NR	26.7	Focal ablation	41	12 month MRI and targeted biopsy	36
Zhang	2023	106	European Multicenter	mpMRI + TTMB	unilateral organ-confined prostate cancer	NR	NR	NR	52.8	Various	NR	6-month MRI and targeted biopsy	30
Popeneciu	2024	24	Goettingen	mpMRI + MRI-targeted + systematic biopsy	GG ≤ 2, PSA ≤ 20, lesion ≤ 1.5 ml, MRI concordant biopsy	58.3	41.7	0	41.7	Focal ablation	NR	6 month MRI and targeted + systematic biopsy	18.6

NCCN National Comprehensive Cancer Network, *GG* grade group, *TRUS* transrectal ultrasound, *TMB* transperineal mapping biopsy, *NR* not reported, *PSA* prostate-specific antigen, *mpMRI* multiparametric magnetic resonance imaging, *DRE* digital rectal examination, *BCR* biochemical recurrence, *TP* transperineal, *PCa* prostate cancer, *ISUP* International Society of Urological Pathology.

Evolution of treatment patterns over time

Overall, 14/49 (28.6%) of cohorts reported using hemi-ablation; 26/49 (53.1%), focal ablation; 1/49 (2.0%), partial gland ablation; 1/49 (2.0%), sectoral ablation; and, 6/49 (12.2%), various combinations. Over time, there was a greater proportion of cohorts utilizing more focal approaches and less hemi-ablations. In the 2008–2012 time period, 3/4 (75%) of cohorts reported utilizing hemi-ablation for FT; from 2013 to 2016, 4/7 (57.1%); from 2017 to 2020, 6/13 (46.2%); and, from 2021 to 2024 only 1/25 (4.0%).

During our evaluation period, cryotherapy was predominant in the earlier years, with an increasing proportion of later-reported cohorts comprising HIFU and IRE. In the 2008–2012 time period, 4/4 (100%) of cohorts reported using cryotherapy; from 2013 to 2016, 4/7 (57.1%) cryotherapy, 2/7 (28.6%) HIFU, and 1/7 (14.3%) IRE; from 2017 to 2020, 5/13 (38.4%) cryotherapy, 7/13 (53.8%) HIFU, and 1/13 (7.7%) IRE; and, from 2021 to 2024, 8/25 (32.0%) cryotherapy, 11/25 (44.0%) HIFU, and 6/25 (24.0%) IRE.

Oncological outcomes

Median follow-up times were reported in 45/49 (91.8%) cohorts, with a median of 27.8 months and a mean of 28.4 months (range 6.0–63.0 months). Overall survival was reported by 22/49 (44.9%) cohorts with a pooled OS of 98.0% (95% CI 96.9–98.7, $I^2 = 33\%$, $p = 0.07$) (Fig. 2A). Cancer-specific survival was reported by 23/49 (46.9%) cohorts with a pooled CSS of 99.3% (95% CI 98.8–99.6, $I^2 = 0\%$, $p = 0.99$) (Fig. 2B). Metastasis-free survival was reported by 23/49 (46.9%) cohorts with a pooled MFS of 98.5% (95% CI $I^2 = 0\%$, $p = 0.46$) (Fig. 2C). There were no differences observed between different modalities for OS, MFS or CSS.

Biochemical progression was reported in 15/49 (30.6%) cohorts. Of these, 12/15 (80.0%) utilized the Phoenix criteria, 2/15 (13.3%) used the ASTRO criteria, and 1/15 (6.7%) used a nadir + 0.5 definition. The average biochemical progression rate per year was 9.3% (95% CI 7.0–12.3, $I^2 = 63\%$, $p < 0.01$) (Fig. 2D). Again, there were no differences observed between different modalities.

Repeat biopsy was mandated within 24 months in 36/49 (73.5%) cohorts and for cause in the remaining 13/49 (26.5%) cohorts. Among cohorts with mandated repeat biopsy in their follow-up protocol, the mean actual repeat biopsy rate was 84.5% (±18.8%), while for cohorts without mandated repeat biopsy, the biopsy rate was 28.7% (±16.0%). Among the 36 mandated repeat biopsy cohorts, 26/36 (72.2%) reported a pooled overall, any cancer-positive biopsy rate of 44.6% (95% CI 38.7–50.6%, $I^2 = 86\%$, $p < 0.01$); 29/36 (80.6%) reported a pooled overall, clinically significant cancer positive biopsy rate of 22.2% (95% CI 17.5–27.7%, $I^2 = 89\%$, $p < 0.01$); 25/36 (69.4%) reported a pooled infield, any cancer positive biopsy rate of 21.4% (16.9–26.8%, $I^2 = 79\%$, $p < 0.01$); 24/36 (66.7%) reported a pooled infield, clinically significant cancer positive biopsy rate of 8.9% (95% CI 6.2–12.5%, $I^2 = 70\%$, $p < 0.01$); 25/36 (69.4%) reported a pooled outfield, any cancer positive biopsy rate of 26.5% (95% CI 21.6–32.0%, $I^2 = 77\%$, $p < 0.01$); and, 22/36 (61.1%) reported a pooled outfield, clinically significant cancer positive biopsy rate of 12.3% (95% CI 8.7–17.1%, $I^2 = 77\%$, $p < 0.01$). These findings are summarized in Fig. 3A, and detailed in Supplementary Figs. 1–24. We did not observe a clinically significant difference in positive repeat biopsy rates between the focal cryotherapy, HIFU, or IRE cohorts. Notably, there was high heterogeneity across the cohorts, and as such, a formal comparison of different modalities was not performed.

The rate of requiring a second FT was reported in 31/49 (63.3%) cohorts with a pooled incidence of 5.0% (95% CI 3.5–7.0%, $I^2 = 76\%$, $p < 0.01$) (Fig. 3B). The rate of salvage radical treatment with prostatectomy or radiation therapy was reported in 37/49 (75.5%) cohorts with a pooled incidence of 10.5% (95% CI 8.1–13.4%, $I^2 = 81\%$, $p < 0.01$) (Fig. 3C). The rate of salvage whole gland ablation was reported in 27/49 (55.1%) cohorts with a pooled incidence of 2.1% (95% CI 1.3–3.4%, $I2 = 54\%$, $p < 0.01$)

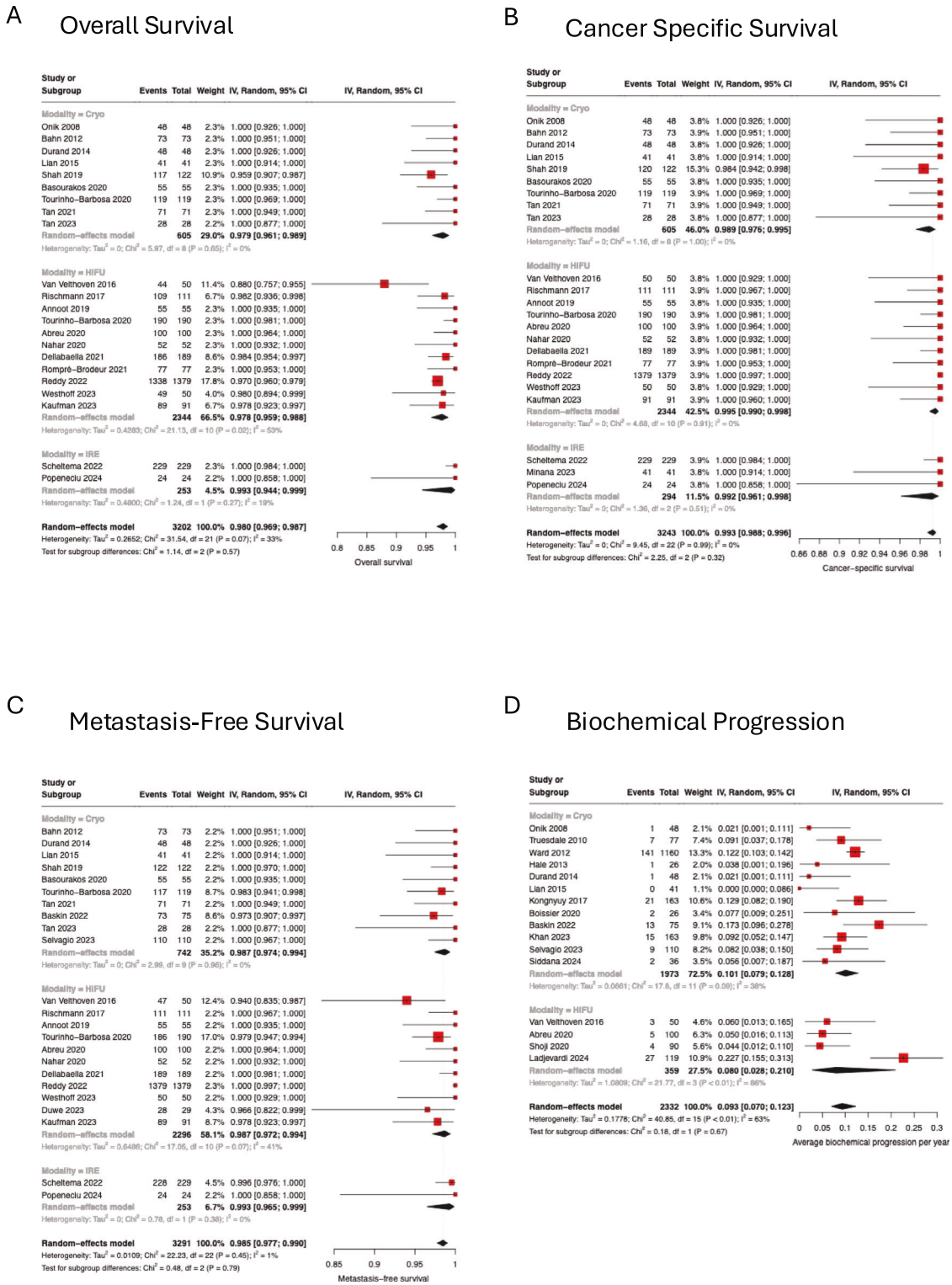
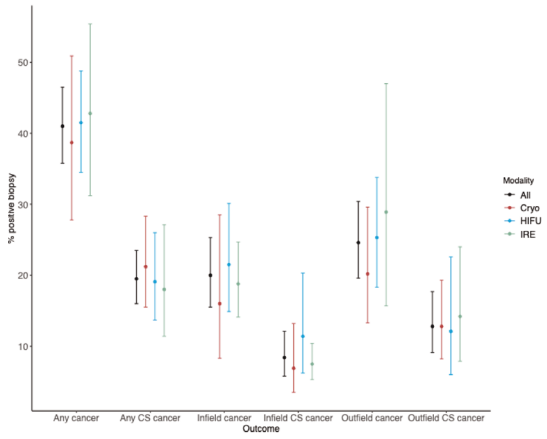


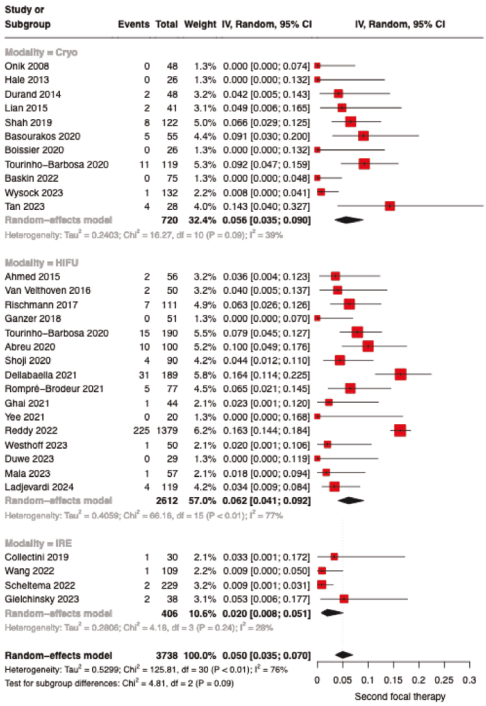
Fig. 2 Oncological outcomes after focal therapy. A Pooled overall survival; **B** pooled cancer-specific survival; **C** pooled metastasis-free survival, **D** pooled yearly biochemical progression rate.

(Supplementary Fig. 25). The use of salvage hormonal therapy was reported in 23/49 (46.9%) cohorts, with a pooled incidence of 3.4% (95% CI 2.5–4.6%, $I^2 = 20\%$, $p = 0.19$) (Supplementary Fig. 26). Transition to watchful waiting was reported in 22/49 (44.9%) cohorts, with a pooled incidence of 3.0% (95% CI 1.7–5.3%, $I^2 = 66\%$, $p < 0.01$) (supplementary Fig. 27). Due to varying definitions of treatment failure, we adopted a composite outcome of radical or whole gland treatment, use of hormonal therapy or a transition to watchful waiting, not including a second FT. Using this definition, 19/49 (38.8%) cohorts had a pooled failure rate of 14.1% (95% CI 10.2–19.2%, $I^2 = 77\%$, $p < 0.01$) (Fig. 3D).

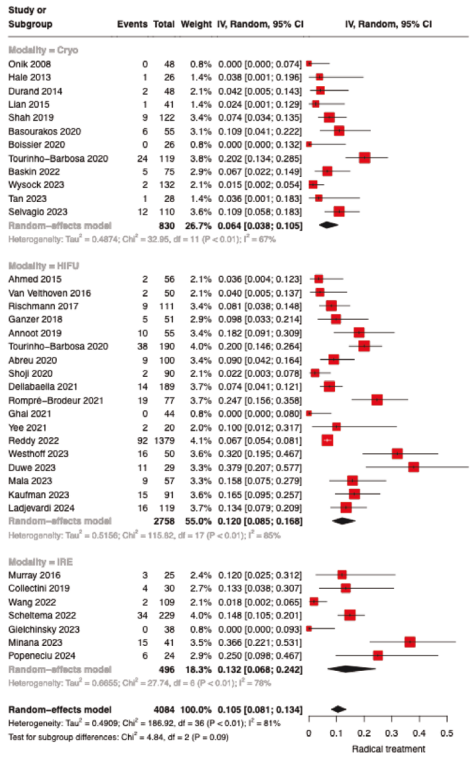
A Mandatory Re-biopsy Outcomes



B Second Focal Therapy



C Need for Radical Treatment



D Treatment Failure Composite Outcome

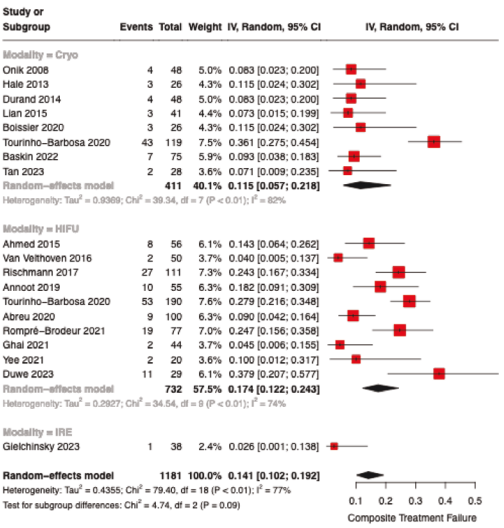


Fig. 3 Short- to intermediate-term oncological outcomes after focal therapy. A Error bar plot of the rate of positive biopsy in any location, infield or outfield, subdivided into any cancer versus clinically significant (CS) cancer, stratified by modality; **B** pooled rate of second focal therapy (FT); **C** pooled rate of salvage radical therapy (both radical prostatectomy and radiation therapy); **D** pooled rate of composite treatment failure (salvage whole gland ablation, salvage radical therapy, salvage hormonal therapy, transition to watchful waiting).

Sexual and urinary function

Of 35/49 (71.4%) cohorts reporting sexual function outcomes, 23/35 (65.7%) used patient-reported outcome measures (17 utilized IIEF/SHIM; 5, EPIC; 1, EORTC QLQC-28), and 12/35 (34.3%) used physician-reported measures (10 reported the ability to penetrate; 2, the need for medications/assistance for sexual intercourse). We summarized the impact on sexual function was categorized as low, moderate, or severe.

Overall, 16/35 (45.7%) cohorts reported a low impact of FT on sexual function, 17/35 (48.6%) reported a moderate impact, and 2/35 (5.7%) a severe impact (Fig. 4A). No significant differences in sexual impact were noted between the different modalities.

Of 34/49 (69.4%) cohorts reporting urinary function outcomes, 21/34 (61.8%) used patient-reported outcome measures (12 reported using the AUA symptom index; 7, EPIC; 1, the ICIQ-UI, and 1, the EORTC QLQC-28), while 13/34 (38.2%) reported pad use only. The impact on urinary function was again categorized as low, moderate, or severe.

Overall, 33/34 (97.1%) cohorts reported a low impact of FT on urinary function, 1/34 (2.9%) cohort reported a moderate impact, and none of the cohorts reported a severe impact on urinary function (Fig. 4B). No significant difference on urinary function impact was noted between different FT modalities.

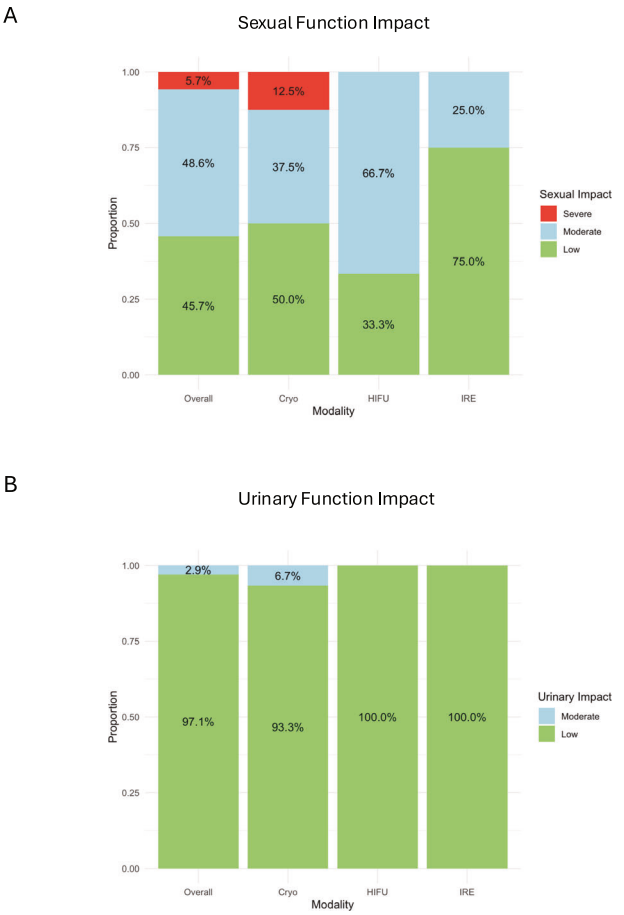


Fig. 4 Functional outcomes after focal therapy. A Sexual function impact: low (<10%), medium (10–30%), and high (>30%), stratified by modality; **B** Urinary function impact: low (<10%), medium (10–30%) and high (>30%), stratified by modality.

DISCUSSION

Where are the randomized controlled trials (RCTs) for FT?

Randomized evidence for the oncological efficacy of FT compared to standard radical treatments remains lacking. One reason being that experience in recruitment for RCTs has not been encouraging: while the Partial ablation versus prostatectomy (PART) trial showed initial feasibility in a 2018 report, the current recruitment at the time of writing shows only 42 of the targeted 800 patients recruited [59, 60]. Similarly, IP4-Chronos concluded that it is not feasible to do a randomized study in FT because of strong patient preferences when it comes to prostate cancer treatment [61]. Perhaps with these experiences in consideration, rather than evaluating oncological outcomes as the primary endpoint, the latest proposed randomized trial comparing FT to standard radical treatment, the Prostate Cancer IRE study (PRIS), will evaluate quality of life as the primary endpoint as this requires a smaller sample size [62].

What can we learn from current observational data?

Here, we evaluated 49 unique cohorts of men undergoing FT for prostate cancer. The studies were highly heterogeneous in terms of patient inclusion, oncological/functional outcomes, and follow-up surveillance measures. For instance, OS, CSS, and MFS were reported only in half the cohorts, though the heterogeneity was low. The pooled OS was 98.0%, CSS 99.3%, and MFS 98.5%. Biochemical progression was generally reported in older cohorts, but heterogeneity was high likely due to different follow-up times and progression criteria. A pooled yearly biochemical progression rate of 9.3% was reported. This was the main trigger for for-cause biopsy for which the pooled rate was 38.7%. Among the 73.5% of studies with mandated biopsies within 24 months, the average biopsy compliance rate was 84.5% and csPCa detection rate was 22.2% overall, 8.9% infield, and 12.3% outfield. Again, there was significant heterogeneity in these results, contributed by the fact that many studies omitted the location of recurrences (infield/outfield) or the grade of the recurrences (GG1 vs ≥2). The pooled rate of repeat with FT was 5.0%, radical treatment 10.5%, and the the pooled yearly composite treatment failure rate, which comprises the use of radical treatment, whole-gland ablation, hormonal therapy, or transition to watchful waiting was 14.1% per year. This appears to be a fairly high rate of failure, but it is notable that these tended to be reported in studies mandating repeat biopsy with a fairly short follow-up time, so they may represent failures detected early on. The longitudinal effect of FT over time remains to be seen with regards to treatment failure as an outcome.

The outcomes of FT are highly dependent on patient selection. The more aggressive tumors included, the higher the risk of recurrence post-FT. We noted an evolving trend including a greater proportion of csPCa in the patient cohorts receiving treatment. This is in accordance with findings from expert consensus over time in which recommendations for patient selection for FT have also evolved. In 2010 and 2012 consensuses, de la Rosette et al and Ahmed et al respectively found that experts recommended eradication of all cancer as the goal of FT [63, 64]. In 2015 and 2017 consensuses, Donaldson et al and Tay et al respectively found that experts recommended eradication of csPCa [65, 66]. In this particular analysis, we did not have enough data to analyze the impact of the proportion of csPCa included with regards to the oncological outcomes. Another important question is that of untreated GG1 cancer whilst the csPCa lesion is being treated. In the 2015 and 2017 consensuses, experts agreed that GG1 cancer could be left untreated during FT to a csPCa lesion [65, 66]. We found that there was very limited reporting on the incidence and fate of untreated low-grade cancer foci in the various cohorts.

We also observed that ablation patterns changed over time with more focal/targeted ablations being done compared to hemi-ablations. This trend follows that of the rapid adoption of imaging and targeted biopsy over the last decade. With the

ability to better identify and localize csPCa, there is greater confidence in treating just the area containing the aggressive tumor for true FT rather than hemi-ablation [67]. In this regard, Zhang et al. demonstrated in a randomized clinical trial that extending ablation to the entire hemi-gland added no advantage to focal ablation using IRE [58]. However, given the small but significant rates of cancer persistence in or around the treatment zone, there is still a necessity to ensure adequate margins around the lesion, and an adequate delivery of ablative energy, regardless of FT modality within the area to be treated itself [68, 69].

We did not observe significant differences between the three established FT modalities in oncological or functional outcome. This could reflect increased familiarity with each modality by the treating physicians over time leading to technical measures to improve outcome such as double freeze-thaw cycles for cryotherapy and double-tap for HIFU. Sivaraman et al proposed that anterior tumors are better treated using cryotherapy whereas posterior tumors are better treated with HIFU, in a concept termed as the a la carte model [70]. Nevertheless, this strategy has never been validated. We observed that the vast majority of cohorts reported only using a single FT modality, with the exception of the UK group which reported an 80% of their focal cryotherapy series comprising of anterior tumors, and the Montsouris group where the a la carte model originated [20, 23]. In the few (12/49, 24.5%) cohorts reporting on tumor location, the proportion of anterior tumors in the cryotherapy cohorts were not observably different than that of the HIFU cohorts. It may be the case that even in academic centers, expertise in a single FT modality is more feasible than having multiple competing modalities that may take more financial resources and time to master.

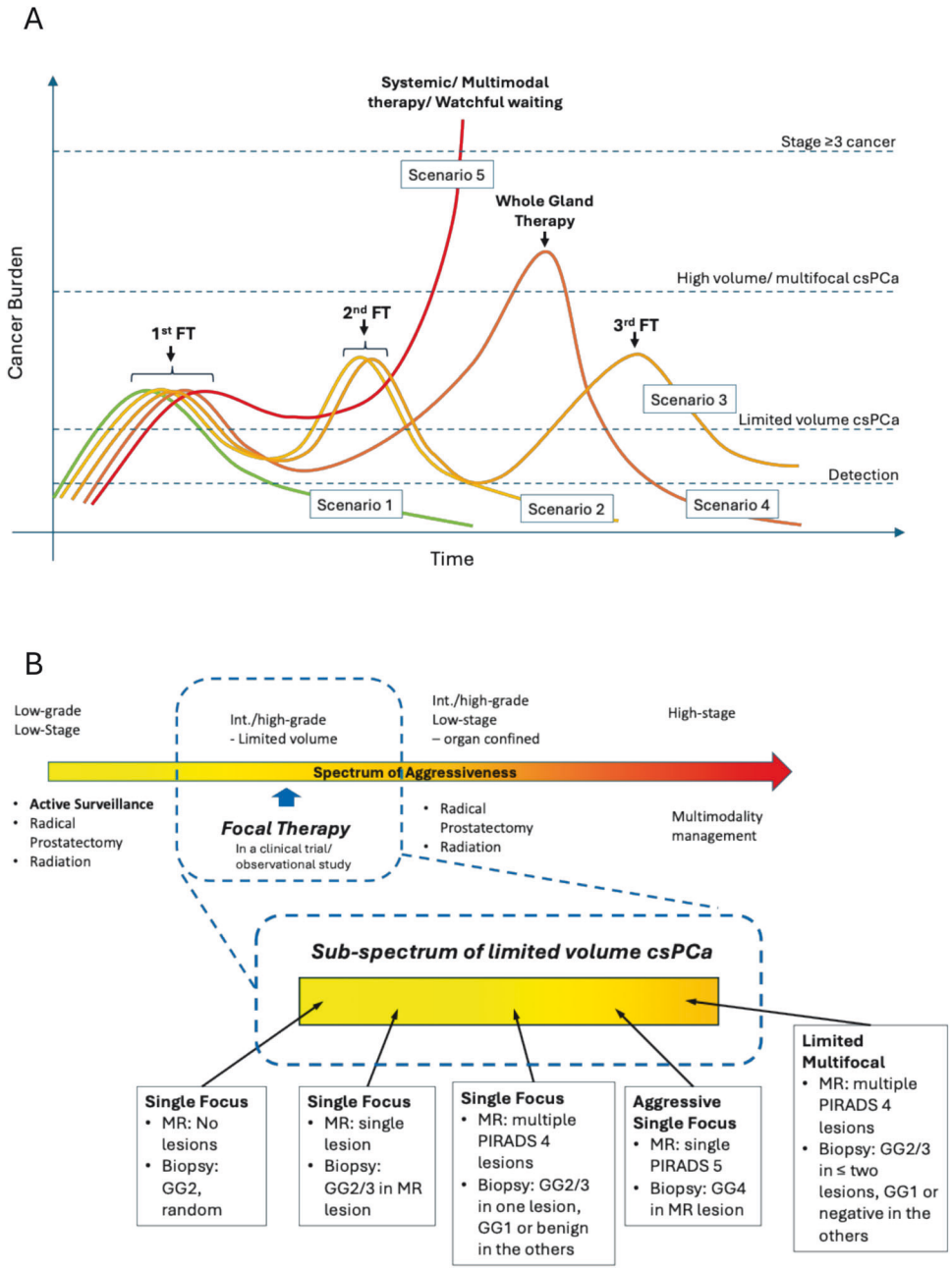


Fig. 5 Failure scenarios and pre-focal therapy cancer patterns. A Potential pathways of prostate cancer progression after focal therapy (FT); **B** pre-FT cancer patterns or "phenotypes" that may impact on interpretation of post-FT imaging/biopsy/progression outcomes.

Limitations of this review

This systematic review must be interpreted with several limitations in mind. First, we included only single-arm cohorts reporting cryotherapy, HIFU, and IRE FT. We did not include outcomes of newer modalities which have been evaluated in randomized or non-randomized comparative studies. Second, the heterogeneity among the included studies was high for aspects ranging from patient inclusion criteria to outcomes measures and follow-up protocol. This limits the generalization of our findings. Third, the follow-up time after FT remains short. The overall median follow-up time of the included cohorts was 25.8 months (range 6–63). This limits evaluation of OS, CSS, and MFS. Biopsy outcomes can be a surrogate measure but are by no means definitive. Fourth, we evaluated only the specific domains of sexual and urinary function. These were the most reported functional domains and it would not be possible to meaningfully assess other functions.

Where does this leave us with focal therapy in 2024 and how do we proceed from here?

Based on our findings, it is clear that significant work remains to be done to define the role of FT in the treatment of prostate cancer. Major guidelines still recommend that FT, even with established modalities, be performed at least within a prospective registry [1]. Until the field is able to provide a clear patient-selection criteria and demonstrate definitive long-term oncological outcomes, these recommendations are likely to stand.

Overall, cancer-specific and metastasis-free survival remain the ideal standards for which FT can be compared to standard radical therapy in an RCT. However, even with sufficient dedication to achieve a long enough follow-up, our experience with RCTs suggest that the cross-over rate among treatments will be high due to patient preference, thus impacting intention to treat analysis. Other proposed outcomes such as various determinations of local, biochemical, or treatment progression (repeat or salvage) would simply be incomparable between standard radical therapy and FT (Fig. 5A). When well recorded, however, they could be suitable surrogate oncological outcomes in prospective FT cohorts.

Is biopsy still necessary after FT? After all, breast surgeons do not do breast biopsies after lumpectomy, and we do not routinely biopsy the kidney after ablation or partial nephrectomy for kidney cancer [71]. An imaging-only approach may be possible in a high-volume FT center with expert radiologists, but many community radiologists may not be experienced in reading post-FT MRIs [72, 73]. Lebastchi et al reported that majority of experts favored repeat biopsy 6–12 months after FT [74]. An early repeat biopsy also serves as a quality indicator of the ablation, and allows for early repeat ablation, or fallback to radical treatment, to ensure adequate oncological care.

What is certainly necessary, is detailed standardized reporting of pre- and post-FT imaging and biopsy. In this systematic review, of cohorts mandating repeat post-FT biopsy, only 27.8% reported complete outcomes (infield, outfield, cs- and non-csPCa). We would argue that the post-FT imaging and biopsy outcomes can only be well understood in the context of the pre-FT cancer pattern. For example, a patient with a unifocal PIRADS 4 lesion, with csPCa in corroborating targeted cores and a negative systematic biopsy would likely do well with FT, while another patient with multiple PIRADS 4 lesions, in which one harbors GG2 cancer treated with FT, and the others have low volume GG1 cancer on surveillance might be at higher risk of needing secondary FT or whole-gland treatment. The pre-FT cancer pattern could possibly be classified into several "phenotypes" which represent different scenarios (Fig. 5B). Identifying and reporting these disparate patterns could help to put the post-FT imaging/biopsy outcomes in context and thus better define oncological outcomes after FT.

As advanced imaging techniques, like PSMA-PET, multiparametric ultrasound, and genomic biomarkers continue to evolve, the necessity for standardized, detailed reporting grows. This ensures accurate identification and definition of the aggressive cancer for treatment. Future work should thus focus on standardized, accurate, and detailed reporting of the patients treated, including both treated and untreated lesions, their imaging and pathological characteristics, treatment zones, follow-up protocols, and detailed failure data.

While other excellent systematic reviews on FT have been done in the past, they have been of a broad scope focused on all available modalities [8, 75]. This systematic review done on established FT modalities is a more recent update (25 FT cohorts have been reported/updated in the last 4 years alone), incorporates what long-term data is available, provides an overview of where we are now with more "mature" oncological and functional outcomes, providing an overview of the gaps in reporting that we need in order to make the next systematic review a definitive one.

CONCLUSION

There is an increased uptake of focal therapy over time with a greater proportion of patients with csPCa rather than low-grade cancer undergoing treatment. FT with cryotherapy, HIFU, or IRE is associated with good short-intermediate term oncological and functional outcomes. However, outcome reporting is heterogeneous and often incomplete. Longer-term follow-up and standardized reporting are required to better define and report FT outcomes.

DATA AVAILABILITY

Data are available for bona fide researchers who request it from the authors.

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Study conception and design: KJT. Data acquisition: KJT, KYF. Data analysis and interpretation: All authors. Statistical analyses: KYF, KJT. Obtained funding: KJT. Administrative, technical, or material support: KJT, KYF. Study supervision: PL. Drafting of manuscript: KJT, KYF. Approval of final manuscript: All authors

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