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Salvage local treatment for recurrent prostate cancer after focal therapy: A systematic review and meta-analysis

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Abstract

Objectives: To evaluate the role of salvage local treatment in managing recurrent PCa following FT, focusing on oncological and functional outcomes.

Methods: A systematic review and meta-analysis were performed following the PRISMA framework. A comprehensive literature search using the PubMed/MEDLINE and EMBASE databases was performed until July 2023. Eligible studies included patients with clinically localised PCa initially treated with FT, who experienced relapse during surveillance and subsequently underwent salvage radical prostatectomy (sRP), salvage external beam radiation therapy (sEBRT) or salvage focal therapy (sFT). The primary endpoint was the biochemical recurrence rate post-salvage treatment. The secondary endpoints were functional outcomes, including urinary incontinence and erectile dysfunction rates.

Results: In 26 retrospective studies including 990 patients, the overall pooled biochemical recurrence rate postsalvage treatment was 26%. The subgroup analysis revealed a biochemical recurrence rate of 20%, 22%, and 42% after sRP, sEBRT, and sFT, respectively. The overall pooled rate of urinary incontinence was 20%. Salvage FT had the lowest prevalence of urinary incontinence, followed by sRP and sEBRT. The overall pooled rate of erectile dysfunction was 43%. Salvage RP had the highest prevalence of erectile dysfunction, followed by sFT and sEBRT. Substantial heterogeneity was observed among the studies, primarily due to different sample sizes. Meta-regression analysis revealed no to low contributions of salvage treatment modalities, extent of ablation, age, prostatic specific antigen level before salvage treatment, proportion of patients with Gleason score ≥7 at recurrence, and time between the primary and salvage therapies to heterogeneity.

Conclusion: Salvage local treatment for recurrent PCa after FT is feasible, and it provides acceptable oncological and functional outcomes. Among all treatment modalities, sRP and sEBRT appeared to have the lowest biochemical recurrence rates, whereas sFT was associated with improved functional outcomes.

Keywords: Focal therapy; Prostate cancer; Prostatectomy; Radiotherapy; Salvage therapy

Abbreviations: CI, confidence intervals; FT, Focal therapy; HIFU, high intensity focused ultrasound; I2, Heterogeneity; PCa, prostate cancer; PSA, prostatic specific antigen; sEBRT, salvage external beam radiation therapy; sRP, salvage radical prostatectomy; $\tau 2$, variance

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1. Introduction

Focal therapy (FT) has emerged as a novel approach for treating patients with localized prostate cancer (PCa). With the adoption of screening tests in daily practice, men are now diagnosed with smaller tumors at earlier stages, raising concerns about potential overtreatment [1]. Therefore, new technologies that attempt to ablate only the region of the prostate containing the tumor have started to gain popularity [2,3]. The aim of these organ-sparing modalities is to achieve oncological benefits similar to those of well-established radical therapies while optimizing Genito-urinary function [4,5].

Nevertheless, while short to medium-term results after FT show acceptable oncological outcomes and low toxicity [6], a proportion of men still experience disease recurrence, with up to 33% of patients requiring additional local treatment [7]. Currently, therapeutic strategies with curative intent for recurrent PCa after FT include salvage radical prostatectomy (sRP), salvage external beam radiation therapy (sEBRT), and repeat FT using the same or a different energy source than the primary setting [8].

Therefore, before considering FT as a primary treatment option for PCa, it is imperative to understand the oncological outcomes and toxicity of secondary treatments if FT fails. Currently, studies and consensus regarding the optimal management of these patients are lacking. Therefore, in this study, we aimed to perform a systematic review and meta-analysis to elucidate the role of salvage local treatment following FT, focusing on oncological and functional outcomes.

2. Patients and methods

2.1. Literature search

A literature review was conducted following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. A comprehensive literature search using the PubMed/MEDLINE and EMBASE databases was performed until July 2023. The review protocol was submitted for registration to the PROSPERO platform (CRD42021258369).

2.2. Selection criteria

The PICOS (patient, intervention, comparison, outcome, and study type) model was used to frame and answer the questions. The patient population (P) comprised men with clinically localized PCa initially treated with focal therapy who experienced relapse during surveillance. The intervention (I) involved subsequent treatment with salvage modalities, which were compared (C) to salvage radical prostatectomy (sRP), salvage external beam radiation therapy (sEBRT), and salvage focal therapy (sFT). The primary outcomes (O) focused on assessing biochemical recurrence, urinary incontinence, and erectile dysfunction rates following salvage treatment. The study types (S) considered for inclusion included randomized controlled trials, cohort studies, case-control, and case-series studies.

The titles and abstracts were screened for inclusion in the initial analysis. Clinical studies published in English with no date restriction were identified and screened for duplicates. Reference lists of the retrieved reports were manually searched and cross-referenced to ensure completeness. Meeting abstracts, reviews, editorials, and commentaries were excluded from the analysis. Inclusion was contingent upon the evaluation of at least one of the main outcomes (biochemical recurrence rate, urinary continence rate, and/or erectile function) in the included studies.

2.3. Data extraction

Data extraction was performed by two independent authors (LT and PC) using an Excel® spreadsheet developed for this purpose. Disagreements were resolved via discussion and consensus among the researchers.

2.4. Outcomes

The primary outcome was the biochemical recurrence rate. A summary of the definitions of biochemical recurrence used in each study is presented in Table S1. Secondary endpoints were functional outcomes, including urinary incontinence and erectile dysfunction rates. Urinary incontinence was defined as the use of $\geq$ 1 pad/day in seven studies [9−15] and $\geq$ 2 pads/day in five studies [16−20]. Four studies on sEBRT [21−24] graded stress urinary incontinence using the Ingelman−Sundberg score [25]. Ten studies, including eight focusing on sEBRT [26−33] and 2 focusing on sFT [34,35], did not evaluate or report continence definitions. Erectile dysfunction was defined as the inability to engage in spontaneous sexual intercourse or the use of phosphodiesterase-5 inhibitors [11,12,14−16,18,19]. Two studies [10,21] evaluated potency using the International Index of Erectile Function [36]. The remaining 17 studies, mainly focusing on sEBRT, did not evaluate or report potency definitions [9,13,17,20,22−24,26−35].

All outcomes were evaluated in the overall cohort and subgroups based on salvage treatment modalities (sRP, sEBRT, and sFT). We performed the same analyses after reassessing the initial studies and checking the extent of the initial focal therapy. Studies were then divided in the following 2 groups: whole-gland or partial-gland ablation (including hemi-ablation, hemi-ablation with "dogleg" approach and wide local ablation). The latter group was called "true foca" for further analyses.

2.5. Evaluation of quality and risk of bias

Quality assessment of the included studies was performed using the Cochrane Risk of Bias tool ROBINS-I for retrospective and nonrandomised prospective studies [37] (Supplementary Figure 1).

2.6. Statistical analyses

To minimise substantial heterogeneity between studies when performing the meta-analysis, we excluded studies including less than 10 patients [24,30−33].

A meta-analysis of single proportions was performed using the inverse variance method for pooling and logit transformation to present overall proportion with 95% confidence intervals (CIs) and standard errors for each effect size. Owing to the expected heterogeneity across studies, a random-effects model was applied for a conservative approach to proportion estimates. Additionally, a common-effects model was applied using a conservative calculation approach and verifying possible differences in the effect estimates. The Hartung−Knapp method [38] was used to adjust test statistics and CIs, the Clopper−Pearson estimator was adopted to calculate 95% CIs for individual studies [39], and the restricted maximum-likelihood estimator was used for the between-study variance ($\tau 2$) calculation [40]. Studies with more than 1 arm were included with repeated control group estimation adjustments to prevent inflated treatment effects [41]. Pooled prevalence estimates were expressed as mean estimates with 95% CIs [42].

Heterogeneity was assessed using the I2 statistic [43]; estimates between 50% and 75% indicated moderate heterogeneity and estimates greater than 75% indicated high heterogeneity. Publication bias was assessed using funnel plots, and funnel plot asymmetry was assessed using the Egger's test [44]. The Baujat and Galbraith plots were used to detect the sources of heterogeneity [45,46].

Subgroup analyses were performed considering the surgical approach as true focal, type of salvage therapy, and salvage type for all outcomes. Subgroup differences were tested through $\chi 2$ test. Results were presented in forest plots with partial results for each subgroup as well as the overall results of the interventions.

Meta-regression was performed using a mixed-effects model and the restricted maximum-likelihood estimator for $\tau 2$ [47]. Moderators were predefined encompassing true focal therapy, type of salvage therapy, salvage type for all outcomes, age, prostatic specific antigen (PSA) level at salvage, time between intervention and salvage, and rates of events for urinary incontinence, erectile dysfunction, Gleason scores 6, 7 and >7, and surgical complications. Results of the meta-regression analysis are presented as regression coefficients with 95% CIs.

Statistical analyses were performed using RStudio version 1.1.383 (The R Foundation for Statistical Computing, Vienna, Austria), using the meta and metafor packages [46,48].

3. Results

3.1. Study selection

A total of 586 articles were searched. After screening for eligibility criteria, 26 studies involving 990 patients were included in the final analysis [9−24,26−35]. Figure 1 shows the PRISMA flow diagram.

3.2. Study characteristics and quality assessment

Only retrospective studies, including 9 sRP studies [9−13,16−19], 13 sEBRT studies [12,21−24,26−33], and 5 sFT studies [14,15,20,34,35] were assessed. One study analyzed both sRP and sEBRT [12]. In the subgroup analysis, 6 studies were considered as "true focal" [11,13,16,17,20,23]. A complete summary of the findings from each study is presented in Table 1. The perioperative results of the sRP are shown in Table 2.

Figure S1 shows details of the quality assessment of the studies. The most common reason for the risk of bias was confounding factors, followed by participant selection.

3.3. Meta-analyses of biochemical recurrence rate

The overall pooled rate of biochemical recurrence after salvage treatment was 26% (95% CI, 23%−30%), with substantial between-study heterogeneity ($I^2 = 71\%$) (Fig 2). The subgroup analysis based on salvage treatment modality revealed a biochemical recurrence rate of 22% after sEBRT (95% CI, 18%−26%; $I^2 = 54\%$), 20% after sRP (95% CI, 16%−25%; $I^2 = 53\%$), and 42% after a second sFT (95% CI, 35%−50%; $I^2 = 20\%$). When considering only the studies in which the primary therapy was "true focal," the biochemical recurrence rate after salvage treatment was 26% (95% CI, 20%−33%; $I^2 = 70\%$) (Fig S2).

Funnel plot asymmetry was observed when the Egger test was applied, indicating a publication bias (intercept = −0.3252, t = −2.23, $P = 0.0378$) (Fig S3 A and B). Meta-regression analysis considering salvage treatment modalities, extent of ablation, and age revealed no or low contribution to the heterogeneity. PSA level before salvage, proportion of patients with Gleason score ≥7 at recurrence, and time between the primary and salvage therapies could not be evaluated because of missing data.

3.4. Meta-analyses of urinary incontinence rate

The overall pooled rate of urinary incontinence after salvage treatment was 20% (95% CI, 18%−24%) with substantial between-study heterogeneity ($I^2 = 68\%$) (Fig 3). The subgroup analysis based on salvage treatment modality revealed a urinary incontinence rate of 25% after sEBRT (95% CI, 20%−30%; $I^2 = 65\%$), 20% after sRP (95% CI, 16%−25%; $I^2 = 57\%$), and 8% after the second sFT (95% CI, 5%−14%; $I^2 = 60\%$). When considering only the studies in which the primary therapy was "true focal," the urinary incontinence rate after salvage treatment was 21% (95% CI, 16%−28%; $I^2 = 46\%$) (Fig S4).

Funnel plot asymmetry was observed when the Egger test was applied, indicating a publication bias (intercept = −2.6292, t = −4.39, $P = 0.0004$) (Fig S3 C and D).

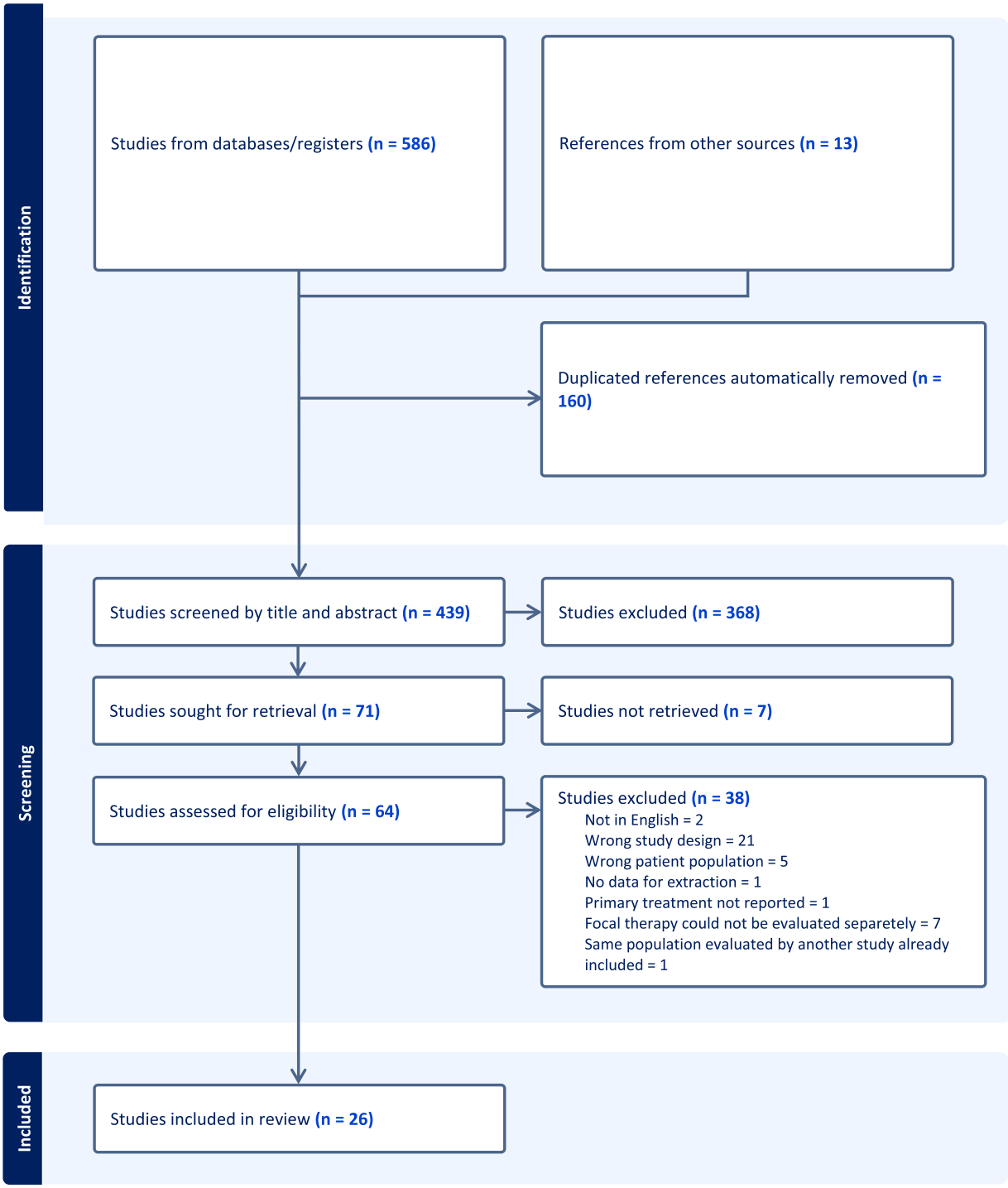

Fig. 1. PRISMA flow diagram.

Meta-regression analysis considering salvage treatment modalities, extent of ablation, age, PSA level before salvage, proportion of patients with Gleason score ≥7 at recurrence, and time between the primary and salvage therapies revealed no or low contribution to heterogeneity. The biochemical recurrence rate after salvage treatment contributed substantially to heterogeneity ($R^2 = 22.07\%$, $P = 0.0230$).

3.5. Meta-analyses of erectile dysfunction rate

The overall pooled rate of erectile dysfunction after salvage treatment was 43% (95% CI, 38%–48%), with considerable between-study heterogeneity ($I^2 = 92\%$) (Fig 4). The subgroup analysis based on salvage treatment modality revealed a erectile dysfunction rate of 26% after sEBRT

Table 1
Selected studies and salvage treatment characteristics, oncologic and functional outcomes

Study	Year	Pts	Age	pTreat	sTreat	sPSA	%sG6	%sG7	%sG>7	sStart	sFollow-up	%BCR	%Incon1	%Incon2	%ED1	%ED2
Burton [26]	2000	49	67	Cryotherapy	EBRT	2.4	N/A	N/A	N/A	N/A	24	38.77	N/A	0	N/A	N/A
Mc Donough [31]	2001	6	71	Cryotherapy	EBRT	2.3	66.6	0	16.6	36	34	33.3	N/A	N/A	N/A	N/A
Blana [34]	2006	49	68.2	HIFU	HIFU	N/A	N/A	N/A	N/A	7	13	N/A	6.1	12.2	38.8	55.1
Pasticier [23]	2008	45	67	HIFU	EBRT	2.8	N/A	N/A	N/A	12	46	25	13.3	17.7	N/A	N/A
Riviere [21]	2010	100	71	HIFU	EBRT	2.1	N/A	N/A	N/A	10	37.2	15	28	32	N/A	N/A
Leonardo [9]	2012	13	61.3	HIFU	sRP	3.31	0	84.6	15.4	N/A	14	7.6	0	30.7	38.4	100
Ripert [24]	2012	6	68.8	HIFU	EBRT	6.08	N/A	N/A	N/A	11.7	36.5	16.6	0	16.6	N/A	N/A
Munoz [22]	2013	24	69	HIFU	EBRT	4.21	N/A	N/A	N/A	26.3	50	25	8.33	16.66	N/A	N/A
Choi [30]	2013	9	65	Cryotherapy	EBRT	4.3	N/A	N/A	N/A	20.5	31	22	N/A	N/A	N/A	N/A
Quarrier [32]	2013	4	70.7	Cryotherapy	EBRT	11.55	0	50	50	44.25	4.25	0	0	0	25	50
Alongi [27]	2014	15	63	HIFU	EBRT	4.59	N/A	N/A	N/A	30	12	20	N/A	0	N/A	N/A
Berge [14]	2014	130	64.6	HIFU	HIFU	8.3	34.6	62.3	4.6	N/A	27	44.8	1.2	2.7	40	44
Lebdai [10]	2015	19	64	Vascular targeted therapy	sRP	3.65	47.36	47.36	0	17	10	15.78	N/A	31.5	42.1	95
Chang [15]	2015	12	77.5	Cryotherapy	Cryotherapy	2.5	N/A	N/A	N/A	7.8	33	41.6	N/A	8.3	N/A	16.6
Holtzman [35]	2016	21	68	HIFU, Cryotherapy	Proton therapy	7	19	48	33	27	37	23.8	N/A	N/A	N/A	N/A
Nunes-Silva [13]	2017	22	63.3	HIFU, Cryotherapy, Brachytherapy, Laser ablation, Vascular targeted therapy	sRP	9.24	45.5	50	4.5	24	7	31.8	N/A	46.2	N/A	N/A
Hopper [33]	2018	8	74	Cryotherapy	EBRT	8.4	12.5	50	37.5	68	55	25	N/A	N/A	N/A	N/A
Pierrard [19]	2019	42	63	Vascular targeted therapy	sRP	5.9	N/A	N/A	N/A	17	23	9	N/A	12	N/A	21.4
Onol [16]	2020	32	66.1	HIFU, Cryotherapy	sRP	5.77	18.8	62.5	18.8	61.1	29.2	31.2	N/A	15.6	43.7	84.3
Thompson [11]	2020	45	63	HIFU	sRP	6	6.7	82.2	11.1	30	17	10.5	4.5	34.5	27	100
Herrera-Caceres [17]	2020	34	61.2	HIFU, Cryotherapy, Brachytherapy, Laser ablation	sRP	5.38	20.6	67.7	11.7	N/A	52	20.6	N/A	8.8	N/A	47.0
Rigo [28]	2020	24	68	HIFU	EBRT	4.6	N/A	N/A	N/A	39	28	29.16	N/A	0	N/A	0
Nathan_a [12]	2022	100	69	HIFU, Cryotherapy, Electroporation	sRP	5.8	6	75	19	N/A	16.5	23	N/A	15.3	N/A	78.8
Nathan_b [12]	2022	100	71	HIFU, Cryotherapy, Electroporation	EBRT	4.6	1	76	21	N/A	37	15	N/A	26	N/A	27
van Riel [18]	2022	39	64	Electroporation	sRP	6	18	71.8	10.3	N/A	17.7	2.56	N/A	5.5	N/A	47.0
Kuroki [29]	2022	17	73	HIFU	EBRT	N/A	41.2	11.8	35.3	N/A	N/A	29.4	N/A	N/A	N/A	N/A
Qaoud [20]	2022	25	65	HIFU	HIFU	3.58	17	67	17	16.8	27.3	52	9	13	N/A	N/A

Pts = patients; pTreat = primary treatment; sTreat = salvage treatment; sPSA = PSA at salvage treatment; %sG6 = % Gleason 6 score at salvage treatment; %sG7 = % Gleason 7 score at salvage treatment; %sG>7 = % Gleason >7 score at salvage treatment; sStart = start of salvage treatment after primary treatment (months); sFollow up = follow up after salvage treatment (months); BCR = biochemical recurrence rate; Incon1 = urinary incontinence rate before salvage treatment; Incon2 = urinary incontinence rate after salvage treatment; ED1 = erectile dysfunction rate before salvage treatment; ED2 = erectile dysfunction rate after salvage treatment; N/A = not available; EBRT = external beam radiation therapy; HIFU = High Intensity Focused Ultrasound; sRP = salvage radical prostatectomy.

Table 2
Salvage radical prostatectomy Perioperative data

Study	Operation time (min)	Blood loss (mL)	Transfusion rate (%)	Catheterization time (days)	Hospital stay (days)	% Positive surgical margins	% Nerve sparing
Leonardo-2012 [9]	220	150	0	7	8	15.38	N/A
Lebdai-2015 [10]	150	400	5.2	7	7	47.36	0
Nunes-Silva-2017 [13]	134.7	465.9	0	8.7	4.4	4.5	90.9
Pierrard-2019 [19]	180	200	3	7	7	31	34
Onol-2020 [16]	122.3	92.5	N/A	10.1	1.0	N/A	34.4
Thompson-2020 [11]	140	200	N/A	N/A	1	44.4	28.9
Herrera-Caceres-2020 [17]	N/A	512	N/A	N/A	2.4	38.2	94.2
Nathan-2022 [12]	170	200	0	N/A	1	38	36
van Riel-2022 [18]	N/A	182	0	N/A	1.9	25.6	89.7

Min = minutes; mL = milliliters, N/A not available.

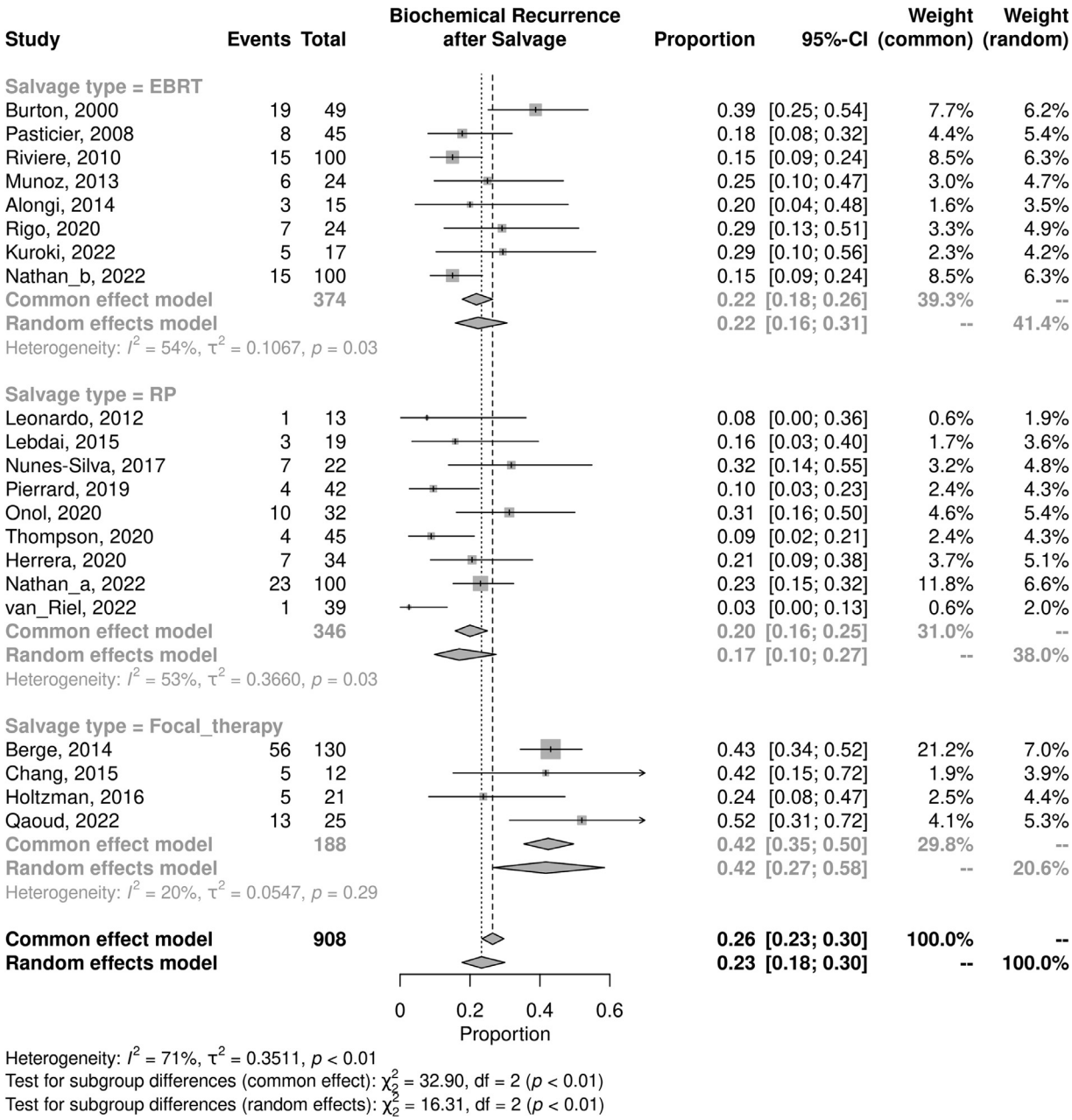

Fig. 2. Biochemical recurrence rate after salvage local treatment.

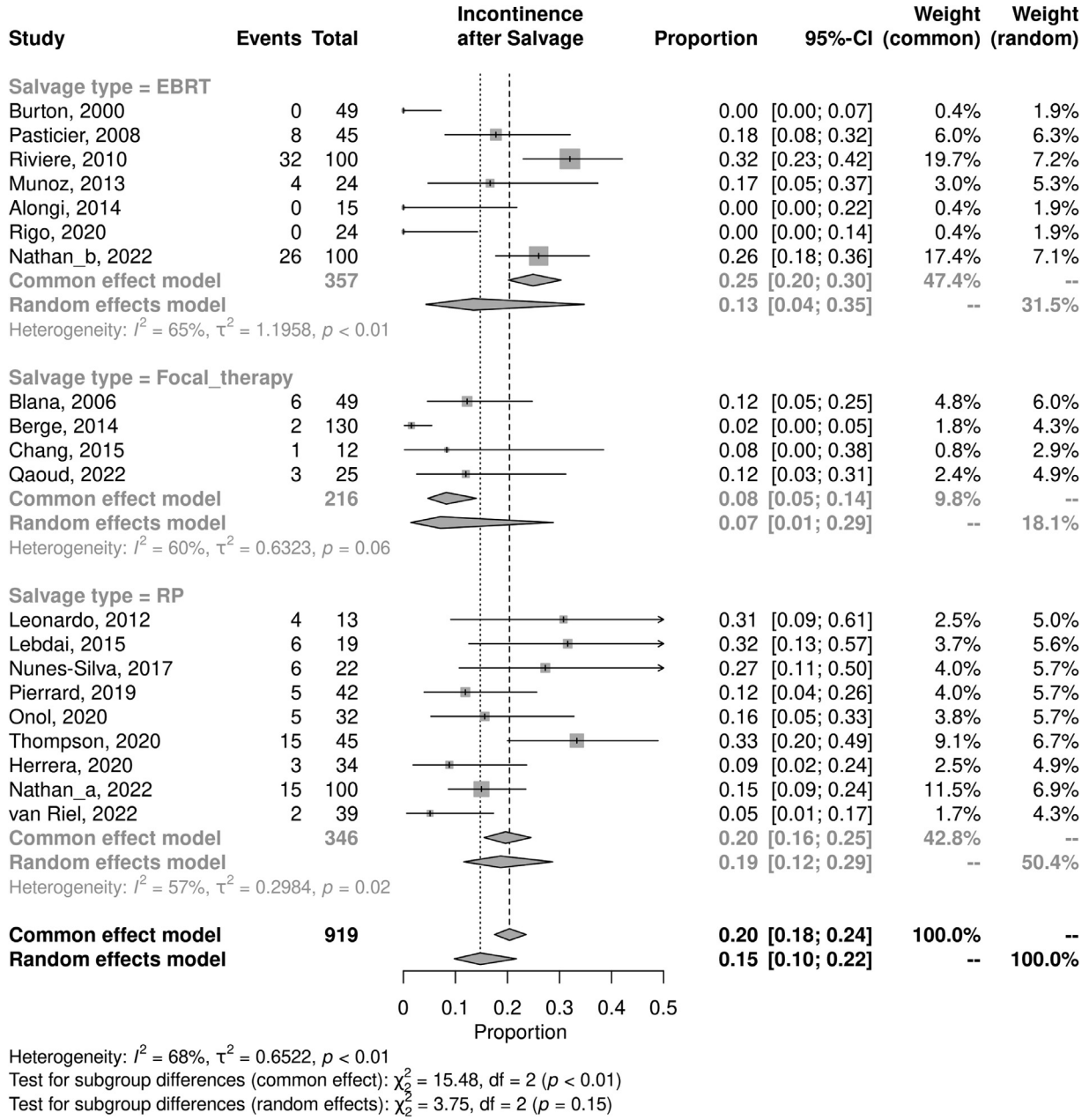

Fig. 3. Urinary incontinence rate after salvage local treatment.

(95% CI, 18%−35%; I^2 = 75%), 61% after sRP (95% CI, 54%−68%; I^2 = 89%), and 29% after a second sFT (95% CI, 22%−36%; I^2 = 92%). When considering only the studies in which the primary therapy was "true focal," the erectile dysfunction rate after salvage treatment was 65% (95% CI, 52%−76%; I^2 = 87%) (Fig S5).

Funnel plot showed no asymmetry when the Egger test was applied, indicating a low publication bias (intercept = −1.7950, t = −0.91, P = 0.3807) (Fig S3 E and F). Meta-regression of the salvage treatment modality revealed a substantial contribution to heterogeneity (R^2 = 37.72%, P < 0.0001), as did the biochemical recurrence (R^2 = 18.97%, P < 0.0001) and urinary incontinence rates (R^2 = 76.34%, P < 0.0056) after salvage treatment. Analyses regarding the extent of ablation, age, PSA level before salvage, proportion of patients with Gleason score ≥7 at recurrence, and time between the primary and salvage therapies revealed no or low contribution to heterogeneity.

4. Discussion

Focal therapy for the treatment of localized PCa has gained popularity in recent years, as studies have consistently shown acceptable oncological outcomes with reduced toxicity and improved functional outcomes compared with that of radical approaches [49]. Despite this, some patients

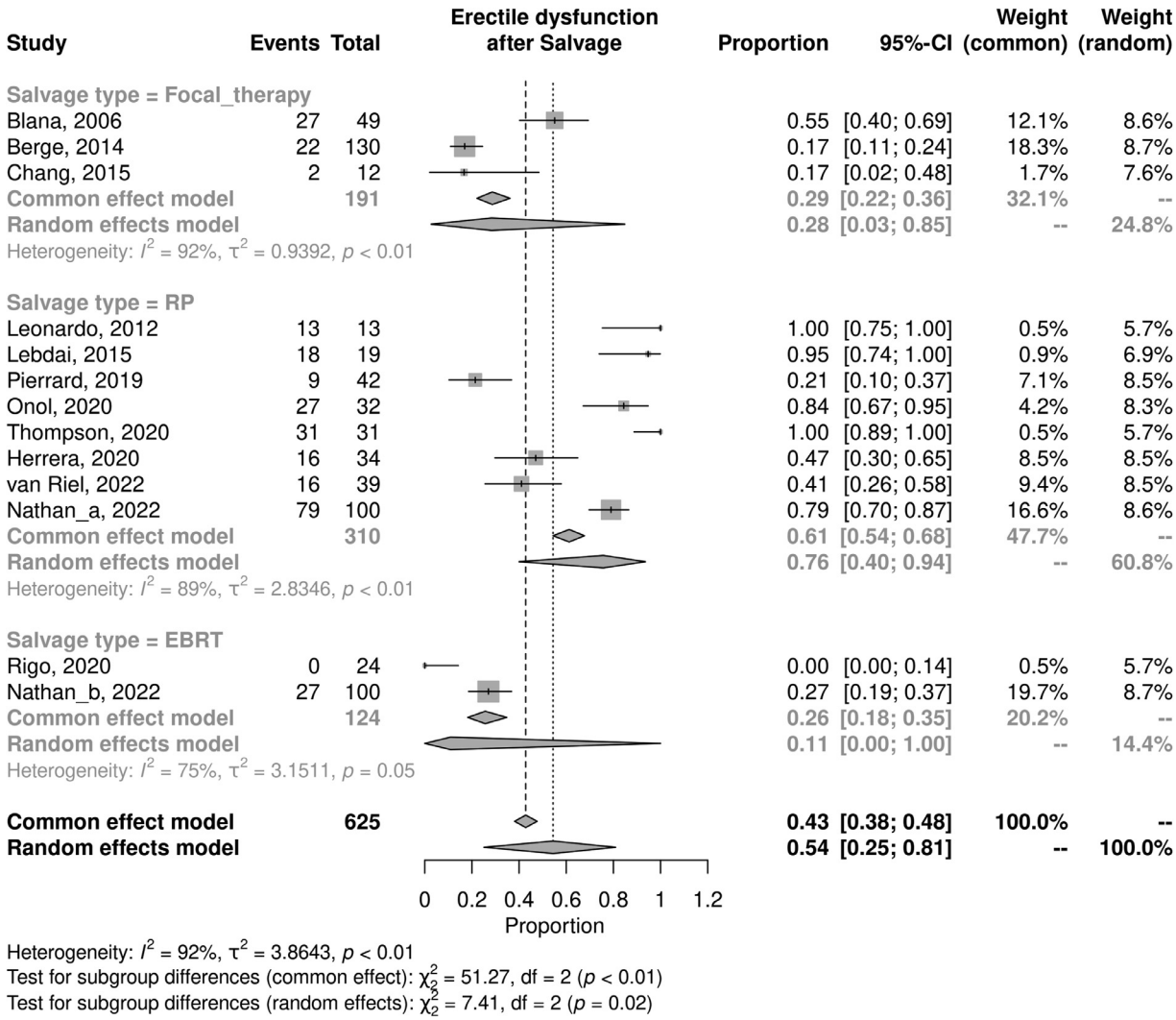

Fig. 4. Erectile dysfunction rate after salvage local treatment.

are expected to experience disease recurrence, eventually requiring salvage local treatment. The next step in managing these patients is uncertain, and we do not have robust data evaluating the safety and subsequent oncological and functional outcomes of different treatment modalities. To the best of our knowledge, in this study, we presented the first systematic review and meta-analysis on this subject.

After FT, the PSA level may not significantly change from baseline, reflecting the amount of residual prostate tissue that has been preserved. The interpretation of a PSA recurrence becomes a challenge, requiring the use of PSA refinements, imaging modalities and tissue sampling [50,51]. According to our findings, if primary FT fails, sRP and sEBRT seem to be reasonable options in terms of oncological control, with biochemical recurrence rates ranging from 20% to 22% in the subgroup analyses. However, if a new FT is chosen, despite of it being feasible, the patient must be aware that the risk of biochemical relapse is higher. These data are in accordance with large multicentre cohorts of salvage robot-assisted radical prostatectomy after FT, showing a progression-free survival of 74% at 12 months after surgery [52].

Regarding functional outcomes, sFT appears to have the lowest rate of urinary incontinence compared to other salvage modalities. Indeed, the continence rate of approximately 92% in the subgroup analysis following sFT was not significantly different from the primary setting results. Overall, studies involving high intensity focused ultrasound (HIFU) reported a median of 95% pad-free patients after first treatment [49].

In our pooled analysis, the risk of erectile dysfunction after salvage treatment was approximately 43% for patients who remained potent after primary FT. In the subgroup analysis, sRP appeared to exhibit the highest chance of potency deterioration. However, some studies have compared functional outcomes after robot-assisted radical prostatectomy in the primary setting and post HIFU, showing similar results [53]. This discrepancy could be explained by

the surgeon's expertise and the number of surgeries performed annually at the hospital. High-volume centers tend to have better overall outcomes than low-volume centers [54].

Although grouped as minimally-invasive procedures, new modalities, such as HIFU, cryotherapy, photodynamic therapy, and irreversible electroporation, were initially developed to treat the whole prostate gland. In recent years, the concept of tissue preservation has gained traction, particularly due to improvements in disease localization using multiparametric magnetic resonance imaging and guided biopsy techniques [55]. Considering this approach, we performed a subgroup analysis to assess whether patients undergoing "true focal" therapies would have better outcomes with salvage treatment. Unfortunately, we could only identify 6 studies that specifically evaluated this scenario, making it difficult to compare to the whole-gland treatment outcomes. This is more evident when analyzing the discrepancy in erectile dysfunction rates postsalvage treatments, showing worse results with the initial "true focal" approach. Probably, this finding is due to the paucity of data (only 3 studies citing this outcome) and study heterogeneity.

Studies on sRP after FT have demonstrated its safety and efficacy. Nathan et al.[12] published the largest case series of robot-assisted sRP, showing a median blood loss of 200 mL, transfusion rate of 0.0%, and median hospital length of stay of 1 day. The catheterization time varied from 7 to 10 days [9,10,13,16,19], similar to our daily practice in a nonsalvage setting.

The present meta-analysis consists of retrospective studies, some with small cohorts and limited follow-up periods. There were also some definitive variations and missing data, particularly regarding functional outcomes, which should be considered when comparing different treatment modalities. Regarding oncological control, we focused on biochemical recurrence rates rather than the location of the disease recurrence, whether it was a locoregional relapse or secondary to distant metastases, and this may differ according to the proposed salvage treatment. Furthermore, the majority of studies did not specify the extent of primary focal therapy, making it difficult to perform a subgroup analysis considering only patients undergoing "true focal" treatment. Therefore, high-quality data from prospective trials are needed to validate the long-term outcomes of salvage local therapies if initial FT fails. We believe that this will become an even bigger discussion topic in the years following the dissemination of these new technologies worldwide.

In conclusion, salvage local treatments for recurrent PCa after FT are feasible and appear to provide acceptable oncological and functional outcomes. Among the treatment modalities, sRP and sEBRT appeared to have the lowest biochemical recurrence rates, whereas sFT was associated with improved functional outcomes, especially urinary continence rates.

Ethical approval and consent to participate

Not applicable since this is a systematic review and meta-analysis.

Registration of research

The protocol of the review was submitted for registration in PROSPERO (CRD42021258369).

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Declaration of competing interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Lucas Seiti Takemura: Writing – original draft, Investigation, Data curation, Conceptualization. **Pedro Henrique Peixoto Costa:** Writing – original draft, Data curation, Conceptualization. **Oliver Rojas Claros:** Writing – original draft, Investigation, Conceptualization. **Rafael Rocha Tourinho-Barbosa:** Writing – original draft. **Saulo Borborema Teles:** Writing – original draft, Investigation. **Rafael Sanchez-Salas:** Writing – review & editing. **Bruno Nahar:** Writing – review & editing. **Ruben Olivares:** Writing – review & editing. **Erik Montagna:** Writing – review & editing, Validation, Software, Formal analysis. **Gustavo Caserta Lemos:** Writing – review & editing, Resources. **Bianca Bianco:** Writing – review & editing, Supervision, Formal analysis. **Arie Carneiro:** Writing – review & editing, Supervision, Project administration, Formal analysis, Conceptualization.

Availability of supporting data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.08.011.

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