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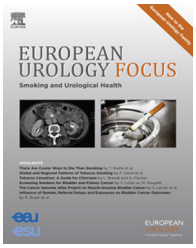

Platinum Priority – Review – Prostatic Disease

Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta–Regression Analysis

Yiannis Philippou [a,†], *Richard A. Parker* [b,†], *Dimitrios Volanis* [c], *Vincent J. Gnanapragasam* [c,d,*]

[a] *Department of Surgery, Basildon and Thurrock University Hospital, Essex, UK;* [b] *Health Services Research Unit University of Edinburgh, Edinburgh, UK;* [c] *Department of Urology, Addenbrooke's University Hospital, Cambridge, UK;* [d] *Academic Urology Group, Department of Surgery and Oncology, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK*

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Abstract

Context: In the absence of randomised controlled trials comparing the oncologic, toxicity, and functional outcomes of salvage radical prostatectomy (SRP), salvage high-intensity focused ultrasound (SHIFU), salvage brachytherapy (SBT), and salvage cryotherapy (SCT), controversy exists as to the optimal salvage modality in radiorecurrent prostate cancer.
Objective: We carried out a meta–regression analysis to determine whether there is a difference in oncologic, toxicity, and functional outcomes using data from original publications of salvage modalities in the postradiation setting.
Evidence acquisition: We performed a systematic review of PubMed/Medline citations according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. We included 63 articles in the analysis (25 on SRP, 8 on SHIFU, 16 on SCT, 14 on SBT).
Evidence synthesis: Median values of the following variables were extracted from each study: patient age, length of follow-up, prostate-specific antigen (PSA) before radiotherapy (RT), PSA before salvage therapy, Gleason score before RT, and time interval between RT and salvage therapy. Functional, toxicity, and oncologic outcomes were measured according to rates of impotence, incontinence, fistula formation, urethral strictures, and biochemical recurrence. Meta–regression adjusting for confounders found no significant difference in oncologic outcomes between SRP and nonsurgical salvage modalities. SBT, SCT, and SHIFU appeared to have better continence outcomes than SRP. No significant difference in toxicity outcomes between modalities was found, although limitations such as reporting, selection, and publication bias and between-study heterogeneity must also be considered with these conclusions.
Conclusions: Oncologic outcomes are comparable for SRP and all three nonsurgical salvage modalities. We found no significant differences in toxicity outcomes among modalities; however, SRP appears to be associated with worse rates of urinary incontinence than SBT, SCT, and SHIFU.
Patient summary: We performed a meta–regression analysis to compare oncologic, functional, and toxicity outcomes between salvage radical prostatectomy and nonsurgical salvage modalities. Oncologic and toxicity outcomes appear to be similar; however, all nonsurgical salvage modalities may be associated with better continence outcomes.

† Contributed equally.
* Corresponding author. Academic Urology Group, Department of Surgery and Oncology, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK. Tel. +44 1223 274316; Fax: +44 1223 769007.
E-mail address: vjg29@cam.ac.uk (V.J. Gnanapragasam).

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1. Introduction

For more than two decades, external-beam radiation therapy (RT) and low-dose-rate brachytherapy have been considered standard practice for the treatment of patients with clinically localised low-risk prostate cancer (PCa). Over the years, technological advances in this field have seen changes in the delivery of RT. The integration of various forms of image-guided RT for external-beam RT and brachytherapy and delivery with intensity-modulated RT have enabled accurate dose escalation to improve outcomes and reduce toxicity [1]. Radiobiological models have also indicated that PCa cells are more sensitive to doses delivered in larger fraction sizes than in smaller frequent doses [2]. Our understanding of this has been critical in the introduction and evolution of high-dose-rate brachytherapy, stereotactic body RT, and proton beam therapy. The introduction of higher radiation doses in addition to the use of adjuvant or neoadjuvant androgen deprivation therapy (ADT) have led to improved outcomes and thus to the hypothesis that this combination would likely produce additive improvements [3]. Even in the current era of dose-escalated RT for PCa and its combination with ADT, biochemical recurrence (BCR) is not uncommon and occurs in approximately 20–30% of patients [4].

According to European and British urologic guidelines, therapeutic options in patients with BCR after primary RT can include salvage radical prostatectomy (SRP), salvage high-intensity focused ultrasound (SHIFU), salvage cryotherapy (SCT), and salvage brachytherapy (SBT). These guidelines, however, advise that strong recommendations regarding the choice of any of these techniques cannot be made, as the available evidence for these treatment options is of very low quality; there are currently no randomised trials to compare the different modalities of salvage treatment in terms of oncologic, functional, and toxicity outcomes. The majority of available data come from single- or multi-institutional retrospective or prospective studies with short to intermediate follow-up. The decision of which modality to use is based largely on institutional practice and the availability of a particular technology rather than high-quality evidence. Evaluating the relative effectiveness of various salvage treatments in terms of relative cancer control and treatment-related morbidity has proved challenging. This is because of differing treatment-specific definitions of BCR, a lack of a standardised reporting system for toxicity outcomes, and large heterogeneity between studies regarding duration of follow-up, patient demographics, tumour risk profiles in terms of prostate-specific antigen (PSA) value and Gleason score, and interval between RT and salvage therapy. To date, the only studies attempting to compare these modalities have been systematic reviews [5–7].

To help inform further discussion on this topic, we carried out a meta–regression analysis to compare treatment biochemical failure rates, functional outcomes, and toxicity among the different available salvage options for radiorecurrent disease. Our primary interest was to compare reported outcomes between the most commonly reported salvage modality, SRP, and nonsurgical modalities.

2. Evidence acquisition

2.1. Search strategy and selection criteria

A systematic review of the literature was conducted using PubMed/Medline electronic databases. The search was restricted to English-language articles from January 1, 1994, to December 31, 2014. Search terms included *prostate cancer recurrence, prostate salvage therapy, radio-recurrent prostate cancer, local salvage treatment, SRP, SCT, SBT*, and *SHIFU*. We combined the search terms *prostate cancer recurrence* with *SHIFU, SRP, SCT*, or *SBT* for four separate searches.

2.2. Inclusion criteria

All authors participated in the design of the search strategy and inclusion criteria. Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria. We included only original articles involving salvage therapy in the postradiation setting. Eligibility criteria for selecting studies included a diagnosis of nonmetastatic recurrent PCa after primary RT. All studies included in this analysis used the American Society for Radiation Oncology (ASTRO) or Phoenix definition of *biochemical recurrence* to identify BCR in patients following primary RT. The absence of nodal or bone metastases was evaluated in most cases using bone scintigraphy or pelvic magnetic resonance imaging to ensure local recurrence only. Eligibility criteria also included reporting of oncologic outcomes in terms of BCR rates, reporting comprehensively on functional outcomes in terms of incontinence and impotence using standardised and validated questionnaires, and reporting toxicity outcomes in terms of fistula and urethral stricture formation. In the included studies, recurrent PCa was diagnosed by either transrectal ultrasound–guided or template prostate biopsies prompted by a rise in PSA defined as recurrence of disease according to the ASTRO or Phoenix definition of BCR. Details as to the number of biopsy cores undertaken and the percentage of cores positive for cancer were not available. Any studies commenting on salvage treatments whereby the primary form of therapy was not RT were excluded from the analysis. The final list of included articles was selected with the consensus of all collaborating authors verifying that the articles met the inclusion criteria.

2.3. Outcomes

The main oncologic outcome of interest was BCR. For a pragmatic approach, we used each study's predefined criteria for biochemical relapse, recognising the lack of consistency of these definitions within and across treatment types. Other end points that determine oncologic efficacy, such as PCa-specific mortality, overall survival, progression to metastases, or extent of follow-up positive biopsies after salvage treatment, were scarcely reported in the literature and thus were not considered. We chose to

include the aforementioned functional and toxicity outcomes because these were the most frequently reported and were common to all of the salvage modalities, allowing comparison of SRP and the nonsurgical salvage modalities. Specific toxicities pertaining to each salvage modality were not considered because comparison would not be possible for the purposes of this analysis. Functional outcomes were determined by measuring impotence and incontinence rates, and toxicity outcomes were evaluated by measuring fistula and urethral stricture formation rates, as reported by the individual studies. *Incontinence* was universally defined in the selected studies as urinary leakage requiring occasional or regular pad use. Patients who required no pads following salvage treatment were considered continent. *Impotence* was defined as the inability to maintain an erection sufficient for sexual intercourse. As mentioned previously, the studies included in this analysis used validated patient questionnaires to accurately determine these functional outcomes after salvage therapy. Pretreatment erectile and urinary function was accounted for when determining the rate of incontinence and impotence after salvage therapy.

2.4. Statistical analysis

The following data were extracted from each study if available: first author, study size, median age, median follow-up duration, Gleason score prior to primary RT, median PSA prior to primary RT, median clinical stage prior to primary RT, median interval between primary RT and salvage therapy, administration of neoadjuvant or adjuvant ADT at the time of salvage therapy, median PSA prior to salvage therapy, Gleason score prior to salvage therapy, and median clinical stage prior to salvage therapy.

The outcomes of BCR, impotence, incontinence, fistula, and urethral strictures formation were compared individually between salvage therapies using meta–regression analysis, with salvage modality included as a moderator. The meta–regression analysis consisted of fitting a logistic mixed-effects model to each of the outcome variables using the "rma.glmm" function within the *metafor* package in R software, with an explanatory factor variable for salvage modality [8,9]. For oncologic outcome defined as biochemical relapse after salvage, and urethral stricture as a functional outcome the model adjusted for another seven moderators (model 3): age, length of follow-up, PSA before RT, PSA before salvage therapy, Gleason score before RT, time interval between RT and salvage therapy, and ADT administration prior to salvage therapy (neoadjuvant ADT). None of the studies administered ADT in combination with salvage therapy (adjuvant ADT); therefore, the use of adjuvant ADT was not considered as a moderator. Gleason score prior to salvage therapy was scarcely reported and also was not included as a moderator. For incontinence as a functional outcome, and fistula formation as a toxicity outcome the meta–regression model adjusted for age, length of follow-up, PSA before salvage therapy, PSA before RT, and Gleason score before RT (model 2). Unfortunately, no covariate adjustment was possible for impotence (model 1). The reason for this modelling strategy was that many studies had missing data on the moderators, and that reduced the data set available for analysis and caused problems with model fitting. We always aimed to include the maximum number of moderators possible in each analysis, and this meant that the analyses for some outcomes included more moderators than others.

The reported median was used to summarise the aforementioned moderators; when missing, the mean was used instead, if available. A value of 0.5 was added to any zero frequencies prior to analysis. The amount of residual heterogeneity between studies was assessed by reporting the absolute value of τ^2 (between-study variance) and the I^2 statistic. Summary effect-size differences in outcomes between the different surgical modalities were expressed as odds ratios (ORs) with 99% confidence intervals (CIs) and p values. Due to the large number of models and outcome variables considered in multiple testing, a 1% significance threshold was used to determine statistical significance. To investigate publication bias, funnel plots were constructed of sample size against model residuals calculated by linear meta–regression models of logit-transformed proportions, with salvage therapy included as the only moderator.

3. Evidence synthesis

The literature search yielded 975 papers, which were individually screened for their suitability for inclusion in this study. Overall, 912 articles were excluded from the study, resulting in 63 articles finally being included in the analysis (Fig. 1) [10–71]. One of the SCT studies included two separate cohorts of patients who underwent SCT, the outcomes of which we considered separately [45]; therefore, a total of 64 studies were included in the analysis: 25 for SRP, 8 for SHIFU, 17 for SCT, and 14 for SBT. Five of the studies provided no data on mean or median age, and three did not record the duration of follow-up. Thirty studies had no data on PSA prior to primary RT, and seven papers had no data on PSA prior to salvage therapy. In addition, 33 of the studies did not mention Gleason score prior to initial RT, and 22 studies provided no data on the interval between RT and salvage therapy. The total number of patients was 4564, with a median study size of 40 (range: 4–404). Further baseline characteristics of the original publications identified by the literature search are shown in Table 1. A funnel plot of the model residuals against sample size showed no clear evidence of publication bias for BCR as an outcome variable (Fig. 2); however, there were some limited indications of publication bias when considering toxicity and functional outcomes, particularly incontinence.

The cohort size of each study and the overall percentage relapse rate at any time as well as toxicity and functional outcomes are represented as bubble plots (Fig. 3). Overall SCT included the largest population sizes (110 participants on average), whereas the SBT studies included the smallest numbers of patients (26 participants on average). Weighted summary statistics for age; length of follow-up; PSA before salvage therapy; PSA before RT; Gleason score before RT;

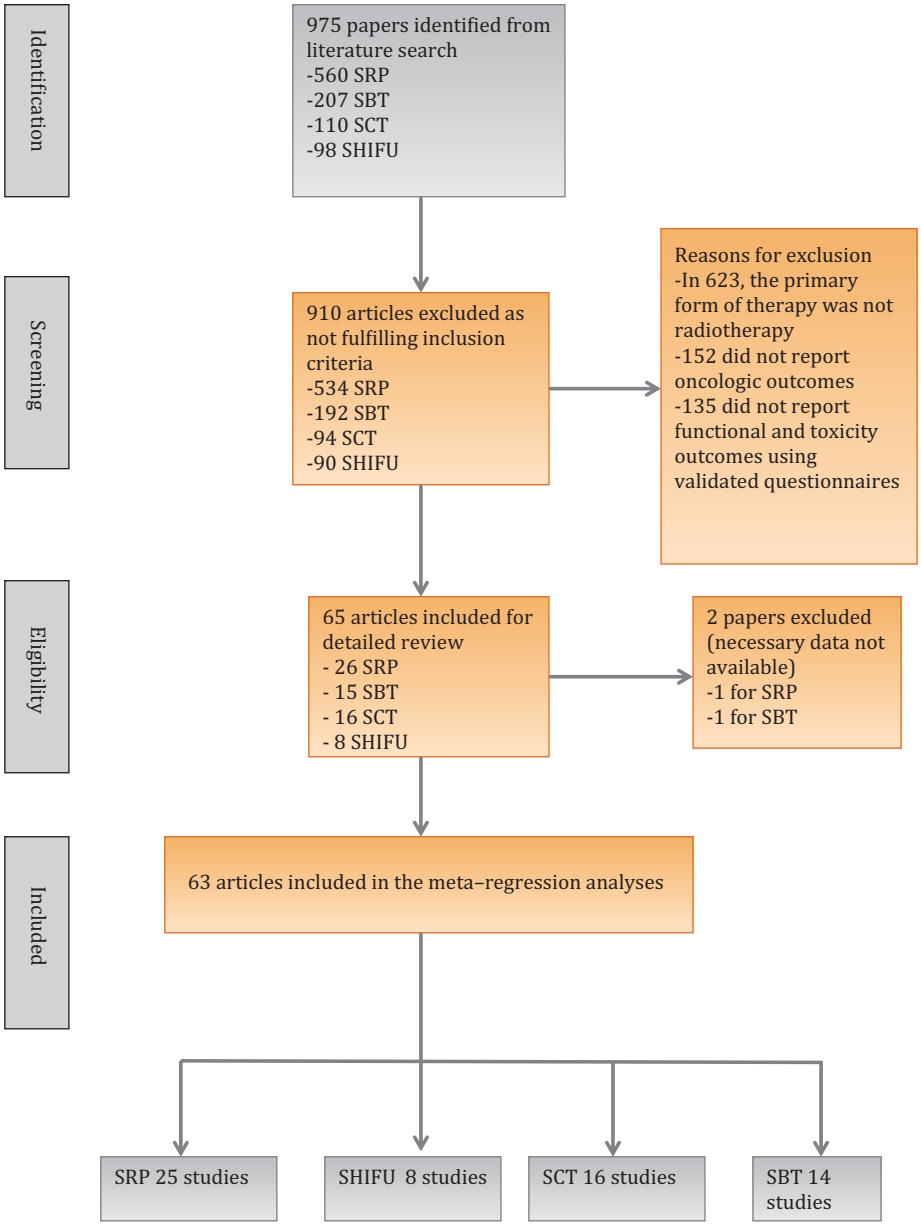

Fig. 1 – Flow diagram of evidence acquisition of original publications on salvage therapies for radiorecurrent prostate cancer.
SBT = salvage brachytherapy; SCT = salvage cryotherapy; SHIFU = salvage high-intensity focused ultrasound; SRP = salvage radical prostatectomy.

interval between RT and salvage therapy; and oncologic, toxicity, and functional outcomes for each salvage modality are displayed in Table 2.

3.1. *Meta–regression analysis for biochemical relapse*

The bubble plot for BCR showed no obvious visual differences among the salvage modalities (Fig. 3), and this was confirmed in the meta–regression analyses. Two analyses were done for BCR. The first adjusted for no additional moderators (model 1) and included 61 studies. This analysis showed no significant difference in biochemical relapse between SRP and the nonsurgical salvage modalities (SBT relative to SRP: OR: 0.98 [99% CI, 0.493–1.95]; $p = 0.939$; SCT relative to SRP: OR: 1.49 [99% CI, 0.816–2.73]; $p = 0.087$; SHIFU relative to SRP: OR: 1.17 [99% CI, 0.537–2.56]; $p = 0.60$). A further analysis to compare the oncologic outcomes between the nonsurgical salvage modalities also revealed no significant difference in BCR (SBT relative to SHIFU: OR: 0.836 [99% CI, 0.355–1.97]; $p = 0.590$; SCT relative to SHIFU: OR: 1.27 [99% CI, 0.577–2.81]; $p = 0.430$; SBT relative to SCT: OR: 0.656 [99% CI, 0.326–1.32]; $p = 0.121$).

The second analyses adjusted for the following variables: age, PSA before RT and salvage therapy, Gleason score

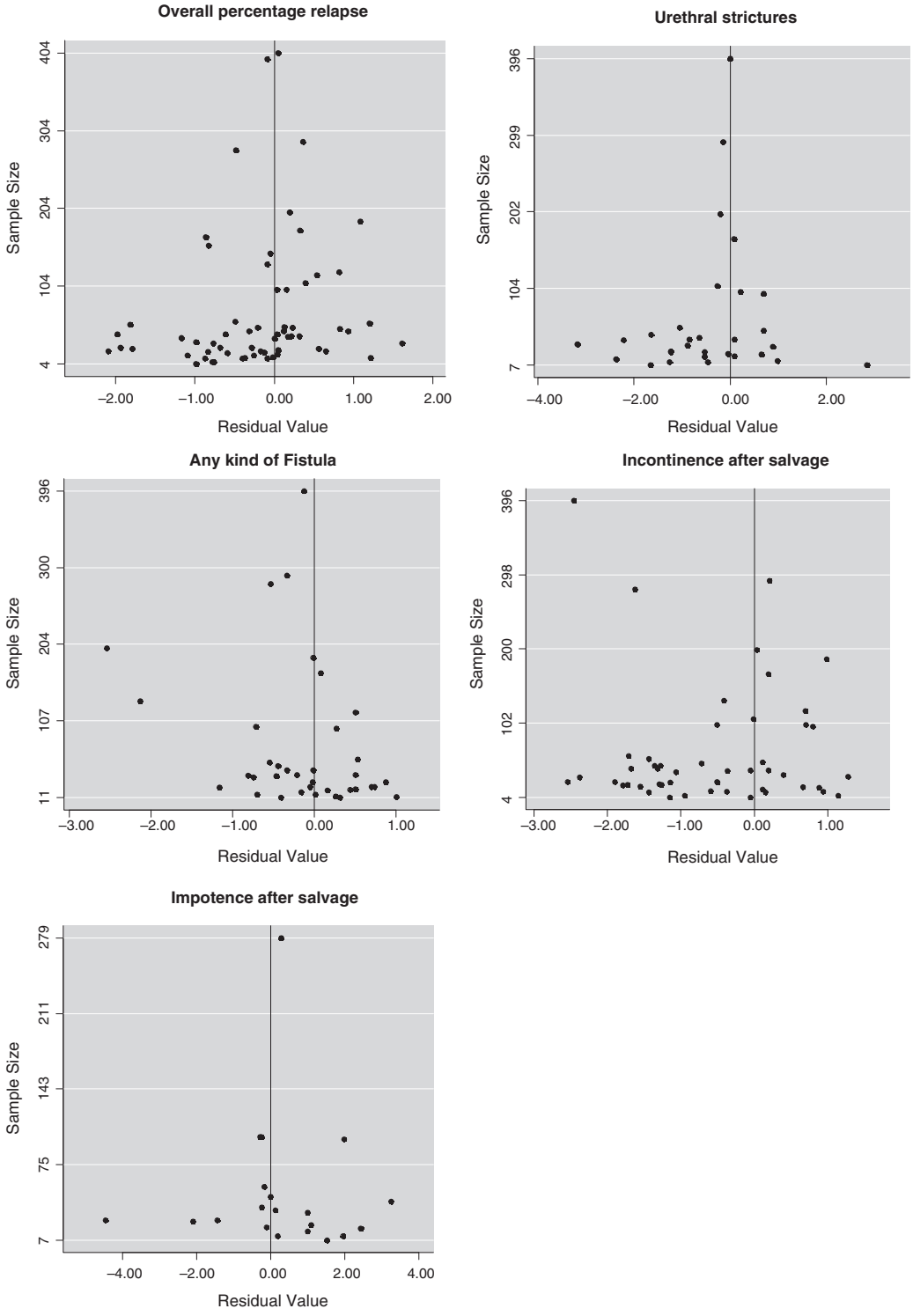

Fig. 2 – Funnel plots of sample size against the model residuals for the main outcome variables. The points represent different studies. If studies are distributed evenly on either side of the zero line, this suggests no clear evidence of publication bias.

before RT, follow-up duration, interval between RT and salvage therapy, and administration of neoadjuvant ADT (model 3). After accounting for the above variables, 17 studies were eligible for the second analysis. The residual heterogeneity between studies for this analysis was estimated to be zero. The meta–regression analysis following adjustment for these variables, again, showed no significant difference in BCR rates between the SRP and the nonsurgical salvage modalities (SBT relative to SRP: OR: 0.647 [99% CI, 0.243–1.73]; $p = 0.254$; SCT relative to SRP: OR: 0.932 [99% CI, 0.241–3.61]; $p = 0.894$; SHIFU relative to SRP: OR: 1.21 [99% CI, 0.38–3.86]; $p = 0.669$). Subsequent

Table 1 – Descriptive baseline characteristics of selected original publications identified by systematic review

			Pre–primary RT data					Pre–salvage therapy data					Salvage oncologic, functional, and toxicity outcomes				
Salvage therapy	Reference	*n*	Age, yr	Gleason score	PSA, ng/ml	T stage	Time from RT to salvage therapy, months	PSA, ng/ml	Gleason score	T stage	Follow-up, months	Definition of relapse	Biochemical relapse, %	Incontinence, %	Impotence, %	Fistula, %	Urethral stricture, %
SHIFU	Song et al [10]	13	68	7	21.12	T2	32.7	4.63	*7	T23	44.5	Stuttgart	46.2	31.00	NA	0.00	38.40
SHIFU	Ahmed et al [11]	39	70.5*	6	19	NA	NA	3.3	7	NA	24.0	Stuttgart and Phoenix	51.0	36.00	NA	0.00	2.50
SHIFU	Rouvière et al [12]	46	NA	NA	5.4*	NA	NA	5.4*	8	T2	NA	Phoenix	69.0	NA	NA	NA	NA
SHIFU	Crouzet et al [13]	290	68.7*	8	6.38*	NA	60*	6.38*	NA	NA	48.0	Phoenix	55.8	50.00	NA	2.00	16.80
SHIFU	Berge et al [14]	46	67.8	NA	NA	NA	NA	4.9	NA	NA	9.0	NA	39.1	17.30	72.00	2.00	4.30
SHIFU	Uchida et al [15]	22	65*	6	14.3	T1c	36	4	NA	NA	24.0	Phoenix	48.0	18.20	NA	4.50	18.20
SHIFU	Zacharakis et al [16]	31	68	NA	7.73*	T2c	NA	7.73*	NA	NA	7.4*	NA	29.0	7.00	NA	6.40	36.00
SHIFU	Murat et al [17]	167	68	NA	6.89*	NA	55.6	4.5	7	NA	18*	Phoenix	27.0	49.50	NA	3.00	20.00
SRP	Kaffenberger et al [18]	34	66.5	6	5.6	NA	48.5	3.86	NA	T1c	16.1	AUA	NA	61.00	79.00	NA	0.00
SRP	Gao et al [19]	4	66	NA	9.4	NA	NA	6.35*	NA	NA	20.0	NA	25.0	50.00	NA	NA	NA
SRP	Gorin et al [20]	24	65*	NA	9*	NA	NA	9*	NA	T2	63*	AUA	61.0	39.00	29.00	NA	17.00
SRP	Ahallal et al [21]	15	62.3	7	5.5	T1c	46	3.49	7	T3	8.0	PSA ≥0.1	23.0	54.00	90.00	0.00	0.00
SRP	Chade et al [22]	404	65	NA	NA	NA	41	4.5	7	T2	120.0	AUA	48.3	NA	NA	NA	NA
SRP	Gontero et al [23]	12	66.5	NA	12.4	NA	49	6.3	NA	T3	40.5	AUA	75.0	42.00	NA	8.00	NA
SRP	Corcoran et al [24]	21	60	7	9.2	T2	52	3.5*	7	T2	68.0	AUA	43.0	23.00	NA	4.70	40.00
SRP	Heidenreich et al [25]	55	65.3	6	7.7	T2	32	7.8	6	T2	23.0	AUA	12.7	20.00	73.30	1.80	10.90
SRP	Darras et al [26]	11	60.5*	6	7.2	T2	36	3.68	NA	T2	63.0	AUA	45.0	55.00	100.00	0.00	18.00
SRP	Boris et al [27]	11	64.9*	NA	5.2	NA	53.2	5.2*	NA	NA	20.5*	NA	27.2	20.00	80.00	0.00	9.00
SRP	Gheiler et al [28]	40	64.2*	NA	NA	T2	58*	13.4*	7	T2	36.1*	PSA >0.4	52.6	50.00	NA	2.50	13.00
SRP	Paparel et al [29]	146	65	7	NA	NA	54	5	7	T2	52.0	AUA	46.0	NA	NA	NA	NA
SRP	Leonardo et al [30]	32	63	6	13	T2	25	3.2	7	T2	35.0	AUA	25.0	79.00	90.00	NA	12.50
SRP	Stephenson et al [31]	100	65	6	7.7	T2	48	5.9	7	T2	60.0	AUA	48.0	68.00	72.00	NA	30.00
SRP	Sanderson et al [32]	51	66	NA	NA	NA	62	8	NA	NA	86.0	PSA >0.4	53.0	54.00	NA	2.00	41.00
SRP	Ward et al [33]	199	65	NA	8.5*	NA	40	5.1	NA	NA	84.0	PSA >0.4	52.0	52.00	NA	0.00	22.00
SRP	Amling et al [34]	108	65*	NA	17.2	NA	36	6.2	NA	NA	NA	AUA	57.0	51.00	NA	NA	21.00
SRP	Eandi et al [35]	18	67	6	NA	NA	79	6.8	7	NA	18.0	AUA	33.0	67.00	100.00	0.00	17.00
SRP	Lerner et al [36]	132	65	NA	NA	NA	38	NA	NA	T2	52.0	AUA	45.0	41.00	NA	0.00	NA
SRP	Rogers et al [37]	40	61.5*	NA	NA	NA	NA	NA	NA	T2	39*	Rising PSA	55.0	56.00	NA	5.00	27.50
SRP	Seabra et al [38]	42	63.3*	NA	NA	NA	17.1*	3.86	NA	NA	17*	AUA	11.0	22.00	100.00	NA	NA
SRP	Van der Poel et al [39]	27	64*	NA	NA	NA	47	8.6	NA	NA	43.0	NA	69.0	NA	NA	NA	NA
SRP	Vallancien et al [40]	7	66.2*	NA	NA	T2	57.4*	8.9*	NA	NA	11.2*	NA	29.0	29.00	100.00	NA	0.00
SRP	Gotto et al [41]	98	NA	NA	NA	NA	60	NA	NA	NA	NA	NA	NA	70.00	96.00	4.00	41.00
SRP	Pisters et al [42]	42	67.5	7	NA	T2	NA	4	NA	NA	92.0	PSA >0.4	39.0	NA	NA	NA	NA
SCT	Bahn et al [43]	59	67.5	NA	NA	NA	NA	5.6	7	T2b	82.3	PSA >0.5	41.0	4.30	NA	3.40	NA
SCT	Donnelly et al [44]	46	68.9	7	19.2	T2b	61.2	5.6	7	T2b	20.0	PSA >0.3	56.0	6.50	NA	2.00	NA
SCT	De Castro Abreu et al [45]	25	73	6	6	T2a	75.6	3.9	7	T2a	53.0	Phoenix	14.0	13.00	0	4.00	NA

Table 1 (*Continued*)

			Pre–primary RT data					Pre–salvage therapy data					Salvage oncologic, functional, and toxicity outcomes				
Salvage therapy	Reference	*n*	Age, yr	Gleason score	PSA, ng/ml	T stage	Time from RT to salvage therapy, months	PSA, ng/ml	Gleason score	T stage	Follow-up, months	Definition of relapse	Biochemical relapse, %	Incontinence, %	Impotence, %	Fistula, %	Urethral stricture, %
SCT	De Castro Abreu et al [45]	25	71	7	7	T2a	99.6	2.8	7	T2a	31.0	Phoenix	46	0	28.5	0	NA
SCT	Pisters et al [42]	56	67	NA	NA	T2	NA	5.4	7	T2	65.0	PSA >0.4	79.0	NA	NA	NA	NA
SCT	Pisters et al [46]	279	70*	NA	NA	NA	NA	7.6*	7	NA	21.6	ASTRO	41.1	4.70	69.20	1.20	NA
SCT	Ng et al [47]	187	70.9	6	11	NA	NA	4.9	7	NA	39*	Phoenix	77.0	40.00	NA	2.00	NA
SCT	Williams et al [48]	176	NA	6	NA	NA	NA	NA	7	NA	89.5*	Phoenix	61.0	NA	NA	NA	NA
SCT	Ng et al [49]	122	70	NA	12.2	NA	NA	6.2	NA	NA	56*	NA	72.0	NA	NA	NA	NA
SCT	Ismail et al [50]	100	66.8	7	NA	NA	NA	NA	NA	NA	33.5*	ASTRO	57.0	13.00	56.00	1.00	NA
SCT	Eisenberg et al [51]	19	70.5*	7	NA	NA	72*	3.3*	NA	NA	18.0	ASTRO	50.0	5.00	60.00	NA	5.00
SCT	Wenske et al [52]	396	65.8	7	8	NA	67.2	4	NA	NA	47.8*	Phoenix	51.0	2.10	NA	1.80	4.60
SCT	Ghafar et al [53]	38	71.9*	NA	NA	NA	73.2*	7.5*	7	NA	20.7	PSA>0.3	26.0	7.90	NA	0.00	NA
SCT	Spiess et al [54]	156	70	NA	NA	T2	NA	NA	6	T2	45.6	Phoenix	33.2	NA	NA	NA	NA
SCT	Chin et al [55]	118	68	NA	NA	T2	NA	NA	7	T3	18.6	PSA >0.5	66.0	33.20	NA	3.30	NA
SCT	Cresswell et al [56]	20	66	NA	NA	T2	NA	7	6	T2	9.0	PSA <0.5	33.0	4.00	NA	0.00	NA
SCT	Cheetham et al [57]	51	69.2	NA	NA	NA	NA	6.43	7	NA	121.2	PSA >0.5	47.8	NA	NA	NA	NA
SBT	Yamada et al [58]	42	72	NA	NA	NA	78	3.54	7	NA	36.0	Phoenix	31.5	2.38	NA	NA	7.00
SBT	Chen et al [59]	52	67.5	6	9.3	T2	55.2	5	NA	T3a	59.6	ASTRO	49.0	NA	NA	NA	NA
SBT	Shimbo et al [60]	15	72.3*	6	NA	NA	45.5*	3.07*	8	T2a	33.0	Phoenix	39.8	NA	NA	0.00	NA
SBT	Jo et al [61]	11	66	7	17.8*	T2a	38	6.9	7	NA	29.0	ASTRO	36.3	NA	NA	0.00	NA
SBT	Burri et al [62]	37	70	6	10.9	NA	NA	5.6	7	NA	86.0	Phoenix	46.0	NA	75.00	3.00	NA
SBT	Moman et al [63]	31	69.3*	7	24.3*	T2	60*	11.4*	7	NA	110.4*	Phoenix	81.0	NA	NA	6.00	NA
SBT	Aaronson et al [64]	24	66	7	9.9	NA	54	3.41	7	NA	30.0	Phoenix	12.0	4.00	NA	0.00	4.00
SBT	Tharp et al [65]	7	71	NA	NA	NA	55	5.45	7	NA	58.0	ASTRO	28.5	29.00	NA	NA	71.00
SBT	Lee et al [66]	21	72	NA	NA	NA	85	3.8	7	NA	36.0	ASTRO	62.0	NA	NA	NA	NA
SBT	Lee et al [67]	21	68.4*	6	NA	NA	NA	5.8	7	T2b	18.7	ASTRO	9.5	0.00	92.00	NA	NA
SBT	Nguyen et al [68]	25	65	6	7.45	T1C	62.4	5.5	NA	NA	47.0	Phoenix	30.0	0.00	NA	12.00	4.00
SBT	Allen et al [69]	12	NA	6	9.55	T1C	69	3.85	7	NA	45.0	ASTRO	37.0	25.00	NA	NA	NA
SBT	Grado et al [70]	49	73.3	NA	26.4	NA	41.7	5.6	NA	NA	64.1	Phoenix	66.0	6.00	NA	NA	NA
SBT	Beyer et al [71]	17	NA	NA	NA	NA	54	2.2	NA	NA	62.0	ASTRO	47.0	24.00	NA	NA	NA

AUA = American Urological Association; ASTRO = American Society for Radiation Oncology; NA = not available; PSA = prostate specific antigen; RT = radiotherapy; SBT = salvage brachytherapy; SCT = salvage cryotherapy; SHIFU = salvage high-intensity focused ultrasound; SRP = salvage radical prostatectomy; n = number of patients; yr = years.

* Mean value.

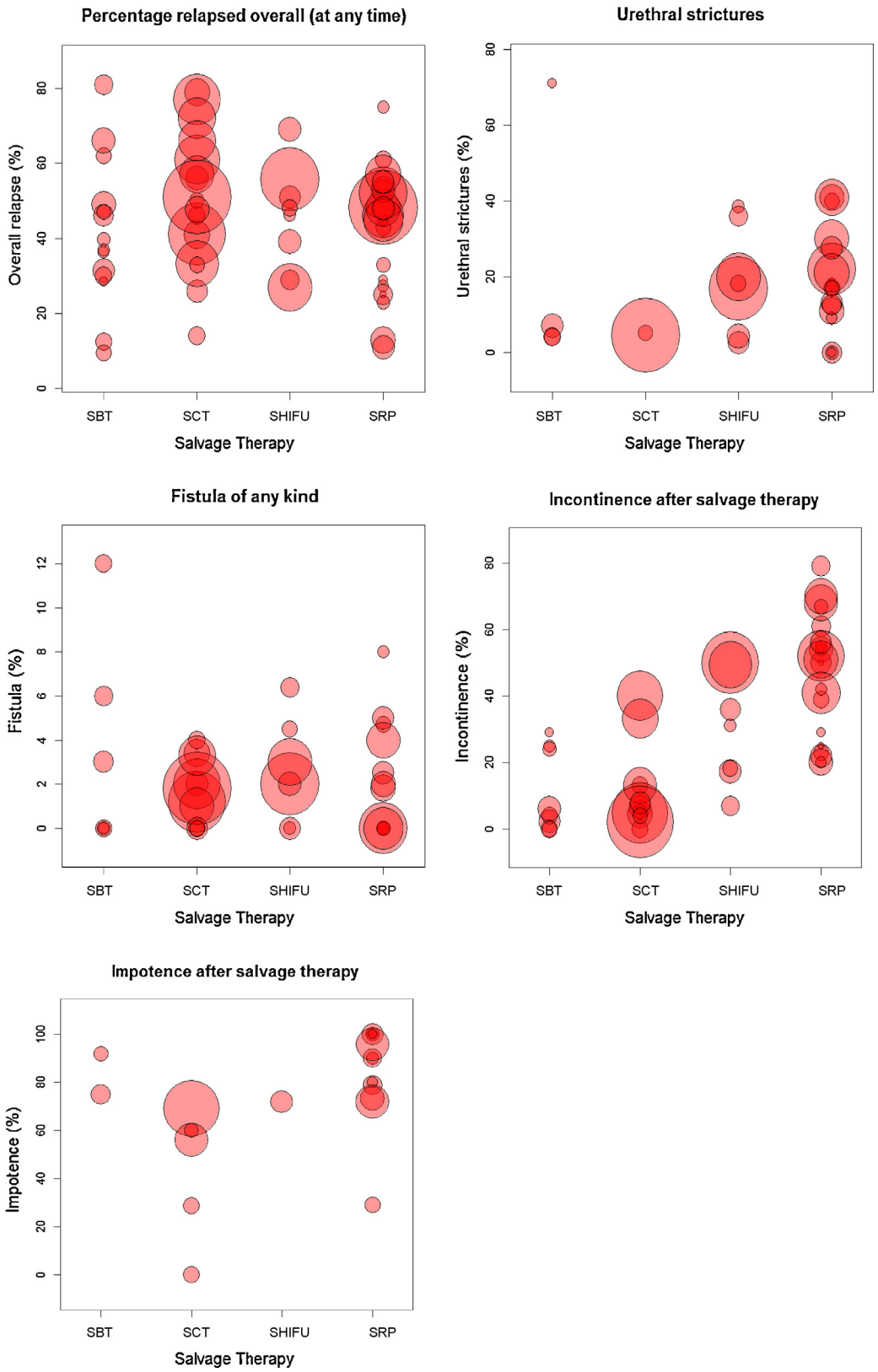

Fig. 3 – Bubble plot showing the oncologic, toxicity, and functional outcomes and the respective size of each study for the four different salvage modalities. The size of the bubble corresponds to the size of the study.
SBT = salvage brachytherapy; SCT = salvage cryotherapy; SHIFU = salvage high-intensity focused ultrasound; SRP = salvage radical prostatectomy.

Table 2 – Weighted summary statistics of data extracted from each paper by salvage modality

Strategy	SHIFU (n = 8)	SRP (n = 25)	SCT (n = 17)	SBT (n = 14)	Overall (n = 64)
Age, yr	68.37 (65.0–70.5) (n = 7)	64.88 (60–73.0) (n = 24)	68.36 (61–71.9) (n = 16)	69.64 (65–73.3) (n = 12)	67.18 (60–73.3) (n = 59)
Length of follow-up, months	32.26 (7.4–48.0) (n = 7)	73.07 (5 – 120) (n = 23)	46.18 (9–121.2) (n = 17)	55.53 (18.7–110.4) (n = 14)	54.05 (5–121.2) (n = 61)
PSA before salvage therapy, ng/ml	5.49 (3.3–7.7) (n = 8)	5.43 (3.2–13.4) (n = 22)	5.48 (2.8–7.6) (n = 13)	5.24 (2.2–11.4) (n = 14)	5.44 (2.2–13.4) (n = 57)
PSA before RT, ng/ml	7.93 (5.4–21.1) (n = 7)	9.85 (5.2–17.2) (n = 13)	9.89 (6.0–19.2) (n = 6)	15.22 (7.4 – 26.4) (n = 8)	9.92 (5.2–26.4) (n = 34)
Gleason score before radiotherapy	7.63 (6–8) (n = 4)	6.47 (6–7) (n = 10)	6.60 (6–7) (n = 8)	6.29 (6–7) (n = 9)	6.72 (6–8) (n = 31)
Time interval between RT and salvage therapy, months	56.71 (32.7–60.0) (n = 4)	43.99 (17.1–79.0) (n = 20)	69.14 (61.2–99.6) (n = 6)	58.57 (38–85) (n = 12)	52.5 (17.1–99.6) (n = 42)
Overall percentage relapse, %	46.19 (27–69) (n = 8)	46.08 (11–75) (n = 22)	53.5 (14–79) (n = 17)	44.8 (9.5–81) (n = 14)	49.14 (9.5–81) (n = 61)
Incontinence, %	42.74 (7–50) (n = 7)	50.86 (20–79) (n = 22)	12.34 (0–40) (n = 12)	7.11 (0–29) (n = 8)	30.68 (0–79) (n = 49)
Impotence, %	72 (n = 1)	82.62 (29–100) (n = 12)	59.73 (0–69.2) (n = 5)	81.16 (75–92) (n = 2)	71.78 (0–100) (n = 20)
Fistula, %	2.42 (0–6.4) (n = 7)	1.55 (0–8) (n = 13)	1.78 (0–4) (n = 11)	4.18 (0–12) (n = 6)	1.99 (0–12) (n = 37)
Urethral strictures, %	17.31 (2.5–38.4) (n = 7)	23.41 (0–41) (n = 17)	4.62 (4.6–5.0) (n = 2)	10.07 (4–71) (n = 4)	16.95 (0–71) (n = 30)

PSA = prostate specific antigen; RT = radiotherapy; SBT = salvage brachytherapy; SCT = salvage cryotherapy; SHIFU = salvage high-intensity focused ultrasound; SRP = salvage radical prostatectomy. Values in brackets indicate the range; n = total number of studies; yr = years.

analysis of the nonsurgical salvage modalities did not find one superior to another in this respect (Table 3). These results are consistent with systematic reviews on the topic in which no difference in oncologic outcomes among the different salvage modalities is demonstrated.

3.2. Meta–regression analysis for toxicity outcomes

The bubble plots for urethral stricture and fistula formation showed no visual difference among the four salvage modalities (Fig. 3). For both urethral stricture and fistula formation, two meta–regression analyses were done. The first adjusted for no additional moderators and included 37 and 30 studies for fistula and urethral stricture, respectively. In this first analysis, no significant difference was demonstrated between SRP and the nonsurgical salvage modalities in the rate of fistula formation (Table 3). In addition, the first meta–regression analysis demonstrated no significant difference in the rate of urethral stricture formation between SRP and the nonsurgical salvage modalities (SBT relative to SRP: OR: 0.603 [99% CI, 0.128–2.85]; $p = 0.402$; SCT relative to SRP: OR: 0.219 [99% CI, 0.0309–1.56]; $p = 0.046$; SHIFU relative to SRP: OR: 0.884 [99% CI, 0.293–2.67]; $p = 0.775$). The second meta–regression adjusted for age, length of follow-up, PSA before RT, PSA before salvage therapy, and Gleason score before RT for fistula formation (model 2). Interval between RT and salvage therapy was also included as moderator in the second meta–regression analysis for urethral stricture formation (model 3). Totals of 18 and 13 studies were eligible for inclusion in the second analysis for fistula and urethral stricture, respectively. The residual heterogeneity between studies for both analyses was estimated to be zero. Following adjustment for these variables, the analysis again found no significant difference in the rate of urethral stricture and fistula between SRP and the nonsurgical salvage modalities across the meta–regression analysis. A further analysis focused only on comparing nonsurgical modalities for both of these outcomes similarly found no significant differences (Table 3). These results suggest that none of the salvage options appear to have an advantage in the context of reduced risk of urethral stricture and fistula formation as complications.

3.3. Meta–regression analyses for functional outcomes

The bubble plot for incontinence demonstrated an apparent benefit of all three nonsurgical salvage modalities compared with SRP when considering the rate of incontinence. This was particularly the case for SBT and SCT and less so for SHIFU (Fig. 3).

For incontinence, two meta–regression analyses were undertaken. The first adjusted for no additional moderators and included a total of 49 studies. In this analysis, SBT and SCT had significantly better outcomes in terms of incontinence compared with SRP; however, SHIFU did not demonstrate significantly better incontinence outcomes compared with SRP at the $p < 0.01$ level of significance (Table 3). A further analysis among the nonsurgical salvage modalities found that SBT and SCT had significantly better incontinence outcomes than SHIFU; however, there was no significant difference when comparing SCT and SBT (SBT relative to SHIFU: OR: 0.184 [99% CI, 0.0445–0.761]; $p = 0.002$; SCT relative to SHIFU: OR: 0.233 [99% CI, 0.0727–0.749]; $p = 0.001$; SBT relative to SCT: OR: 0.789 [99% CI, 0.211–2.95]; $p = 0.644$).

The second analysis adjusted for age, length of follow-up, PSA before RT, PSA before salvage therapy, and Gleason score before RT (model 2). A total of 18 studies were eligible for inclusion in this analysis. The residual heterogeneity was calculated to be 65.67%, implying that substantial between-cohort differences remained, even after taking into account surgical modality and other factors. Following adjustment for these variables, evidence showed that all three nonsurgical salvage modalities were significantly superior to SRP in terms of incontinence outcomes (SBT relative to SRP: OR: 0.00595 [99% CI, 0.000245–0.144]; $p < 0.001$; SCT

Table 3 – Meta–regression analysis comparing oncologic, toxicity, and functional outcomes of salvage radical prostatectomy versus nonsurgical modalities

Outcome variable	Model	*n*	SBT relative to SRP	SCT relative to SRP	SHIFU relative to SRP	SBT relative to SHIFU	SCT relative to SHIFU	SBT relative to SCT	I^2 statistic, %	τ^2 (logit-scale)
Overall percentage relapse	1	61	0.980 (0.493–1.95), $p = 0.939$	1.49 (0.816–2.73), $p = 0.087$	1.17 (0.537–2.56), $p = 0.600$	0.836 (0.355–1.97), $p = 0.590$	1.27 (0.577–2.81), $p = 0.430$	0.656 (0.326–1.32), $p = 0.121$	86.16	0.413
	3	17	0.647 (0.243–1.73), $p = 0.254$	0.932 (0.241–3.61), $p = 0.894$	1.21 (0.38–3.86), $p = 0.669$	0.534 (0.205–1.39), $p = 0.092$	0.769 (0.272–2.17), $p = 0.516$	0.694 (0.292–1.65), $p = 0.277$	0	0
Fistula of any kind, %	1	37	2.76 (0.729–10.4), $p = 0.050$	1.14 (0.44–2.95), $p = 0.724$	1.59 (0.567–4.47), $p = 0.247$	1.73 (0.487–6.15), $p = 0.265$	0.716 (0.302–1.70), $p = 0.319$	2.42 (0.726–8.06), $p = 0.059$	0	0
	2	18	4.96 (0.246–100), $p = 0.170$	4.99 (0.175–142), $p = 0.216$	7.18 (0.17–304), $p = 0.175$	0.69 (0.0391–12.2), $p = 0.739$	0.695 (0.12–4.03), $p = 0.593$	0.993 (0.114–8.69), $p = 0.994$	0	0
Urethral strictures, %	1	30	0.603 (0.128–2.85), $p = 0.402$	0.219 (0.0309–1.56), $p = 0.046$	0.884 (0.293–2.67), $p = 0.775$	0.682 (0.126–3.70), $p = 0.560$	0.248 (0.0312–1.97), $p = 0.083$	2.75 (0.266–28.5), $p = 0.264$	82.78	0.671
	3	13	0.296 (0.0169–5.21), $p = 0.275$	0.362 (0.0221–5.9), $p = 0.348$	1.61 (0.165–15.8), $p = 0.589$	0.184 (0.011–3.07), $p = 0.121$	0.224 (0.0327–1.54), $p = 0.045$	0.82 (0.0909–7.39), $p = 0.816$	0	0
Incontinence after salvage therapy, %	1	49	**0.0807** (0.024–0.272), $p < 0.001$	**0.102** (0.0413–0.253), $p < 0.001$	0.438 (0.154–1.25), $p = 0.042$	**0.184** (0.0445–0.761), $p = 0.002$	**0.233** (0.0727–0.749), $p = 0.001$	0.789 (0.211–2.95), $p = 0.644$	86.16	0.697
	2	18	**0.00595** (0.000245–0.144), $p < 0.001$	**0.0142** (0.00209–0.0965) $p < 0.001$	**0.0822** (0.00868–0.778), $p = 0.004$	0.0723 (0.00278–1.88), $p = 0.038$	**0.173** (0.0372–0.804), $p = 0.003$	0.418 (0.0179–9.79), $p = 0.477$	65.67	0.391
Impotence after salvage therapy, %	1	19	0.581 (0.0162–20.9), $p = 0.664$	**0.0567** (0.00428–0.751), $p = 0.005$	–	–	–	10.3 (0.217–484), $p = 0.097$	92.64	2.148

PSA = prostate specific antigen; RT = radiotherapy; SBT = salvage brachytherapy; SCT = salvage cryotherapy; SHIFU = salvage high-intensity focused ultrasound; SRP = salvage radical prostatectomy.
Outcomes are represented as odds ratios and 99% confidence intervals with significant results marked in bold. Model 1 adjusts for no additional moderators; model 2 adjusts for age, length of follow-up, PSA before RT, PSA before salvage therapy, and Gleason score before RT; model 3 is the same as model 2 with the addition of time between RT and salvage therapy and administration of neoadjuvant androgen deprivation therapy.

relative to SRP: OR: 0.0142 [99% CI, 0.00209–0.0965]; $p < 0.001$; SHIFU relative to SRP: OR: 0.0822 [99% CI, 0.00868–0.778]; $p = 0.004$). When considering the nonsurgical salvage modalities alone, SCT was found to be superior to SHIFU. In contrast to the first analysis, there was insufficient evidence that SBT improved incontinence outcomes compared with SHIFU (Table 3). These results suggest that of all modalities, SRP appears to have the highest risk of urinary incontinence. A caveat to this finding is the high residual heterogeneity in our analysis.

Impotence outcomes were the poorest recorded parameter and thus the least reliable in our study. The bubble plots for impotence demonstrated an apparent benefit of SCT over SRP; however, due to the limited available data on impotence outcomes, an adjusted meta–regression model was not possible. Furthermore, SHIFU was not included in this analysis because only one of the included studies on SHIFU reported impotence outcomes; therefore, only SRP, SCT, and SBT were considered in the statistical analysis. A total of 19 studies were included in the analysis. The residual heterogeneity was calculated to be 92.64%, which is very high and suggests that substantial between-study differences in reported impotence rates remained, even after taking into account surgical modality. The only finding was that SCT might have superior outcomes in terms of impotence compared with SRP. No other significant difference was found between modalities, although, as stated, we were unable to compare SHIFU with the other modalities (SBT relative to SRP: OR: 0.581 [99% CI, 0.0162–20.9]; $p = 0.664$; SCT relative to SRP: OR: 0.0567 [99% CI, 0.00428–0.751]; $p = 0.005$; SBT relative to SCT: OR: 10.3 [99% CI, 0.217–484]; $p = 0.097$).

3.4. Discussion

SRP is currently the most widely reported salvage modality in the literature, and there has been resurgence in its popularity with the introduction of robotic assisted prostatectomy [72]. More recently, the advent of new minimally invasive modalities and the concept of focal therapy have also been increasingly applied in the salvage therapy context [73,74]. There is currently, however, no consensus as to which salvage modality should be used or is optimal for radiorecurrent disease. Our meta–regression analysis of the currently available literature showed no significant difference in oncologic outcomes between SRP and the three nonsurgical salvage modalities. Further analyses of the nonsurgical salvage modalities did not find one to be superior to another in this respect. With regard to toxicity outcomes, our results suggest that, again, there is no significant difference in the rate of fistula and urethral stricture formation between SRP and the other nonsurgical salvage modalities. SRP, however, was associated with a greater rate of incontinence in comparison to all three nonsurgical salvage modalities. Of note, despite correction for variables potentially associated with incontinence outcomes, we still identified a degree of residual heterogeneity in the results. This, coupled with the possibility of publication bias, as demonstrated by the funnel plots, urges us to interpret our results with some caution. Nevertheless, our analysis of incontinence outcomes agrees with a systematic review by Parekh et al, who noted that incontinence rates were highest among SRP patients, with a rate of 49.7% across series [6]. Publication bias and heterogeneity were also identified in our analysis of impotence outcomes, primarily due to the limited data reporting. Consequently, we were unable to draw any robust conclusions about a superior modality with regard to this outcome.

This study has a number of inherent limitations. Most important, data were extracted from original published manuscripts rather than from individual patient data, so a degree of reporting bias is inevitable. The studies published in the literature provide no data on patient comorbidities or American Society of Anesthesiologists classifications, and therein lies additional bias from patient selection for the different salvage modalities. This is in addition to publication bias, which was demonstrated by the funnel plots. Not all studies reported patient age, length of follow-up, PSA before salvage therapy, PSA before RT, Gleason score before RT, and time between RT and salvage therapy, which meant that missing data were extensive, and the data available for analysis were often limited. For every outcome, we attempted to adjust for as many confounders possible in the final meta–regression model. As mentioned, our assessment of residual heterogeneity indicated that for incontinence and impotence outcomes, a significant amount of unexplained variability for which we have not been able to account remains in the data. We also note the relatively short follow-up durations of studies reporting outcomes for SCT, SBT, and SHIFU compared with SRP. Studies with longer follow-up duration will be necessary to accurately compare SRP with nonsurgical salvage modalities, particularly in terms of oncologic outcomes. Another limitation is that although all papers included in this analysis reported salvage outcomes of patients with nonmetastatic PCa, some studies did not explicitly state how metastatic disease was excluded; therefore, it is conceivable that some men may not have been staged completely. Finally, the interpretation of biochemical failure in our study depended on the definition used by individual published series and was based on a pragmatic approach due to the diverse interpretation of relapse among the salvage modalities. Although we acknowledge that this is not ideal for our analysis, a unified definition of BCR among the different salvage modalities does not currently exist, in the same way that there is also no uniform definition of BCR for primary treatment modalities. Nevertheless, despite these limitations, our conclusions are in strong agreement with the findings of recently published systematic reviews, which have found no significant differences in oncologic outcomes among the salvage modalities but suggest that SRP may have worse functional outcomes, particularly in rates of incontinence.

4. Conclusions

This study is unique in that it endeavoured to adjust for heterogeneity prior to statistical analysis and is the first to

use a meta–regression model to compare salvage modalities. Our findings in this study reinforce conclusions from systematic reviews suggesting that current salvage modalities appear to have similar oncologic and toxicity outcomes. In particular, SRP does not appear to confer any added benefit in terms of disease control compared with more minimally invasive approaches but instead may potentially increase functional debility. The wide variation in study parameters, outcome measures, and end points reinforces the urgent need for prospective randomised controlled studies directly comparing modalities and for standardised definitions of outcomes and longer follow-up times. Until then, we hope our data and findings will help inform clinicians and patients when deciding among different salvage therapy options.

Author contributions: Vincent J. Gnanapragasam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gnanapragasam, Parker.
Acquisition of data: Philippou, Volanis.
Analysis and interpretation of data: Philippou, Parker, Volanis, Gnanapragasam.
Drafting of the manuscript: Philippou, Parker.
Critical revision of the manuscript for important intellectual content: Gnanapragasam, Parker.
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References

[1] Zaorsky NG, Harrison AS, Trabulsi EJ, et al. Evolution of advanced technologies in prostate cancer radiotherapy. Nat Rev Urol 2013;10:565–79.
[2] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–31.
[3] Pilepich MV, Winterk K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma–long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005;61:1285–90.
[4] Zelefsky MJ, Yamada Y, Fuks Z, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys 2008;71:1028–33.
[5] Punnen S, Cooperberg MR, D'Amico AV, et al. Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. Eur Urol 2013;64:905–15.
[6] Parekh A, Graham PL, Nguyen PL. Cancer control and complications of salvage local therapy after failure of radiotherapy for prostate cancer: a systematic review. Semin Radiat Oncol 2013;23:222–34.
[7] Kimura M, Mouraviev V, Tsivian M, Mayes JM, Satoh T, Polascik TJ. Current salvage methods for recurrent prostate cancer after failure of primary radiotherapy. BJU Int 2010;105:191–201.
[8] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
[9] R Development Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing Web site. http://www.R-project.org. Accessed March 2015.
[10] Song W, Seok Jung U, Suh YS, et al. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after radiotherapy. Korean J Urol 2014;55:91–6.
[11] Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer 2012;118:4148–55.
[12] Rouvière O, Sbihi L, Gelet A, Chapelon JY. Salvage high-intensity focused ultrasound ablation for prostate cancer local recurrence after external-beam radiation therapy: prognostic value of prostate MRI. Clin Radiol 2013;68:661–7.
[13] Crouzet S, Murat F-J, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol 2012;105:198–202.
[14] Berge V, Baco E, Karlsen SJ. A prospective study of salvage high-intensity focused ultrasound for locally radiorecurrent prostate cancer: early results. Scand J Urol Nephrol 2010;44:223–7.
[15] Uchida T, Shoji S, Nakano M, et al. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. BJU Int 2011;107:378–82.
[16] Zacharakis E, Ahmed HU, Ishaq A, et al. The feasibility and safety of high-intensity focused ultrasound as salvage therapy for recurrent prostate cancer following external beam radiotherapy. BJU Int 2008;102:786–92.
[17] Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol 2009;55:640–9.
[18] Kaffenberger SD, Keegan KA, Bansal NK, et al. Salvage robotic assisted laparoscopic radical prostatectomy: a single institution, 5-year experience. J Urol 2013;189:507–13.
[19] Gao X, Wang HF, Fang ZY, Lu X, Wang Y, Sun YH. Salvage radical prostatectomy for radiorecurrent prostate cancer: the Chinese experience. Chin Med J (Engl) 2013;126:4592–3.
[20] Gorin MA, Manoharan M, Shah G, Eldefrawy A, Soloway MS. Salvage open radical prostatectomy after failed radiation therapy: a single center experience. Cent European J Urol 2011;64:144–7.
[21] Ahallal Y, Shariat SF, Chade DC, et al. Pilot study of salvage laparoscopic prostatectomy for the treatment of recurrent prostate cancer. BJU Int 2011;108:724–8.
[22] Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol 2011;60:205–10.
[23] Gontero P, Spahn M, Marchioro G, et al. Salvage radical prostatectomy in nonmetastatic castration-resistant prostate cancer patients who received previous radiotherapy: a feasibility study. Eur Urol 2014;65:254–5.
[24] Corcoran NM, Godoy G, Studd RC, et al. Salvage prostatectomy post-definitive radiation therapy: the Vancouver experience. Can Urol Assoc J 2012;24:1–6.
[25] Heidenreich A, Richter S, Thüer D, Pfister D. Prognostic parameters, complications, and oncologic and functional outcome of salvage

radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. Eur Urol 2010;57:437–45.
[26] Darras J, Joniau S, Van Poppel H. Salvage radical prostatectomy for radiorecurrent prostate cancer: indications and results. Eur J Surg Oncol 2006;32:964–9.
[27] Boris RS, Bhandari A, Krane LS, Eun D, Kaul S, Peabody JO. Salvage robotic-assisted radical prostatectomy: initial results and early report of outcomes. BJU Int 2009;103:952–6.
[28] Gheiler EL, Tefilli MV, Tiguert R, et al. Predictors for maximal outcome in patients undergoing salvage surgery for radio-recurrent prostate cancer. Urology 1998;51:789–95.
[29] Paparel P, Cronin AM, Savage C, Scardino PT, Eastham JA. Oncologic outcome and patterns of recurrence after salvage radical prostatectomy. Eur Urol 2009;55:404–10.
[30] Leonardo C, Simone G, Papalia R, Franco G, Guaglianone S, Gallucci M. Salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. Int J Urol 2009;16:584–6.
[31] Stephenson AJ, Scardino PT, Bianco Jr FJ, DiBlasio CJ, Fearn PA, Eastham JA. Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. J Urol 2004;172:2239–43.
[32] Sanderson KM, Penson DF, Cai J, et al. Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. J Urol 2006;176:2025–31.
[33] Ward JF, Sebo TJ, Blute ML, Zincke H. Salvage surgery for radio-recurrent prostate cancer: contemporary outcomes. J Urol 2005; 173:1156–60.
[34] Amling CL, Lerner SE, Martin SK, Slezak JM, Blute ML, Zincke H. Deoxyribonucleic acid ploidy and serum prostate specific antigen predict outcome following salvage prostatectomy for radiation refractory prostate cancer. J Urol 1999;161:857–63.
[35] Eandi JA, Link BA, Nelson RA, et al. Robotic assisted laparoscopic salvage prostatectomy for radiation resistant prostate cancer. J Urol 2010;183:133–7.
[36] Lerner SE, Blute ML, Zincke H. Critical evaluation of salvage surgery for radio-recurrent/resistant prostate cancer. J Urol 1995;154: 1103–9.
[37] Rogers E, Ohori M, Kassabian VS, Wheeler TM, Scardino PT. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. J Urol 1995;153:104–10.
[38] Seabra D, Faria E, Dauster B, Rodrigues G, Fava G. Critical analysis of salvage radical prostatectomy in the management of radioresistant prostate cancer. Int Braz J Urol 2009;35:43–8.
[39] Van der Poel HG, Beetsma DB, van Boven H, Horenblas S. Perineal salvage prostatectomy for radiation resistant prostate cancer. Eur Urol 2007;51:1565–72.
[40] Vallancien G, Gupta R, Cathelineau X, Baumert H, Rozet F. Initial results of salvage laparoscopic radical prostatectomy after radiation failure. J Urol 2003;170:1838–40.
[41] Gotto GT, Yunis LH, Vora K, Eastham JA, Scardino PT, Rabbani F. Impact of prior prostate radiation on complications after radical prostatectomy. J Urol 2010;184:136–42.
[42] Pisters LL, Leibovici D, Blute M, et al. Locally recurrent prostate cancer after initial radiation therapy: a comparison of salvage radical prostatectomy versus cryotherapy. J Urol 2009;182:517–25, discussion 525–7.
[43] Bahn DK, Lee F, Silverman P, et al. Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. Clin Prostate Cancer 2003;2:111–4.
[44] Donnelly BJ, Saliken JC, Ernst DS, et al. Role of transrectal ultrasound guided salvage cryosurgery for recurrent prostate carcinoma after radiotherapy. Prostate Cancer Prostatic Dis 2005;8:235–42.
[45] De Castro Abreu AL, Bahn D, Leslie S, et al. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU Int 2013;112:298–307.
[46] Pisters LL, Rewcastle JC, Donnelly BJ, Lugnani FM, Katz AE, Jones JS. Salvage prostate cryoablation: initial results from the cryo on-line data registry. J Urol 2008;180:559–63.
[47] Ng CK, Moussa M, Downey DB, Chin JL. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. J Urol 2007;178:1253–7.
[48] Williams AK, Martínez CH, Lu C, Ng CK, Pautler SE, Chin JL. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. Eur Urol 2011;60: 405–10.
[49] Ng CK, Touma NJ, Chalasani V, Moussa M, Downey DB, Chin JL. The pattern of prostate cancer local recurrence after radiation and salvage cryoablation. Can Urol Assoc J 2011;5:E125–8.
[50] Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int 2007;100:760–4.
[51] Eisenberg ML, Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. Urology 2008;72:1315–8.
[52] Wenske S, Quarrier S, Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol 2013;64:1–7.
[53] Ghafar MA, Johnson CW, De La Taille A, et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. J Urol 2001;166: 1333–7.
[54] Spiess PE, Levy DA, Pisters LL, Mouraviev V, Jones JS. Outcomes of salvage prostate cryotherapy stratified by pre-treatment PSA: update from the COLD registry. World J Urol 2013;31:1321–5.
[55] Chin JL, Pautler SE, Mouraviev V, Touma N, Moore K, Downey DB. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. J Urol 2001;165:1937–41.
[56] Cresswell J, Asterling S, Chaudhary M, Sheikh N, Greene D. Third-generation cryotherapy for prostate cancer in the UK: a prospective study of the early outcomes in primary and recurrent disease. BJU Int 2006;97:969–74.
[57] Cheetham P, Truesdale M, Chaudhury S, Wenske S, Hruby GW, Katz A. Long-term cancer-specific and overall survival for men followed more than 10 years after primary and salvage cryoablation of the prostate. J Endourol 2010;24:1123–9.
[58] Yamada Y, Kollmeier MA, Pei X, et al. A phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 2014;13:111–6.
[59] Chen CP, Weinberg V, Shinohara K, et al. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J Radiat Oncol Biol Phys 2013;86: 324–9.
[60] Shimbo M, Inoue K, Koike Y, Katano S, Kawashima K. Salvage I seed implantation for prostate cancer with postradiation local recurrence. Urol Int 2013;90:294–300.
[61] Jo Y, Fujii T, Hara R, et al. Salvage high-dose-rate brachytherapy for local prostate cancer recurrence after radiotherapy - preliminary results. BJU Int 2012;109:835–9.
[62] Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;77: 1338–44.

[63] Moman MR, van der Poel HG, Battermann JJ, Moerland MA, van Vulpen M. Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 2010;9:119–25.

[64] Aaronson DS, Yamasaki I, Gottschalk A, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 2009;104:600–4.

[65] Tharp M, Hardacre M, Bennett R, Jones WT, Stuhldreher D, Vaught J. Prostate high-dose-rate brachytherapy as salvage treatment of local failure after previous external or permanent seed irradiation for prostate cancer. Brachytherapy 2008;7:231–6.

[66] Lee HK, Adams MT, Motta J. Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. Brachytherapy 2008;7:17–21.

[67] Lee B, Shinohara K, Weinberg V, et al. Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. Int J Radiat Oncol Biol Phys 2007;67:1106–12.

[68] Nguyen PL, Chen M-H, D'Amico AV, et al. Magnetic resonance image-guided salvage brachytherapy after radiation in select men who initially presented with favorable-risk prostate cancer: a prospective phase 2 study. Cancer 2007;110:1485–92.

[69] Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. Cancer 2007;110:1405–16.

[70] Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology 1999;53:2–10.

[71] Beyer DC. Permanent brachytherapy as salvage treatment for recurrent prostate cancer. Urology 1999;54:880–3.

[72] Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol 2012;61:961–71.

[73] Kanthabalan A, Arya M, Punwani S, et al. Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer. World J Urol 2013;31:1361–8.

[74] Mouraviev V, Spiess PE, Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. Eur Urol 2012;61:1204–11.