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Review Article

Re-irradiation to the prostate using stereotactic body radiotherapy (SBRT) after initial definitive radiotherapy – A systematic review and *meta*-analysis of recent trials

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ABSTRACT

Background: There is increasing data on re-irradiation to the prostate using stereotactic body radiotherapy (SBRT) after definitive radiotherapy for prostate cancer, with increasing evidence on prostate re-irradiation using a C-arm LINAC or an MR LINAC in recent years. We therefore conducted this systematic review and *meta*-analysis on prostate re-irradiation including studies published from 2020 to 2023, to serve as an update on existing *meta*-analysis.

Methods: We searched the PubMed and Embase databases in October 2023 with queries including combinations of "repeat", "radiotherapy", "prostate", "re-irradiation", "reirradiation", "re treatment", "SBRT", "retreatment". Publication date was set to be from 2020 to 2023. There was no limitation regarding language. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. After data extraction, heterogeneity testing was done by calculating the I^2. A random effects model with a restricted maximum likelihood estimator was used to estimate the combined effect. Funnel plot asymmetry was assessed visually and using Egger's test to estimate the presence of publication and/or small study bias.

Results: 14 publications were included in the systematic review. The rates of acute $\geq$ grade 2 (G2) genitourinary (GU) and gastrointestinal (GI) toxicities reported in the included studies ranged from 0.0-30.0 % and 0.0–25.0 % respectively. For late $\geq$ G2 GU and GI toxicity, the ranges are 4.0–51.8 % and 0.0–25.0 %. The pooled rate of acute GU and GI toxicity $\geq$ G2 were 13 % (95 % CI: 7–18 %) and 2 % (95 % CI: 0–4 %). For late GU and GI toxicity $\geq$ G2 the pooled rates were 25 % (95 % CI: 14–35 %) and 5 % (95 % CI: 1–9 %). The pooled 2-year biochemical recurrence-free survival was 72 % (95 % CI: 64–92 %).

Conclusions: SBRT in the re-irradiation of radiorecurrent prostate cancer is safe and effective. Further prospective data are warranted.

1. Introduction

Radiotherapy is one of the main treatment modalities of prostate cancer treatment for localized disease [1]. However, up to a third of patients develop a recurrence after primary radiotherapy [2,3]. With modern imaging like PSMA-PET/CT, distinguishing between a local and regional recurrence or even metastatic disease is possible with high sensitivity and specificity [4–6]. For patients with an isolated local recurrence, there are different treatment options like salvage surgery but also non-surgical options like high-intensity focused ultrasound (HIFU), cryotherapy and re-irradiation, with both brachytherapy and external beam radiotherapy (EBRT). A *meta*-analysis by Valle et al. found no significant difference for 2- and 5-year recurrence-free survival between radical prostatectomy and SBRT or brachytherapy in radiorecurrent prostate cancer. They did however find significantly lower rates of severe GU toxicity in patients treated with any form of radiotherapy [7].

Regarding EBRT, stereotactic radiotherapy (SBRT) has proven to be feasible with a promising oncological outcome and acceptable toxicity

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rates not only after EBRT but also brachytherapy [8].

Early series on prostate re-irradiation using SBRT date back more than 10 years [9,10]. In 2019, a large Meta-analysis on non-surgical local therapies for recurrent prostate cancer by Ingrosso et al. showed good outcomes for biochemical and local control as well as incontinence rates when using EBRT as salvage therapy. In this analysis only five out of the seven EBRT studies used SBRT for all patients in the re-irradiation setting [8]. There was another systematic review in 2021 by Munoz et al. including studies on prostate re-irradiation using mostly brachytherapy but also EBRT or SBRT until 2019. They found acceptable biochemical failure rates with pooled 2- and 4-year BF rates of 24 % and 35.6 % and pooled high grade (≥G3) late toxicity was 8.7 % [11].

Noticeably, earlier studies on SBRT for radiorecurrent prostate cancer were often done using a Cyberknife treatment machine [9,10,12–16]. In the last years, however, there has been increasing evidence on prostate re-irradiation using a C-arm LINAC or a MR LINAC [17–33] as well as an increase in prospective data [24,26–28,30,33,34].

We therefore conducted this Systematic Review and Meta-Analysis on prostate re-irradiation using SBRT including studies published from 2020 to 2023 to serve as an update of the above-mentioned Meta-analyses.

2. Materials and methods

2.1. Study search and selection process

The PICO criteria (Population, Intervention, Control, Outcome) were used for this Systematic Review with the following criteria: population – patients with radiorecurrent prostate cancer after primary radiotherapy; intervention – SBRT to radiorecurrent cancer in the prostate; control – historical controls from published phase II/III studies; outcome – a) rate of acute and late toxicities after SBRT and b) biochemical control after SBRT [35,36].

This analysis was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [37] using a similar approach as we have conducted before [38]. We searched the Pubmed and Embase databases with the following full-text queries in October 2023: “repeat” AND “radiotherapy” AND “prostate”, “re-irradiation” AND “prostate”, “re irradiation” AND “prostate”, “reirradiation” AND “prostate”, “re treatment” AND “prostate” AND “SBRT”, “retreatment” AND “prostate” AND “SBRT”. As for publication date, we applied a filter for the years 2020–2023. At this stage there was no language limitation. All initially identified records were copied to an Excel sheet (Microsoft Cooperation, Redmond, WA, USA), which was used to automatically identify and remove duplicates. Additional manual removal of duplicates was done were necessary. Out of the initially identified records, only full-text articles in English reporting primary data were included in the further process. The references of review articles, opinions, etc. were checked to identify any further records which had not been identified, yet. For cross reference, also terms like “extreme hypofractionation” or “ultra-hypofractionation” were considered. As the next step, only papers reporting data on prostate re-irradiation using SBRT and re-irradiation to the prostate in at least a part of the cohort were selected. Mixed cohorts including patients receiving re-irradiation to the prostate bed were allowed. However, to identify the final papers included in this analysis, papers without independent reporting of the outcome in patients with SBRT after primary radiotherapy were excluded. The identification and selection process was done twice by two of the co-authors independently (CS and RF). A third co-author served as the final judge as to which papers were included (PW). Quality assessment of the included publications was done using a modified Delphi tool for case-series studies [8,39]. The results are shown in Table S1 in the supplement.

2.2. Data extraction process

The following data were extracted from the included manuscripts: first author, year of publication, journal, study design (retrospective, prospective), study period, overall number of patients included, number of patients included after definite radiotherapy, radiation treatment technique at first irradiation, total treatment dose at first irradiation, treatment machine, diagnosis criteria for recurrence, number of patients with biopsy at recurrence, defined minimum interval between RT courses, median time between RT courses, median follow up, total radiation treatment dose, Isodose line (IDL), target of treatment (entire prostate vs. focal vs. mixed), scheduling (alternating vs. consecutive days vs other), staging at re-irradiation, number of patients receiving ADT at re-irradiation, rates of acute and late toxicities (according to the Radiation Therapy Oncology Group (RTOG) or Common Terminology Criteria for Adverse Events (CTCAE) classification), data on biochemical control, data on target delineation for SBRT. The data were extracted by two independent co-authors (CS and RF) with third co-author serving as the referee in case of potential disagreements (PW).

2.3. Statistical analysis

All statistical analyses were performed using R (v. 4.3.1) and RStudio (v. 2023.09.1 + 494) with the robometa (v. 2.1), metafor (v. 4.4.0) and dpyler (v. 1.1.3) libraries.

Following heterogeneity testing by calculating the I^2, a random effects model with a restricted maximum likelihood estimator [40] was used to estimate the combined effect. Funnel plot asymmetry was assessed visually and using Egger’s test to estimate the presence of publication and/or small study bias [41].

3. Result

3.1. Selected studies

We identified a total of 1294 studies from the initial search of the databases. From these records, 677 duplicates were removed. From the resulting 617 records, 295 records were removed due to no available full text, no record in English language or no recording of primary data being present. Of the remaining 322 records used for screening, another 284 were excluded because no data on re-irradiation after initial treatment for PCA and/or no outcome data was reported, resulting in 38 records. In the final step, 14 papers included data on patients treated with SBRT for radiorecurrent prostate cancer after primary radiotherapy and were selected for the Systematic Review while 24 papers were removed during this step [23–34,42,43]. Fig. 1 shows the consort diagram of the study selection process.

Among the 14 selected papers, there were five prospective analyses, seven were retrospective analyses, one retrospective analysis of a prospective database and one was a small case series. Two publications included patients with re-irradiation to the prostate or the prostate bed and separate reporting for both groups. Table 1 shows an overview of the included publications.

3.2. Target volume and prescription dose

There were differences regarding both, target volume delineation and dose prescription between the included publications. In five publications, focal re-irradiation was done while whole prostate re-irradiation was used in four publications. Another five publications included cohorts with mixed focal or whole prostate re-irradiation. The most common dose concepts were 5 x 6 Gy, 5 x 7 Gy or 6 x 6 Gy given either on alternating or consecutive days. Further details on target delineation and dose prescription can be found in Table S2 in the supplement.

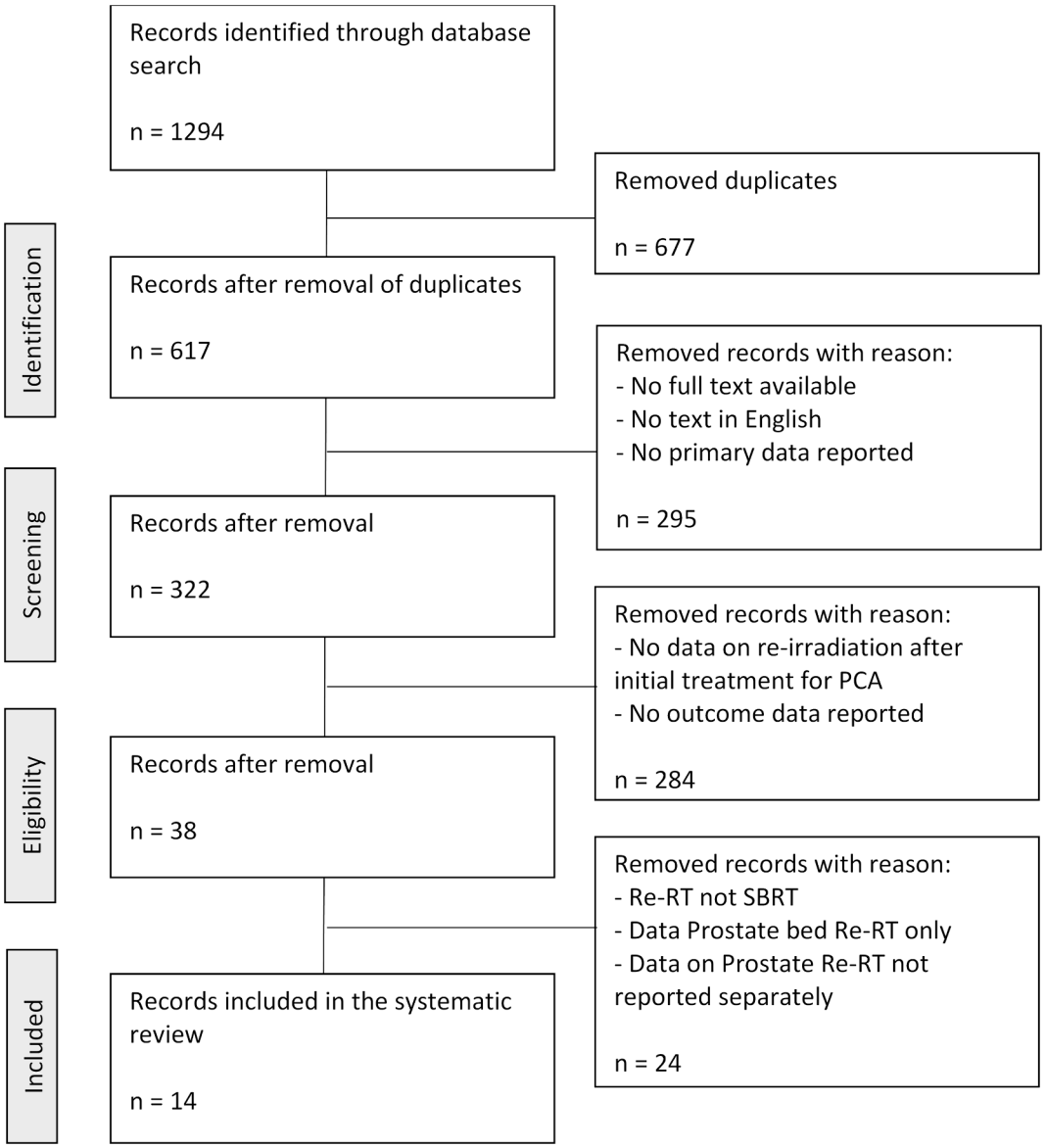

Fig. 1. Paper selection process.

3.3. Acute and late toxicities

Toxicity scoring was done using the RTOG/EORTC toxicity scoring system in two publications [23,29] and the CTCAE scoring system (versions 3 to 5) in nine publications [25–28,31,33,34,42,43]. In two publications, CTCAE was used for acute toxicity while RTOG was used for late toxicity [24,32]. The scoring system was not specified in one publication [30]. Both toxicity systems overall have a moderate inter-scale agreement with more G1-2 toxicities being identified with the CTCAE scoring system [44,45].

The rates of acute ≥ G2 GU and GI toxicities reported in the included studies range from 0.0 to 30.0 % and 0.0 to 25.0 % respectively. The rate of acute G3 GU and GI toxicity range from 0.0 – 3.8 % and 0 – 9.4 %. There were no > G3 acute toxicities reported.

For late ≥ G2 GU and GI toxicity, values ranged from 4.0 – 51.8 % and 0.0 – 25.0 %. The rates for late ≥ G3 toxicity ranged from 0.0 % – 10.7 % for GI and 0.0 % – 23.2 % for GU, with rates of up to 5.4 % of > G3 late GU and GI toxicities being reported.

3.4. Meta-analysis of acute toxicity

While the calculated I^2 statistics for acute GU and GI toxicity ≥ grade 2 did not indicate a high degree of heterogeneity (0 and 39.9 %, respectively), the confidence intervals were wide due to the limited number and size of the included studies (95 % CI: 0 % – 85.4 % and 0 % – 79.7 % respectively).

The pooled rate of acute GU toxicity ≥ grade 2 was 13 % (95 % CI: 7 % – 18 %) and the pooled rate of acute GI toxicity ≥ grade 2 was 2 % (95 % CI: 0 % – 4 %).

The pooled rate of acute GU toxicity ≥ grade 3 was 2 % (95 % CI: 0 % – 3 %) and the pooled rate of acute GI toxicity ≥ grade 3 was 2 % (95 % CI: 0 % – 3 %).

Egger's test found significant funnel plot asymmetry for both acute GU toxicity greater than or equal to grade 2 ($p = 0.007$) and acute GI toxicity greater than or equal to grade 2 ($p = 0.02$) with larger studies reporting lower rates of toxicity.

The Forest plots for acute ≥ grade 2 toxicity are shown in Fig. 2 a) and b) and for acute ≥ grade 3 toxicity in Fig. 2 c) and d). The associated Funnel plots as Figures S1 a) – d) in the supplement.

Table 1
Details of included studies.

Author/ year	Design	No of patients (total)	No of patients (after def. RT)	Type of initial RT	Total Dose initial RT	Treatment machine (Re-RT)	Years treated (Re-RT)	Diagnosis of Recurrence	Patients with ADT at Re-RT (%)	No of patients with Re-Biopsy	Minimum intervall from 1st RT	Median Time between RT	Median FU after Re-RT (months)
Allali et al./ 2023	R	41	41	EBRT or BT	EBRT 65–80 Gy	CK	2016–2021	Phoenix criteria or PSA kinetics or visualization via PET	not reported	not reported	not reported	8.1 years (range, 1.9—–20.1)	35
Matrone et al./2021	R	44	44	EBRT	BED 177.3 Gy (range, 151.7–186.7)	LINAC	2012–2019	Phoenix criteria	27.3	5	12 months	60 months (range, 16.9–615.5)	25.4
Greco et al./ 2022	R (P)	30	30	EBRT and/or BT	74 Gy (range, 71.6–74)	LINAC	2013–2020	Phoenix criteria	53.3	not reported	24 months	55.8 months (IQR 53.0–83.5)	44
Bergamin et al./2020	P	25	25	EBRT and/or BT	not reported	LINAC	2016–2019	Phoenix criteria	0.0	25	48 months	8.3 years (range, 4.5–13.6)	25
Lewin et al./ 2021	P	30	30	EBRT or BT	EBRT 80 Gy (range, 74–82), LDR 145 Gy	LINAC	2015–2018	Phoenix criteria	50.0	18	not reported	9 years (range 2–20 years)	28
Pasquier et al./2023	P	21	21	EBRT	74 Gy (range, 74–76)	CK or LINAC	2018–2021	Phoenix criteria	0.0	21	24 months	8.6 years (IQR:6.3–10.7)	12.3
Cozzi et al./ 2023	R	20	20	EBRT	70 Gy (35–78.2 Gy)	LINAC	2019–2022	Phoenix criteria	65.0	not reported	not reported	73.8 months (range, 21–146)	26.7
Ozyigit et al./ 2020	R	11	11	EBRT	70–76 Gy	CK or LINAC	2016–2019	Phoenix criteria	36.4	not reported	18 months	63 months (range, 23–178)	19
Cuccia et al./ 2022	P	22	12	EBRT and BT	not reported	MR LINAC	2019–2021	Phoenix criteria	18.2	not reported	12 months	72 months (range, 12–1460)	8
Montalvo et al./2022	C	5	4	EBRT or LDR BT	EBRT 79.2 Gy	MR LINAC	not reported	Phoenix criteria	60.0	3	not reported	range 5—–22 years	not reported
Augugliaro et al./2021	R	26	26	EBRT	EQD2 (1.5) 78 Gy (range, 60.5–85)	CK or LINAC	2012–2016	Phoenix criteria	84.6	not reported	not reported	5.6 years (range, 2.3–14.1)	47.7
Miszczyk et al./2023	R	56	56	EBRT and/or BT	not reported	CK	2012–2020	not specified	73.2	42	not reported	87.5 months (range, 60.3–124.5)	38.6
Fuller et al./ 2020	P	50	50	EBRT or BT	75.6 Gy (range, 35–145)	CK	2009–2018	Biopsy proven	14.0	not reported	24 months	98 months (range, 32–241)	44
Nikitas et al./ 2023	R	11	11	LDR Brachy	not reported	LINAC or MR LINAC	2018–2021	not specified	36.4	2	not reported	7 years (range, 2–11)	37.9

FU – Follow up, R – retrospective, P- prospective, R (P) – retrospective analysis of prospective database, C – case report, EBRT – external beam radiotherapy, BT – brachytherapy, HDR – high-dose-rate, LDR – low-dose-rate, CK – Cyberknife, IQR – interquartile range.

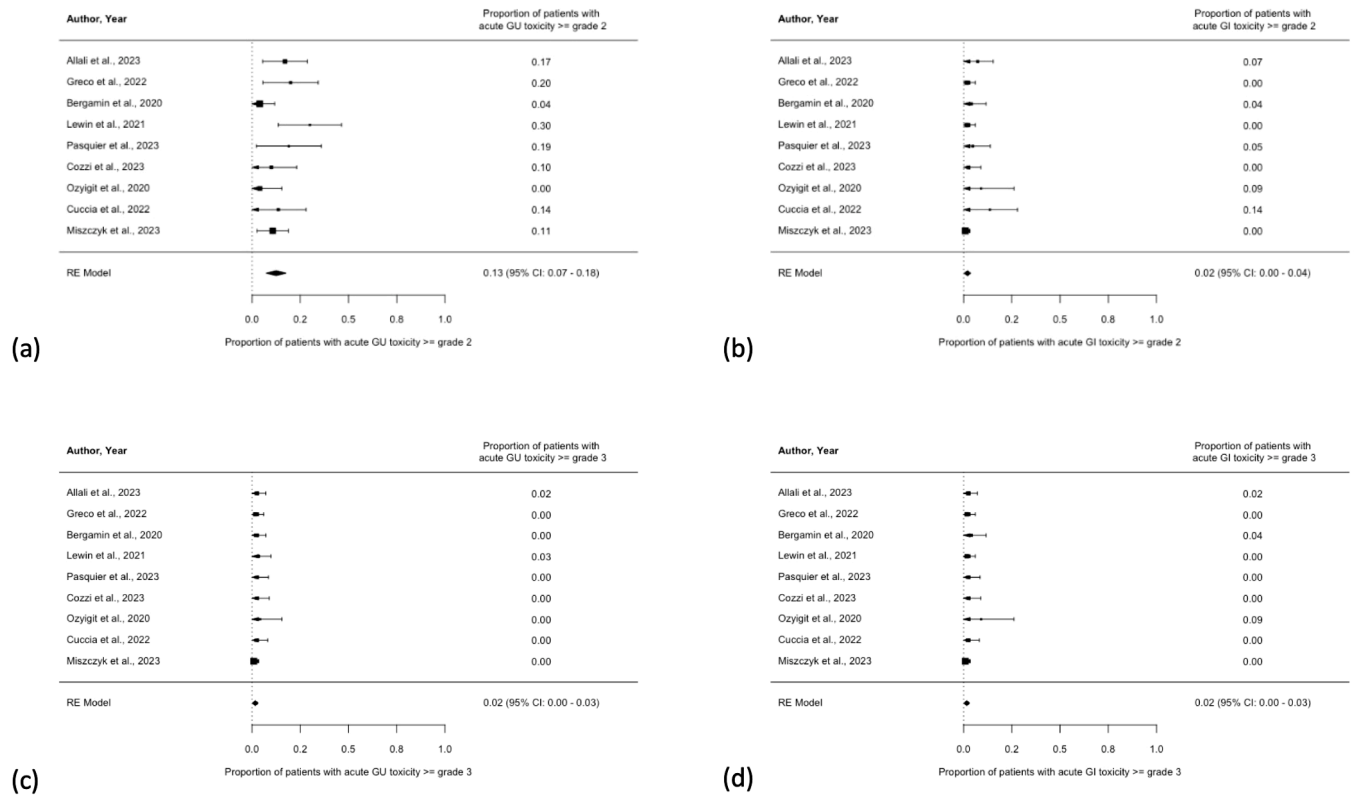

Fig. 2. Forest Plots of the included publications – a) and b) acute >=G2 GU (a) and GI (b) toxicity, c) and d) acute >=G3 GU (c) and GI (d) toxicity.

3.5. Meta-analysis of late toxicity

The calculated I^2 statistics for late GU and GI toxicity greater ≥ grade 2 were 77.9 % (95 % CI: 49.5 % – 94.1 %) and 68.4 % (95 % CI: 19.2 % – 94.9 %), respectively.

The pooled rate of late GU toxicity ≥ grade 2 was 25 % (95 % CI: 14 % – 35 %), and the pooled rate of late GI toxicity ≥ grade 2 was 5 % (95 % CI: 1 % – 9 %).

The pooled rate of late GU toxicity ≥ grade 3 was 4 % (95 % CI: 2 % – 6 %), and the pooled rate of late GI toxicity ≥ grade 3 was 2 % (95 % CI: 0 % – 3 %).

Egger's test did not find significant funnel plot asymmetry for late GU toxicity greater than or equal to grade 2 ($p = 0.097$). However, there was significant funnel plot asymmetry for late GU toxicity greater than or equal to grade 2 ($p = 0.0007$) with larger studies reporting lower rates of toxicity. The Forest plots for ≥ grade 2 late toxicity are shown as Fig. 3 a) and b) and those for ≥ grade 3 late toxicities as Fig. 3 c) and d). The respective Funnel plots can be found as Figures S2 a) and d) in the supplement.

Only few studies reported on factors associated with the occurrence of toxicity. Miszczyk et al. found an association with G3 + toxicity for PTV size, the extent of salvage radiotherapy (focal vs. whole prostate) and the use of ADT in the univariate analysis of which PTV size and ADT remained significant in the multivariate analysis [43]. For G3 + GU toxicity, Fuller et al found a significant difference for patients receiving EBRT as first radiotherapy versus more intensive first therapies [34]. Greco et al. reported an association of G2 GU toxicity and gland volume [27] in univariate analysis.

3.6. Biochemical control

Data on 2-year BRFS was reported in 10 studies [23–25,27,29,31,32,34,42,43]. 2-year BRFS in those studies ranged from 48 % to 91 %. Median follow-up in those studies ranged from 19 months to 47.7 months.

3.7. Meta-analysis of biochemical control

The calculated I^2 statistic for 2-year BRFS was 65.5 % (95 % CI: 26.3 % – 91.8 %). The pooled 2-year BRFS was 72 % (95 % CI: 64 % – 92 %). Egger's test did not find significant funnel plot asymmetry ($p = 0.135$). Fig. 4 shows the Forest plot for the 2-year bRFS and the Funnel Plot is shown as Figure S3 in the supplement.

Several factors associated with the biochemical outcome were reported in the included studies. Matrone et al. reported favourable outcomes in patients with a longer interval between the RT courses, a higher BED at first RT and the use of ADT at re-irradiation. Greco et al. identified the treatment modality at first RT (EBRT vs. brachytherapy) as a significant factor [27]. Other factors that were associated with biochemical outcome were ISUP risk group at first RT and pre-salvage PSA level [34,43].

However, Ozyigit et al. found no association for the use of ADT, primary RT dose, pre-salvage PSA or treatment machine and Greco et al. found no association for the interval between the RT courses, NCCN risk group at first RT or the use of ADT at re-irradiation [27,32].

4. Discussion

Up to a third of patients who receive definitive radiotherapy for prostate cancer will develop a recurrence [2,3].

PSA monitoring is used for surveillance after radiotherapy. A benign PSA bounce can occur in a proportion of patients in the first few years after definitive radiotherapy, and may be associated with favourable outcomes [46–48]. Biochemical failure after radiotherapy was historically variably defined. The 2005 RTOG-ASTRO Conference sought to develop a consensus definition that better correlated with outcomes, and could also be used for patients who received hormone therapy with radiotherapy [49]. From this conference, biochemical failure was

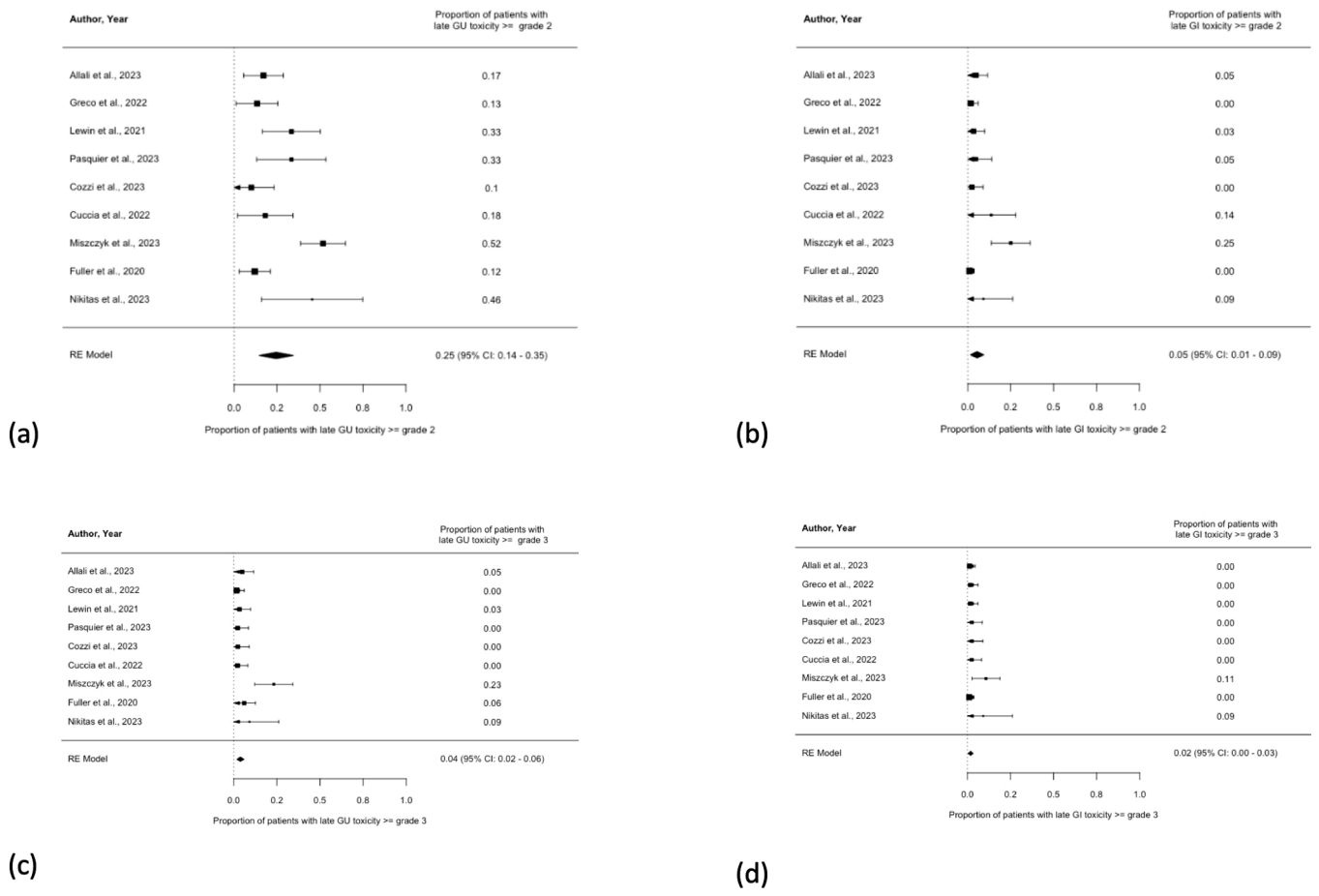

Fig. 3. Forest Plots of the included publications – a) and b) late >=G2 GU (a) and GI (b) toxicity, c) and d) late >=G3 GU (c) and GI (d) toxicity.

defined as PSA rise of more than 2 ng/ml above nadir, which remains in use today and is otherwise known as the "Phoenix" definition.

At time of biochemical failure, PSMA PET-CT and MRI can be used to assess extent of local, nodal and metastatic disease, and to define sites of intraprostatic recurrence [4,50–52]. Biopsies should be strongly considered to confirm and characterise the recurrence [53,54]. Around 10 % of patients will develop localized intraprostatic recurrence after radiotherapy [3,55]. A *meta*-analysis by Valle et al reviewed the outcomes of the surgical and non-surgical local salvage options used in this cohort [7]. The *meta*-analysis found no difference in 2-year or 5-year recurrence-free survival for radical salvage prostatectomy, as compared to SBRT, LDR brachytherapy or HDR brachytherapy. However they did find significantly lower rates of severe (defined as ≥ G3) GU toxicity for any type of radiotherapy, as well as significantly lower rates of severe GI toxicity for HDR brachytherapy [7].

Non-surgical approaches for radio recurrent prostate cancer include high-intensity focused ultrasound (HIFU), cryotherapy, normofractionated external beam radiotherapy, SBRT, and HDR or LDR brachytherapy [8]. Both brachytherapy and external beam radiotherapy were found to be good treatment options for locally recurrent disease. The latter is nowadays mostly done using SBRT, which next to technical advantages might also have biological advantages due to the low alpha/beta value of prostate cancer of approximately 1.5 [56,57].

SBRT as salvage therapy for radiorecurrent prostate cancer has been used for more than 15 years [9,10,12]. Early case series were usually done with a Cyberknife treatment machine whereas newer studies included cohorts treated with C-arm Linacs or MR Linacs [10,12–17,19,22–34,42,43,58–64]. Of the 14 studies included in this *meta*-analysis, only three included patients that were exclusively treated on a Cyberknife [34,42,43].

There is no consensus on target delineation, fractionation or scheduling (alternating vs. consecutive days). Regarding treatment dose, common fractionation schemes used in the included studies are 5 x 6 – 7.25 Gy or 6 x 6 Gy. With an estimated alpha/beta value of 1.5 for prostate cancer this results in EQD2 doses of 64 – 90 $Gy_{1.5}$ and 38 – 49 Gy_3 for organs at risk with an estimated alpha/beta value of three. In nine of the included studies, multiple dose fractionation schemes were used which further limits the possibility of making statements on the dose–response relationship. Target delineation in the included studies was also heterogeneous ranging from focal to whole prostate re-irradiation, even including the seminal vesicles where necessary.

Regarding toxicity, there is overall a large range of the reported acute and late GU and GI toxicity. The reported acute ≥ G2 GU and GI toxicities range from 0 – 30 % and 0 – 25 %, ≥G3 from 0.0 – 3.8 % and 0 – 9.4 %. This is well within the range of older data on acute toxicity after re-irradiation [9,10,13–16,19,63,65,66]. In the *meta*-analysis, it is evident that despite the outliers with high toxicity range, the overall reported ≥ G2 acute toxicity is rather low with 13 % for GU (95 % CI 7 – 18 %) for GU and 2 % (95 % CI 0 – 4 %) for GI. The same can be stated for ≥ G3 toxicity with pooled toxicity rates in the low single digits.

For late toxicity the overall range of ≥ G2 toxicity is large with 4 – 51.8 % for GU and 0 – 25 % for GI. A smaller but still considerable range can be seen for ≥ G3 toxicity with 0 – 23.2 % for GU and 0 – 10.7 % for GI. However, since most studies reported low rates of ≥ G3 toxicity, the resulting values in the *meta*-analysis are also low with 2 % for acute GU and GI, 4 % for late GU and 2 % for late GI. This is again overall consistent with older data on late toxicity [9,10,13–16,19,63,65,66].

It has to be noted that only one included publication reported data on a brachytherapy-only cohort as first RT [31]. Eight studies included mixed cohorts but usually with a low amount of brachytherapy patients

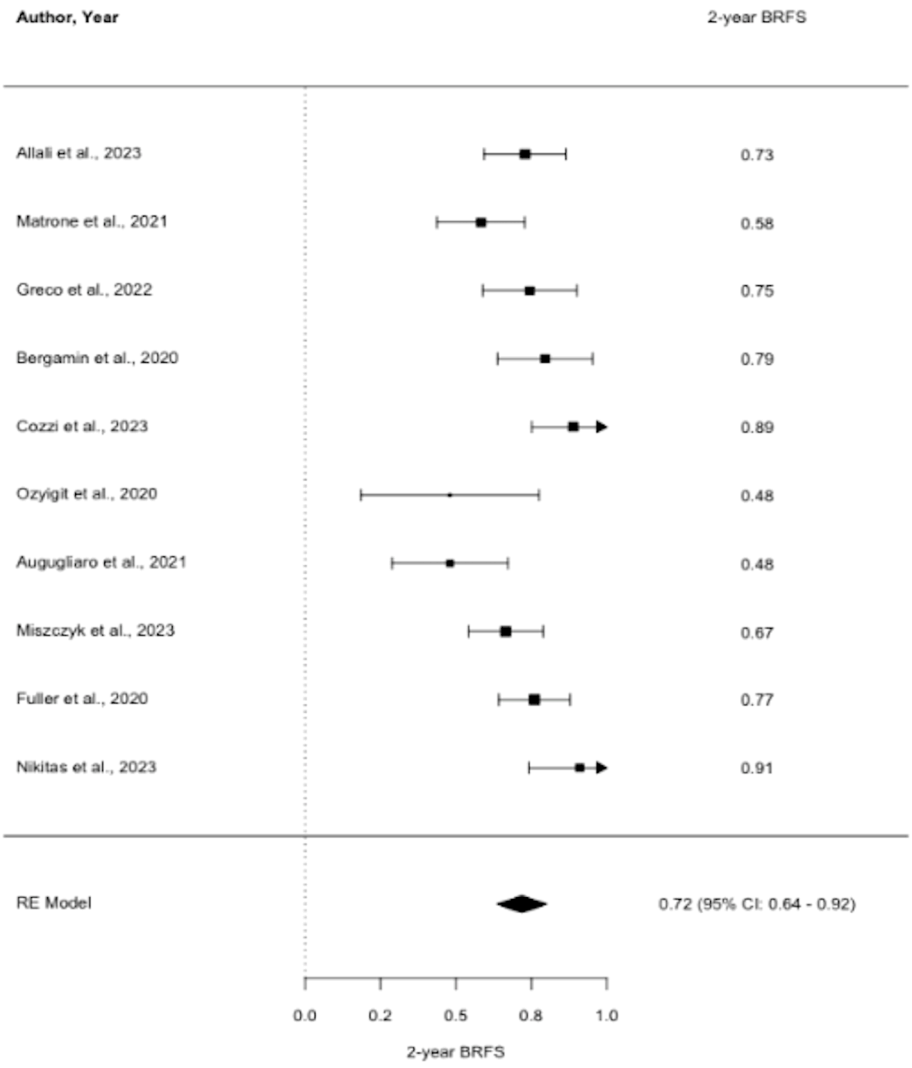

Fig. 4. Forest plot for 2-year bRFS.

(<20 %) except for Greco et al. where 44 % of patients had initial brachytherapy (37 % LDR and 7 % EBRT with LDR boost) [24,26–28,30,31,34,42,43]. There is another study on mildly hypofractionated external re-irradiation after LDR showing low toxicity rates with 30 % late G1 toxicity [67]. More intensive first treatment was a risk factor for higher G3 + toxicity reported by Fuller et al. However, next to the 5 patients with initial brachytherapy this group also included one patient with RP and one patient with SBRT [34]. Contrary to this, Pasquier et al. found no association of toxicity and kind of first treatment (EBRT vs. brachytherapy) [68].

There however seems to be higher reported toxicity rates for whole gland re-irradiation versus focal irradiation, especially for GI (0——4.7 % for focal vs. 0 – 25 % for whole gland). PTV size was one of the factors associated with the risk of G3 + toxicity reported by Miszczyk et al. [43]. However, a large retrospective analysis of the GETUG including 100 patients found no differences in toxicity depending on the treated volume (whole-prostate vs partial SBRT) or PTV [68].

As for the efficacy of SBRT in the re-irradiation setting of radiorecurrent prostate cancer, the 2-year bRFS rates reported in the ten studies included in the *meta*-analysis range from 48 % to 91 % [23–25,27,29,31,32,34,42,43]. In the random effects model the 2-year bRFS was 72 % (95 % CI 64 – 92 %). This seems to be overall consistent with older data [10,13–15,65,68].

It has to be noted that two studies included in the *meta*-analysis included node-positive or oligometastatic patients at re-irradiation. Greco et al included 13 % node-positive and 10 % oligometastatic patients and Miszczyk et al. even 19.6 % oligometastatic patients. However, the reported 2-year bRFS of 74.5 % and 66.5 % were not the lowest of all included studies [27,43]. Also, Lewin et al. included node-positive (23.3 %) and oligometastatic (3.3 %) patients but reported no 2-year bRFS [28].

The use of ADT was very heterogeneous within the included publications. The range of patients that received ADT at the time of reirradiation range from 0.0 % to 84.6 %. Given the relatively short follow-up after reirradiation in some of the included studies this may influence oncological outcome. Generally the role of ADT in the setting of prostate reirradiation remains unclear. An AIRO survey conducted by Zerini et al. in 2020 79 % of participants stated that it is case-by-case analysis [65]. However in the ESTRO ACROP Delphi consensus by Jereczek-Fossa et al. a major agreement was reached for the recommendation that ADT should not be delivered concomitantly with reirradiation [69]. One argument they stated is that reirradiation is often used to defer ADT and associated detrimental effects on QoL.

Although this systematic review and *meta*-analysis includes five prospective studies, more prospective data will be important. There results of several trials are currently awaited. This includes the phase II results of the GETUG AFU 31 trial, with only the phase I results included in this *meta*-analysis [33,70]. Also the follow-up after reirradiation of the included studies in still rather short ranging from 8 – 47.7 months. While a longer follow-up is certainly warranted regarding oncological outcome

and late toxicity, the median follow-up of the included studies is overall equal or even longer compared to that in older studies.

Due to the overall low number of studies and the heterogeneity of the included cohorts a comparison between treatment machines is not feasible. The comparison is further complicated by the fact that especially older CK data was often collected retrospectively whereas most of the C-arm LINAC or MR Linac publications included in this *meta*-analysis were done prospectively. Still, a comparison of treatment machines to determine the role of adaptive treatments, especially in the light of the increasing implementation and utilization of different adaptive treatment delivery systems would be warranted in the future.

Also comparing the results of this Meta-Analysis with that of former ones is somewhat difficult. Although both included some studies reporting on outcomes of Re-RT using SBRT, the individual focus was different. Ingrosso et al. reported on several non-surgical retreatment options for radiorecurrent prostate cancer [8]. The included reirradiation studies included both SBRT and EBRT cohorts with very few studies included in the *meta*-analysis of the individual toxicities like obstruction. Munoz et al included 38 publications using brachytherapy or SBRT for reirradiation [11]. They did a subanalysis for publications using SBRT after EBRT. However, some of the included publications used cohorts of patients that received either definite EBRT or salvage EBRT after radical prostatectomy as first radiation treatment.

Additionally, a randomized comparison of salvage options in the radiorecurrent setting would be interesting, for example between brachytherapy and SBRT.

5. Conclusion

SBRT in the re-irradiation of radiorecurrent prostate cancer is overall safe and effective. Open questions remain, e.g. regarding optimal target delineation and the use of ADT. Especially regarding the potential benefit of of adaptive treatment options like MR Linac, long-term outcome data is warranted.

CRediT authorship contribution statement

Christina Schröder: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Hongjian Tang:** Data curation, Writing – original draft, Writing – review & editing. **Bianca Lenffer:** Writing – review & editing. **André Buchali:** Writing – review & editing. **Daniel Rudolf Zwahlen:** Writing – review & editing, Supervision. **Robert Förster:** Writing – review & editing, Supervision. **Paul Windisch:** Formal analysis, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100806.

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