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Systematic or Meta-analysis Studies

Outcomes and toxicities of re-irradiation for prostate cancer: A systematic review on behalf of the Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

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ABSTRACT

Aims: The best therapeutic approach for local relapses of previously irradiated prostate cancer (PC) is still not defined. Re-irradiation (Re-I) could offer a chance of cure for highly selected patients, although high quality evidences are lacking. The aim of our study is to provide a literature review on efficacy and safety of Re-I.
Methods: Only studies where Re-I field overlaps with previous radiotherapy were considered. To determine 2 and 4 years overall mortality (OM), 2 and 4 years biochemical failure (BF) and pooled acute and late G $\geq$ 3 toxicities rate, a meta-analysis over single arm study was performed.
Results: Thirty-eight studies with 1194 patients were included. Median follow-up from Re-I was 30 months (10–94 months). Brachytherapy (BRT) was the most used Re-I technique (27 studies), followed by Stereotactic Body Radiotherapy (SBRT) (9) and External Beam Radiation Therapy (EBRT) (2). Re-I prescription doses ranged from 19 Gy in single HDR fraction to 145 Gy (interstitial BRT). The pooled 2 and 4 years OM rates were 2.1% (95%CI:1.1–3.7%, P < 0.001) and 12.5% (95%CI:8.1–19.5%; P < 0.001). The pooled 2 years BF rate was 24% (95% CI: 19.1–30.2%, P < 0.001). The pooled 4 years BF was 35.6% (95% CI: 28.7–44.3%, P < 0.001). The pooled result of G $\geq$ 3 acute toxicity was 1.4% (95%CI: 0.7–3%, *P* < 0.001). One hundred and three G $\geq$ 3 late adverse events were reported, with a pooled result of G $\geq$ 3 late toxicity of 8.7% (95%CI: 5.8–13%, *P* < 0.001).
Conclusions: Re-I of local failures from PC showed promising OM and biochemical control rates with a safe toxicity profile.

Introduction

Prostate cancer (PC) still keeps the higher incidence in men among cancers type and remains the second cause of death, even if a general reduction in rate and mortality was experienced in the last decades, mostly due to development in earlier diagnosis and treatment [1].

Nowadays, among treatment modalities, radiation therapy (RT) plays an important role in many different settings of PC, as curative,

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adjuvant or either palliative [2]. The introduction of even more advanced technological modalities and techniques, as Intensity-Modulated radiotherapy (IMRT), Stereotactic Body Radiotherapy (SBRT) and Image-Guided Radiotherapy (IGRT), has allowed a dose escalation on tumours with limited toxicities on adjacent organ at risks (OARs) [2,3].

Despite these more accurate loco-regional treatments, failure rate remains still high, with one third of patients experimenting biochemical failure and clinical relapse occurring in 30–47% of previously irradiated patients and in 38–54% post-prostatectomy [2]. In this clinical scenario of local failure after a prior RT, the optimal management is not still standardized. Many options could be used, as salvage radical prostatectomy in selected cases [4], but with possible high local complication rate. Other local therapies, as cryosurgery or high-intensity focused ultrasound, could be considered, even if not reaching a diffuse consensus, because of the possible adverse effects, including fistula or rectal damage, of these not so rarely therapies [5]. To date, Androgen Deprivation Therapy (ADT) is the preferred treatment choice [6], although with side effects and probable development of ADT resistant cancer, despite low effects on local disease [7,8].

Beyond these treatment modalities, re-irradiation (Re-I) after a local failure could be a possibility.

The critical issue in Re-I is the tolerability of previously irradiated OARs that could preclude a dose with curative intent [9]. However, with the implementation of modern RT modalities, the challenge of Re-I has been considered more feasible in clinical practice, for prostate as other tumours [10]. In particular, IGRT combining with High Dose Rate-BRT (HDR-BRT) and SBRT, allow a higher sparing of OARs, with their shaper gradient of dose, still maintaining ablative dose, with promising results [7,11].

The choice of the more appropriate RT technique is currently not supported by solid literature evidences. Then, the aim of this study is to provide a literature review and a systematic review on Re-I for PC local relapses in order to evaluate efficacy and safety of this treatment strategy.

Methods

Selection of studies

A search of the literature was performed on MEDLINE, EMBASE, OVID, and Cochrane database from the time to inception to 2019. The search strategy included terms related to Re-I and prostate malignancies. “Radiotherapy”, “radiation therapy”, “re-irradiation”, “reirradiation”, “prostatic cancer” and “prostate cancer” were used as terms of search. The computer search was supplemented with hand searches of reference lists for all available review articles, primary studies, meetings abstracts and bibliographies of books to identify other studies not found in the computer search. The present systematic review was performed by following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

Criteria for inclusion and exclusion

Studies included were prospective or retrospective, analysing more than 10 patients. Only studies analyzing outcomes of patients re-treated where Re-I involved overlap with previous radiotherapy were taken into consideration. Abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, case reports, studies lacking control groups, repetitive data, non-English language papers and animal studies were excluded. The final inclusion of articles was determined by consensus between 2 authors (FF and LB), discrepancies among reviewers were infrequent (overall inter-observer variations $<10\%$) and were solved by discussion.

Review of the trials

Studies were first reviewed using a list of predefined, pertinent issues concerning the characteristics of patients and treatments. Methodological quality of studies was assessed with a checklist for quality appraisal of case series studies produced by Institute of Health Economics (IHE) and modified to improve applicability [13]. The following items were evaluated for each study: a clearly stated aim, prospective data collection, multicenter study, consecutive patients, described characteristics of patients, clearly stated eligibility conclusions of the study supported by the results.

Overall mortality (OM) and biochemical failure (BF) were analyzed and to improve the comparability of the different Re-I studies and to assess the relationship between Re-I and 2 and 4 year OM and 2 and 4 year BF, patients’ classification in low, intermediate and high risk was extrapolated according to D’Amico *et al.* criteria [14].

Aiming to evaluate toxicity, we have hypothesized that OARs close to recurrences received a cumulative dose calculated for acute and late responding tissue. To determine the pooled $G \geq 3$ toxicities rate, 2 and 4 years OM, 2 and 4 years BF, a meta-analysis over single arm study was performed. We calculated the estimated population proportion of toxicity acute and late grade ≥ 3, 2 and 4 years OM and 2 and 4 years BF with 95% CI for every separate study [15]. Pooled effect size aided the general evaluation of Re-I risk and effect. Heterogeneity across studies was examined by the Cochrane Q chi-square test and the I2 statistic. Studies with an I2 statistic of 25–50%, 50–75%, and $>75\%$ were deemed to have low, moderate, and high heterogeneity, respectively [16]. We used random-effects models because there was great subjectivity given the lack of related control groups in the no comparative studies, and a tendency toward high heterogeneity.

To detect and evaluate clinically significant heterogeneity of OM, BF and toxicity, we performed several sensitivity analyses in order to identify potential differences in treatment across the studies. First, we estimated whether the type of study (prospective vs retrospective) or publication data (before or after 2015) could influence the heterogeneity of this systematic review. Secondly, we performed a sensitivity analysis by excluding those studies with median follow-up ≤ 24 months. The third factor evaluated was the influence of different combination of irradiation technique (previous RT and Re-I). Finally, we analyzed the influence of combination of Re-I and suppressive hormonal therapy.

Study-level characteristics (such as median patients age, number of low risk patients, of intermediate risk and of high risk patients, number of patient treated with hormone-suppressive treatments) were prespecified for assessment of heterogeneity, which was done using regression analysis [17].

Results

The search of the literature yielded 73 citations. Of these, 38 studies met the inclusion criteria. The main features of the studies included in this systematic review are shown in Table 1. These studies were published between 2003 and 2019, in 10 countries. Eight studies were prospective trials [3,18–24]. The analyzed population of each study varied greatly, ranging from 11 [25,26] to 115 [27] patients. Overall, the 38 studies included 1194 patients who were re-irradiated within the pelvis for PC recurrences. Treatment intent (i.e. palliation versus cure) was generally not well described. Median follow-up from Re-I in studies specifically examining re-irradiated patients was 30 months, ranged from 10 to 94 months, with only two studies [22,28] having 10 months median follow-up.

Site, dose and interval of radiotherapy

Pelvic Re-I was reported for local disease recurrence and/or lymph node disease. In the analyzed studies, the degree of overlap between the previous RT and Re-I fields was not clearly described. On the other

Table 1
Patients characteristics, doses and re-irradiation technique of the studies included.

Authors and years	Study design	N° pts	P-RT (Gy): median dose (range)	Median Follow-up: months (range)	Median time elapsed since previous RT: months (range)	Re-I technique	Re-I dose (Gy): median dose (range)
Koutrouvelis et al. 2003	R	31	103Pd: 120; 125I: 144	30	30 (12–87)	LDR-BRT	103Pd:100–120; 125I: 100–144
Wong et al. 2006	P	17	68 (64.8–70.2)	44 (13–77)	–	BRT: 125I BRT:103Pd	126
Allen et al. 2007	R	12	70 (59.4–70.2)	45 (11–64)	69.12(39.96–109.2)	BRT	97 Gy (90–113)
Nguyen et al. 2007	P	25	EBRT: 66–70.2; BRT: 137	47 (14–75)	62.4 (30–153.6)	BRT: 125I	137
Lee et al. 2008	R	21	66.6 (61.2–70.2)	36	85 ± 30.1	BRT: 103Pd	90 (70–100)
Aaronson et al. 2009	R	24	66–70.2	30 (13–65)	49 (26–109)	BRT: 125I BRT:103Pd	72 (65–80)
Lyczek et al. 2009	R	115	52 (30–76)BRT: 27	–	49.5 (20–220)	HDR BRT	30
Burri et al. 2010	R	42	128.8	86	62	BRT	122
Moman et al. 2010	R	31	–	29	60	BRT	145
Chen et al. 2012	R	52	–	59.6 (5.9–154.7)	51.6 (10.8–135.6)	HDR-BRT	36
Hsu et al. 2012	R	15	125I: 144 (144–160); 103Pd: 90–100. EBRT: 45	23.3 (8–88)	69 (28–132)	BRT: 125I BRT:103Pd EBRT	125I: 144 (108–144); 103Pd: 125. EBRT: 40
Jo et al. 2012	R	11	EBRT 36.8 + HDR 24; HDR-BT: 37.5 Proton: 74	29 (18–41)	41.5	HDR-BRT	22
Lahmer et al. 2013	P	18	69.3 (49.9–73.8)	21 (8–77)	64.5 (27–271)	PDR-BRT, Ir192	60
Peters et al. 2014	R	20	I125: 145 EBRT: 70 IMRT: 76	36 (10–45)	94	BRT: 125I	144
Kukielka et al. 2014	R	25	74.1	13 (4–48)	43 (17–122)	BRT: 192Ir	60
Yamada et al. 2014	P	42	70	36	73	HDR-BRT	32
Vargas et al. 2014	R	60	68.4	60	150	BRT	100
Rose et al. 2015	R	18	70.5 (66–78)	31.5 (12–104)	93.6 (42–204)	BRT: 125I	137 (130–144)
Detti et al. 2015	P	16	–	10	126	SBRT	30
Shimbo et al. 2015	R	15	70	33	45.5	BRT	144
Fuller et al. 2015	P	29	73.8 (64.8–81)	24 (3–60)	88 (32–200)	SBRT (Cyberknife)	34
Wojcieszek et al. 2016	R	83	74 (52–76)	41 (11–76)	67 (22–124)	HDR BRT: 192Ir	30
Lacy et al. 2016	R	21	144	49 (10–149)	45 (4–287)	BRT: 125I	140 (108–144)
Rutenberg et al. 2016	R	11	145	26.5 (1–53.6)	49 (13–136)	IMRT/3D CRT	70.2 (64.8–75.6)
Janoray et al. 2016	R	21	71.1 (45–76.5)	11.7 (2.5–46.5)	111 (38–398)	SBRT (Cyberknife)	36 Gy (35–36.25)
Zilli et al. 2016	R	14	74 (66–98.4)	94 (48–172)	73 (56–122)	EBRT +/−BRT boost	85.1 (70–93.4) NTD_{2Gy}
Baumann et al. 2017	R	33	70.2 (61.2–79.2)	61 (7–150)	56 (18–118)	BRT: 103Pd BRT: 192Ir	103Pd: 100; I192: 30
Barbera et al. 2017	R	19	73.6 (70–78)	24 (6–45)	84 (12–187)	BRT: 125I	130
Maenhout et al. 2017	R	17	–	10	96	BRT	19
Kollmeier et al. 2017	R	98	81	31 (2–97)	72 (12–172)	LDR-BRT HDR-BRT	103Pd: 125 125I: 144
Loi et al. 2017	R	50	74 (60–80)	21.3 (6.1–49.2)	76 (9–205)	SBRT (Cyberknife)	30
Leroy et al. 2017	R	23	75.6 (70–75.6)	22.6 (6–40)	65 (28–150)	SBRT (Cyberknife)	36
Miszczyk et al. 2018	P	38	76 (45–78) BRT: 10–30-36	14.4 (1.6–46.4)	101 (22–179)	SBRT	36.25 (18–36.25)
Mbeutcha* et al. 2017	R	10	–	22.5	69 (55–85)	HDR-BRT	35
Mbeutcha* et al. 2017	R	18	–	14.5	49 (37–70)	SBRT (Cyberknife)	35
D'Agostino et al. 2018	P	23	–	33	90	SBRT	25
Jereczek-Fossa et al. 2019	R	64	70.2 (45–145)	26.1 (3.1–82.4)	100 (23–208)	SBRT	30
Olivier et al. 2019	R	12	66	34.2 (3.5–64.4)	77.6 (21.4–160.8)	SBRT (CyberKnife)	36

Legend: N = number: Pts = patients; P-RT = previous radiotherapy; Re-I = re-irradiation; R = retrospective; P = prospective; BRT = Brachytherapy; EBRT = External Beam Radiotherapy; LDR-BRT = low dose rate Brachytherapy; HDR-BRT = high dose rate Brachytherapy; PDR-BRT = pulse dose rate Brachytherapy; IMRT = Intensity Modulated Radiotherapy; SBRT = Stereotactic Body Radiotherapy; NTD = normalized total dose in 2 Gy fractions; *: study comparing salvage prostate Re-I using HDR-BRT and SBRT, both arms was analyzed as single study.

hands, we reported re-irradiated volumes as contained within at least the 50% isodose of the previous RT plan and most often, wholly or partly, within the high dose region. Previous RT was delivered in 18 studies with only EBRT, instead in 4 studies [25,29–31] was delivered with exclusive BRT, in the remaining 16 studies with a combination of EBRT and BRT. In all studies, the median radiation dose was 72.5 Gy, ranged from 52 [27] to 145 Gy [25,32]; in most studies there was not information about used fractionation. The mean time elapsed since previous irradiation was 69 months, ranged from 30 [29] to 150 months [33]. In 27 studies [8,11,18–19–20–21,26–45], an interstitial BRT was normally used to re-irradiate patients. A SBRT technique was used in nine studies [2,3,22–24,47–50]. Finally, in 2 studies treatment was delivered using an EBRT, in one after a previous BT [25]and in the other after an EBRT [46]. Mbeutcha *et al.* [11] compared salvage prostate Re-I using HDR-BRT and focal SBRT, both arms analyzed as single study. Re-irradiation prescription doses were variable, ranging from 19 Gy in single HDR fraction to 145 Gy (interstitial BRT). ADT was given with Re-I in 502 patients (41.1%).

Outcomes

In terms of efficacy OM and BF rates were analyzed. Thirty-five studies reported the 2 years OM rate; the pooled 2 years OM rate was 2.1% (95%CI:1.1–3.7%) with moderate heterogeneity ($I^2 = 65.53\%$, $P < 0.001$) (Fig. 1a). No difference in heterogeneity was evidenced after omitting studies using different modalities of Re-I.

Twenty-four studies report the 4 years OM rate; the pooled 4 years OM rate was 12.5% (95%CI:8.1–19.5%) with high heterogeneity ($I^2 = 86\%$, $P < 0.001$) (Fig. 1b). Excluding studies using EBRT to re-irradiate, there is not difference in heterogeneity.

Thirty-five studies reported the 2 years BF rate. The pooled 2 years BF rate was 24% (95% CI: 19.1–30.2%) with high heterogeneity ($I^2 = 82.13\%$, $P < 0.001$) (Fig. 2a). Excluding studies using EBRT to re-irradiate, the pooled result was 20% (95% CI: 15.6–25.7%) with moderate heterogeneity ($I^2 = 73.9\%$, $P < 0.001$).

Finally, twenty-four studies evaluated 4 years BF rate. The pooled analysis showed that 35.6% (95% CI: 28.7–44.3%) of patients experienced 4 years BF with high heterogeneity ($I^2 = 87.1\%$, $P < 0.001$) (Fig. 2b). No difference in heterogeneity was evidenced after omitting studies using different modalities of Re-I.

Toxicity and radiation tolerance of organ at risk

Regarding tolerance, data on toxicity were analyzed in all 38 studies. Globally, grade ≥ 3 (acute and late adverse events) was observed in 148 patients (12.1%), scored by CTCAE scale version 3 [20,21,26,30,36,38,42,44,46] or 4 [2,8,11,22,24,25,28,32,37,39–41, 43,45,47,48,50] or RTOG/EORTC scale [18,19,23,27,31,35,49]. Toxicity scale was not specified in three studies [29,33,34]. Acute toxicity was analyzed in 29 studies, recording 25 grade ≥ 3 acute toxicities. The pooled result of grade ≥ 3 acute toxicity was 1.4% (95%CI: 0.7–3%) with high heterogeneity ($I^2 = 77.2$, $P < 0.001$) (Fig. 3a). After omitting 11 studies using external radiotherapy to re-irradiate, the pooled result was 1.3% (95% CI: 0.5–3.4%) with a high heterogeneity ($I^2 = 81.4\%$, $P < 0.001$). The same 29 studies analyze grade ≥ 3 late toxicity, recording 103 grade ≥ 3 late adverse events. The pooled result of grade ≥ 3 late toxicity was 8.7% (95%CI: 5.8–13%) with high heterogeneity ($I^2 = 78.9$, $P < 0.001$) (Fig. 3b). Excluding studies using EBRT to re-irradiate, there is not difference in heterogeneity.

Twenty-five studies stated dose-constraints of OARs; constraints were always reported as not-cumulative dose, from previous RT and the Re-I (appendix 1).

In the majority of the studies, the most significant acute and late toxicities occurred in the genito-urinary (GU) domain, with few grade ≥ 3 events [2, 3, 11, 21, 24, 28, 32, 33, 38, 40, 41, 45, 47, 48, 49, 78].

No acute and late grade ≥ 3 gastrointestinal (GI) toxicities occurred in the majority of the analyzed studies [3, 11, 22, 24, 28, 33, 38, 39, 43, 45, 47, 49, 50, 78], when OARs constraints were respected [32], also in case of high doses of previous EBRT [21].

Subgroup analyses

We performed subgroup analyses to evaluate whether there was evidence of differences in heterogeneity among different studies. The analysis of prospective studies did not seem to change heterogeneity in 2 years OM: 1.1% (95%CI: 0.2–6.1%), in 4 years OM: 10.3% (95%CI: 2.8–37.5%), in 2 years BF: 27.6% (95%CI: 16.9–45%), in 4 year BF: 40.3% (95%CI: 19.2–84.7%) and in acute > G3 toxicities: 4.5% (95%CI:

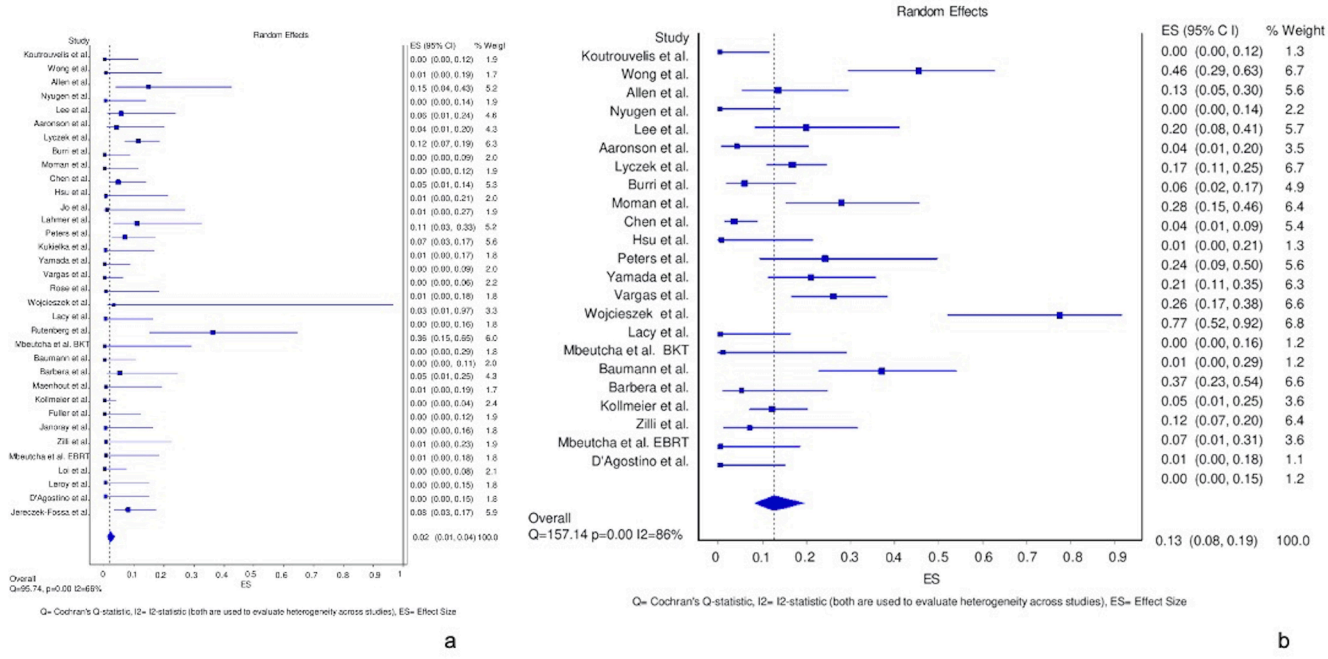

Fig. 1. Pooled objective 2 and 4 years Overall mortality in Re-Irradiated patients for included studies.

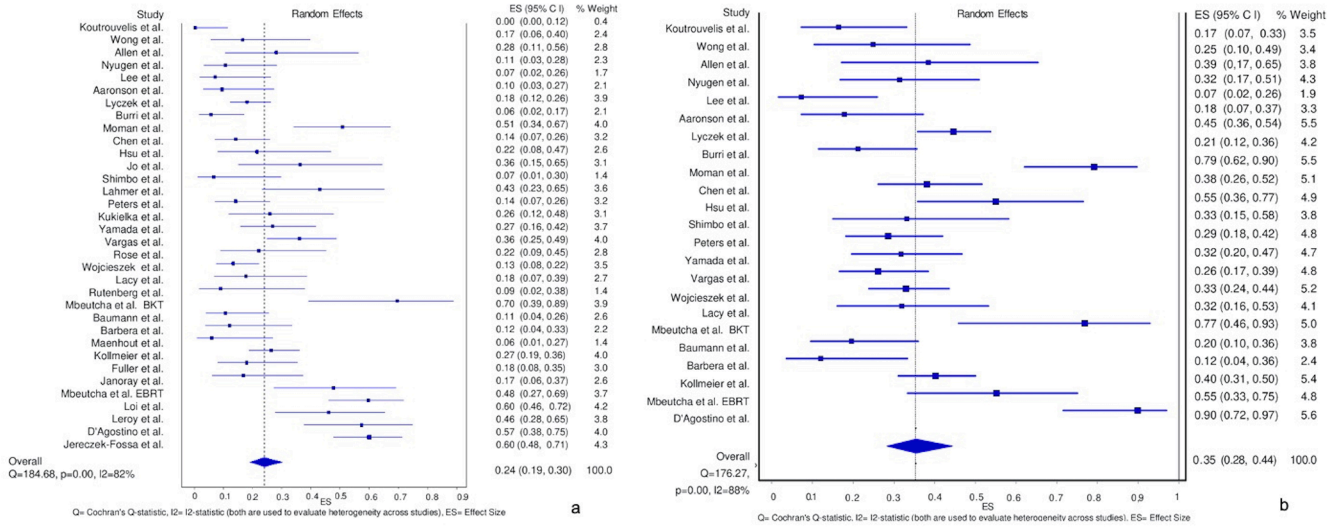

Fig. 2. Pooled objective 2 and 4 years Biochemical Failure in Re-Irradiated patients for included studies.

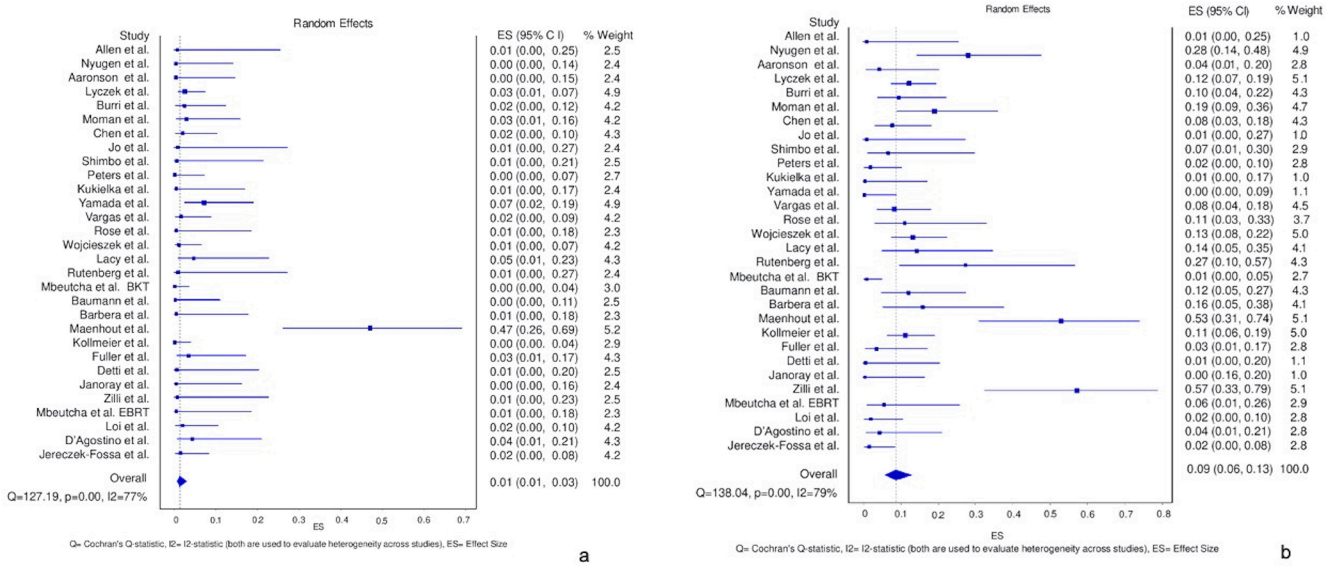

Fig. 3. Pooled rate of ≥ G3 Acute and Late Toxicity in Re-Irradiated patients for included studies.

2.1–9.3%) and late > G3 toxicities: 3.7% (95%CI: 0.7–19.6%). To the same conclusion subgroup the analysis of studies published after 2015, of studies with a follow-up > 24 months, of studies including patients with almost 50% treated with hormonal blockage. All data are shown in Table 2. A reduction in heterogeneity was highlighted analyzing studies using previous BRT and Re-I with BRT in 2 years OM: 0.4% (95%CI: 0.1–2.3%) with a not important heterogeneity and in 4 years OM: 1.7% (95%CI: 0.3–9.1%) with low heterogeneity. Similar results were obtained analyzing studies using previous EBRT and BRT as Re-I in 2 years BF: 0.196% (0.153–0.251) and 4 years BF: 0.30% (0.263–0.389).

A regression analyses was performed using study-level characteristics, as median patients age, number of low risk patients, of intermediate risk and of high risk patients, time to Re-I, number of patient treated with hormone-suppressive treatments (table 3). This analyses showed that LDR-BRT for low risk patients is the only covariate with a marginal influence on 2 year OM. Instead, no covariates influenced 2 and 4 year BF and 4 year OM.

Discussion

The best therapeutic proposal for previously irradiated local relapses (LR) from PC is still to be defined since solid scientific data of prospective nature are lacking.

Despite ADT is offered to a large population, patients with long-life expectation, negative distant work up imaging and low aggressive pattern of disease could still benefit from a local treatment in order to achieve disease local control and to postpone systemic therapies [51,52].

Salvage prostatectomy could offer a chance of cure for these patients although it is burdened with important sequelae, some potentially heavily affecting patient's quality of life [51,53].

As regards open salvage prostatectomy, in literature incidence rates of anastomotic stricture, urinary incontinence, and rectal injury are reported up to 32%, 68% and 7%, respectively [51]. Despite robotic prostatectomy showed lower risks of major complications and better functional outcomes than an open approach, anastomotic stricture and urinary incontinence rates remain still high [4].

Table 2
Subgroup analysis for: prospective studies, published studies after 2015, a follow-up > 24 months, different combination of radiotherapy technique and studies including hormonal blockage.

Strata of sensitivity-analysis results for each end point	Effect size % (CI)	I-s	References
Prospective studies			
2-yrs OM	1 (0.2–6.1)	55.01	3;18;19;20;21;24
4-yrs OM	10.3 (2.8–37.5)	86.89	18;20;21;24
2-yrs BF	27.6 (1.69–45)	19.72	3;18;19;20;21;24
4-yrs BF	40.3 (19.2–84.7)	92.05	18;19;21;24
Acute toxicities > G3	4.5 (2.1–9.3)	0	3;19;21;22;24
Late toxicities > G3	3.7 (0.7–19.6)	78.01	3;19;21;22;24
Published studies after 2015			
2-yrs OM	0.01 (0.003–0.031)	73.93	2;3;8;11;24;26;28;31;40;41;44;45;46;47;48
4-yrs OM	0.099 (0.039–0.255)	88.87	8;11;24;31;40;41;45;46
2-yrs BF	0.292 (0.216–0.396)	83.89	2;3;8;11;24;26;28;31;40;41;44;45;46;47;48
4-yrs BF	0.416 (0.277–0.625)	91.06	8;11;24;31;40;41;45
Acute toxicities > G3	0.013 (0.004–0.042)	83.09	2;3;11;22;24;25;28;31;41;44;45;46;47;49
Late toxicities > G3	0.097 (0.053–0.176)	83.12	2;3;11;22;24;25;26;28;31;40;41;44;45;46;47;49
Follow-up > 24 months			
2-yrs OM	2 (1–4)	66.67	3;8;18;19;21;24;25;26;29;30;31;32;33;34;35;36;37;40;41;42;44;44;46;47;48
4-yrs OM	14.8 (9.1–24.1)	87.67	8;18;19;21;24;29;30;31;32;33;34;35;36;37;41;42;44
2-yrs BF	20.4 (15.1–27.5)	82.54	3;8;18;19;21;24;25;26;29;30;31;32;31;33;36;37;38;41;42;44;45;49
4-yrs BF	31.8 (23.7–42.7)	90.06	8;18;19;21;24;29;30;31;32;33;34;35;36;37;41;42;45
Acute toxicities > G3	2.1 (1.3–3.4)	0	8;19;21;24;26;30;31;32;33;34;36;37;38;41;42;44;45;49
Late toxicities > G3	9.8 (6.5–14.8)	73.59	3;8;19;21;24;25;26;30;31;32;33;34;35;37;38;40;41;42;44;45;46;47;49
Only studies using BRT (previous RT) and BRT (Re-I)			
2-yrs OM	0.4 (0.1–2.3)	15.1	29;30;31;43
4-yrs OM	1.7 (0.3–9.1)	35.28	29;30;31;43
2-yrs BF	10.6 (4–28.3)	62.44	29;30;31;43
4-yrs BF	29.4 (16.8–51.7)	75.79	29;30;31;43
Acute toxicities > G3	3.4 (1–11)	0	30;31
Late toxicities > G3	11.4 (6–22)	0	30;31
Only studies using EBRT (previous RT) and BRT (Re-I)			
2-yrs OM	0.032 (0.016–0.063)	40.95	8;18;19;20;21;26;27;28;32;33;34;35;36;37;39;40;44;45
4-yrs OM	0.174 (0.099–0.303)	90.04	18;19;21;27;32;33;34;35;36;37;45
2-yrs BF	0.196 (0.153–0.251)	55.98	8;18;19;20;21;26;27;28;32;33;34;35;36;37;39;40;44;45
4-yrs BF	0.30 (0.263–0.389)	48.59	18;21;27;32;33;34;35;36;37;45
Acute toxicities > G3	0.023 (0.013–0.041)	11.21	19;21;26;27;32;33;34;36;37;39;40;44
Late toxicities > G3	0.096 (0.054–0.17)	79.03	19;21;26;27;28;32;33;34;36;37;39;40;44;45
Only studies using EBRT (previous RT) and SBRT (Re-I)			
2-yrs OM	0.009 (0.002–0.054)	58.25	2;3;24;48;49
4-yrs OM	0.071 (0.013-0.314)	n.a.	24
2-yrs BF	0.462 (0.349–0.612)	71.62	2;3;24;47;48;49
4-yrs BF	0.9 (0.716–0.970)	n.a.	24
Acute toxicities > G3	0.023 (0.01–0.05)	2.2510	2;3;22;47;49
Late toxicities > G3	0.023 (0.01–0.05)		2;3;22;24;47;49
Only studies combining Re-I with hormonal blockage in > 50% of patients			
2-yrs OM	0.028 (0.012–0.066)	57.96	8;11;18;27;29;32;34;35;39;45;46;48
4-yrs OM	0.211 (0.121–0.368)	70.86	8;11;18;27;29;32;34;35;45;46
2-yrs BF	0.179 (0.12–0.269)	68.3	8;18;27;29;32;34;35;39;45;48
4-yrs BF	0.362 (0.268–0.489)	75.91	11;18;27;29;32;34:35;45
Acute toxicities > G3	0.0.13 (0.006–0.025)	0	11;27;32;34;39;45;46;49
Late toxicities > G3	0.066 (0.023–0.187)	89.02	11;27;32;34;39;45;46

Legend: I-s: I-squared; yrs: years; OM: Overall Mortality; BF: Biochemical Failure; RT = Radiotherapy; BRT = Brachytherapy; EBRT = External Beam Radiotherapy; SBRT = Stereotactic Body Radiotherapy; Re-I = re-irradiation.

Conservative local options, such as Cryotherapy, High-intensity focused ultrasound (HIFU), BRT and EBRT, showed promising results in several studies [51,54,55]. In the systematic review by Ingrosso *et al.*, the Authors compared the biochemical control rate and the toxicity profile of these techniques [54]. BRT and EBRT showed the best therapeutic window with the highest biochemical control rate and the lowest prevalence of urinary incontinence and obstruction. Conversely, HIFU was associated with lower local control rates and higher incidence of toxicities.

A possible debate regards the possibility that a relapse after RT could be related to a radioresistant cancer cell clone suggesting that a second treatment course might not achieve a good oncological outcome. However, several studies reported biochemical response rates after Re-I to be similar to RT naive patients [3,50] hinting the persistence of radiosensitive cancer cells. The absence of local control after the primary treatment course could be related to an insufficient dose delivered as reported in many studies (median dose primary treatment < 76 Gy) [3,49]. Indeed, it is well known the radiobiological rationale for dose escalation in PC RT [56], and, in this setting, SBRT or BRT could offer a chance of cure for selected patients [54,57–59].

Our systematic review focused on outcomes and safety of Re-I for local relapses.

Concerning clinical outcomes, we reported a 2 and 4 years OM rate of 2.1% and 12.2%, respectively, with a high heterogeneity for the latter. Additionally, 2 and 4 years BF rates were 23.6% and 35.6%, respectively, in accordance to the results of other meta-analyses [54], with high I^2values. A regression analysis performed considering several characteristics (median patients age, number of low risk patients, of intermediate risk and of high risk patients, time to Re-I, number of patient treated with hormone-suppressive treatments) showed an

Table 3
Regression analysis for prostate re-irradiation effect on 2 and 4 year OM and BF.

Covariates	2-yr OM			4-yr OM			2-yr BF			2-yr BF		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Patient median age	−0.04	0.03	0.19	0.07	0.04	0.11	0.03	0.02	0.18	−0.014	0.02	0.41
Low risk patients	−0.01	0.02	0.54	−0.01	0.02	0.54	0.002	0.01	0.87	0.004	0.01	0.54
Intermediate risk patients	−0.02	0.01	0.08	0.02	0.01	0.09	0.005	0.01	0.49	0.0002	0.004	0.96
High risk patients	−0.02	0.01	0.17	0.04	0.02	0.06	−0.007	0.01	0.47	−0.006	0.01	0.42
Re-I with LDR-BRT in low risk patients	−0.06	0.02	0.04	−0.02	0.04	0.53	0.03	0.02	0.23	0.02	0.01	0.1
Re-I with LDR-BRT in intermediate risk patients	−0.02	0.02	0.36	0.05	0.03	0.09	0.02	0.02	0.41	−0.01	0.01	0.45
Re-I with LDR-BRT in high risk patients	0.03	0.22	0.23	0.02	0.01	0.1	−0.03	0.02	0.16	−0.009	0.01	0.45
Re-I with HDR-BRT in low risk patients	0.04	0.03	0.13	0.01	0.04	0.92	−0.01	0.01	0.4	−0.003	0.01	0.79
Re-I with HDR-BRT in intermediate risk patients	0.004	0.03	0.89	0.05	0.03	0.21	−0.02	0.02	0.31	−0.014	0.01	0.34
Re-I with HDR-BRT in high risk patients	−0.01	0.01	0.41	−0.003	0.01	0.79	−0.01	0.01	0.29	−0.01	0.01	0.34
Re-I with SBRT in low risk patients	0.07	0.12	0.55	0.004	0.04	0.92	0.005	0.04	0.89	–	–	–
Re-I with SBRT in intermediate risk patients	−0.09	0.05	0.08	−0.11	0.09	0.48	0.05	0.02	0.07	–	–	–
Re-I with SBRT in high risk patients	0.005	0.04	0.89	–	–	–	0.005	0.01	0.72	–	–	–
Time to Re-I	−0.004	0.01	0.44	0.01	0.01	0.14	−0.004	0.01	0.44	0.0005	0.002	0.85
Hormonal blockage	−0.003	0.01	0.82	−0.01	0.01	0.3	−0.01	0.01	0.29	−0.003	0.004	0.52

yr: years; OM: Overall Mortality; BF: Biochemical Failure; Re-I = re-irradiation; LDR-BRT: low dose rate brachytherapy; HDR-BRT: high dose rate brachytherapy; SBRT: Stereotactic Body Radiotherapy.

influence on 2 year OM in low risk patients treated with LDR-BRT.

Moreover, in order to investigate the causes of the high heterogeneity among different studies a subgroup analyses was performed. The results were not different after considering only prospective studies, studies published after 2015 and studies with a follow up period longer than 24 months. Another source of heterogeneity investigated by subgroup analyses was the different radiation techniques used in the analyzed studies (for both primary RT and Re-I). The only reduction in heterogeneity was found for studies using BRT as previous RT and Re-I, with 2 years OM (0.4%) and 4 years OM (1.7%), and previous EBRT and BRT as Re-I in 2 years BF (0.2%) and 4 years BF (0.3%). No difference was observed in heterogeneity in patients undergoing ADT.

Different definition of biochemical relapse and inclusion criteria of the analyzed studies could have been an impact on heterogeneity in clinical outcomes and patient selection is very crucial when a local Re-I is offered [51].

Indeed, patients with high risk features at diagnosis, short pre-salvage PSA doubling time, higher PSA value at the time of Re-I, ongoing ADT, a disease free interval less than 30 months, high PSA nadir values after Re-I as well as a long time to achieve it, showed to have a worse prognosis [2,25,30,42,45,51,52], because of the high risk of distant microscopic spread at the time of Re-I, leading to the loss of oncological significance of a local approach. The majority of the studies analyzed in our review did not clearly identified if the Re-I had been performed for an intraprostatic recurrence or on a tumor bed recurrence, except for fourteen studies [2,11,22,24,25,27,37,39,40,47–50]. Despite this, looking at the doses and techniques delivered for the first RT, we can infer in the majority of the studies that Re-I had been performed for an intraprostatic relapse after a definitive RT. All patients were re-irradiated for biochemical failure, confirmed by imaging (Magnetic Resonance Imaging, MRI, and Positron Emission Tomography, PET CT) in 16 studies [2,11,19–24,32,40,41,45,48–50] and by biopsy in all studies, except eight [2,18,20,22,31,34,40,47].

All studies declared to re-irradiated patients without distant metastases, except for 15 [11,18,19,22,30,33–35,37,42,43,45–48]. In this regard, the distant work up imaging is of paramount importance. Among the analyzed studies, many used Computed Tomography (CT) scan and bone scintigraphy [19,21,31], while most recent ones performed pelvic MRI and Choline PET CT for local and distant staging, respectively [2,20,22,23,28,47]. PET imaging with prostate-specific tracers such as PSMA, showed promising sensitivity and specificity rates and could be very useful to optimally detect patients with a true local relapse [60,61].

As far as toxicity is concerned, our analyses reported a pooled ≥ G3 acute and late toxicity rate of 1.4% and 8.7% respectively.

In accordance with findings from Re-I of other cancers [62,63],the time interval between primary RT and Re-I is related to the risk of toxicity. In particular, the time elapsed between the two RT courses is correlated to acute and late genitourinary side effects in the studies by D'Agostino and Nguyen, respectively, with the latter showing a HR of 12 for grade 3 or 4 toxicity and 25 for colostomy and/or urostomy for an interval time shorter than 4.5 years [19,24].

Our systematic review reports dosimetric parameters available in 25 studies, as not-cumulative dose constraints (appendix 1). The most significant acute and late toxicities occurred in the GU domain. Using stringent bladder and urethral D_{max} dose constraints, few cases of acute and late grade ≥ 3 were reported in 29 patients re-irradiated with SBRT [3].

In a study of 17 patients treated with HDR-BRT, the dose constraint of the urethra was set as a $D_{10\%} = 17.7$ Gy. In four patients, although the dose constraint was exceeded, reaching a maximum of 18.2 Gy, no late stenosis occurred. Only one patient, receiving a $D_{10\%}$ of 17.9 Gy, showed a late grade 3 urethral stenosis, but it should be noted that in this patient the tumor completely surrounded the urethra and was partially abutting the internal urinary sphincter [28].

This data underlined the impact of the prostatic volume on consequent toxicity of surrounding OARs, specially concerning urethra, as also reported by different authors in both BRT and SBRT Re-I [3,32].

Moreover, it was noted as patients with late complications tended to have a higher whole prostate D_{90} than those without complications (151 vs. 134 Gy, $p < 0.04$). Therefore, minimizing both V_{150} and V_{200} could reduce late toxicity. A potential planning goal should be to treat the disease with adequate dose while maintaining a conservative whole prostate D_{90} [44]. So, the respect of the D_{90}, V_{100} and V_{125} constraints for the urethra could help to obtain no acute grade ≥ 3 GU toxicity [8].

In addition, dosimetric parameters were reported in two studies not meeting our inclusion criteria. Crook *et al.*, in their prospective series of patients undergoing low dose rate BRT Re-I, found V100% (percentage of prostate covered by the prescription isodose) relating to late GU and could be considered as a surrogate of bladder neck dose, advising to lower the dose to this structure as much as possible [64].

Even if not included in our review because not reporting outcomes, Dipasquale and colleagues [65] demonstrated that the volume of rectum that received > 70 Gy at primary RT course was a strong predictor of late rectal toxicity. Moreover, when summing the primary and Re-I doses

delivered to 1 cc of rectum, a threshold dose of 130 Gy (a/b of 3 Gy) was found to be significantly related to the risk of late rectal adverse events.

On the other hand, no dosimetric values, as V_{100} or D_{90}, were significantly associated with the risk of complication or disease progression in another experience using HDR-BRT [21].

Even in the SBRT study conducted by Loi *et al.*, no statistical correlation was found between dosimetric variables and overall grade GU and GI toxicity, keeping as low as possible the doses given to 30% and 60% of the rectal volume and to 50% of the urinary bladder volume. Only the average dose to the rectum (12.12 versus 8.92 Gy, $p = 0.035$) showed a correlation with rectal toxicity, regardless all grades, even if further analysis failed to show a linear increase in toxicity in proportion with the average dose to the rectum ($p = 0.06$). The good toxicity profile in this study, as stated by the authors, seems to be correlated to the long-time interval between prior RT and Re-I (76 months) [2].

Nor correlation was found between dosimetric factors and previous treatment or post-SBRT toxicity, confirming as SBRT could be considered a good option for its ability to spare normal tissue [47,48].

Therefore, no conclusive data on dose constraints and toxicity correlation could be provided. The prostate volume to re-irradiate and the time interval between previous and Re-I remain important issues connected to toxicity. In addition, other factors have to be considered for Re-I tolerability, as an appropriate learning curve in treatment planning in order to respect dose-volume goals [20] and the high volume of experience of the Center, allowing to validate dose constraints in a larger population and with longer follow-up [24,38,49].

To the best of our knowledge, this is the first systematic review focusing only on RT treatment options for local relapses from PC, differently from others evaluating all possible approaches [5,66–68], or only BRT option [69] or SBRT [70]. Furthermore, our analyses have some limitations. High studies heterogeneity does not permit a comparison of all outcomes. Moreover, a subgroup analyses has been performed in order to quantify clinical data.

Despite these limitations, our analyses showed promising results, in terms of efficacy and safety, independently by the variables we have analyzed. Furthermore, thanks to the subgroup and regression analyses performed, we can identified LDR-BRT as an influencer on 2 year OM for low risk patients.

Several issues potentially weighing on outcomes and safety of Re-I remain open. First, it is not clear the optimal retreatment clinical target volume definition. Radiation oncologists have to balance the risks of an oncological missing of a focal approach [71] and the supposed higher toxicity of a whole gland target delineation. The Delphi consensus by the Uro-Gec group also showed a divided opinion on this topic, with the most experienced participants choosing whole gland RT as BRT retreatment volume [72].

Second, the optimal prescription dose has yet to be defined. The analyzed studies reported a wide range of delivered doses and the Delphy consensus showed a disagreement between experts too [72]. In the retrospective series of patients undergoing SBRT by Jereczek [49], dose escalation confirmed its role in PC even in the Re-I setting since BED2Gy > 130 Gy was prognosticator of a better biochemical free survival.

Thirdly, no comparison studies have been conducted to establish the radiation technique to choose for Re-I. Zilli *et al.* [46] reported high late toxicity rates and poor biochemical and local control n a population of 14 patients undergoing whole gland EBRT +/− BRT as salvage treatment after a medium follow up of 94 months. 3DRT was administered in 10 out of 14 patients. This result probably suggests the need of highly conformed techniques that could allow a deep dose fall-off in order to deliver high doses to the target while sparing as much as possible the surrounding healthy tissues. BRT and SBRT could meet these requirements and, in addition, their shorter overall treatment time could enhance treatment effectiveness.

Similarly, the role of concomitant ADT to Re-I is still controversial because some studies found it not related to prognosis [30], while others found it to be a negative prognosticator for BFS [2]. Interestingly, the Delphy group reached a consensus about this issue advising not to administer ADT during Re-I probably because the advantage could be twofold that is postponed an effective systemic treatment option and avoid its potential side effects [72].

Lastly, the presence of biases affecting the safety profile assessment cannot be excluded.

On one hand, it is noteworthy that in most studies the primary treatment was 2D or 3DRT with higher doses to OARs. In addition to the conformed dose distribution warranted by IMRT, IGRT and modern tumor tracking systems have allowed to shrink the uncertainties related to organ and target motion, consequently reducing the dose to OARs.

On the other hand, toxicity rates could be underestimated since in most studies the primary RT course was given before the era of dose escalation with total doses considered inadequate today.

Moreover, a median follow-up of 30 months is too short for analyzing late toxicities and longer follow up time is needed to properly assess the late toxicity profile.

Additionally, no data exist about Re-I after moderate or extremely hypofractionation so further data are eagerly awaited in this setting.

Conclusions

In our systematic review, Re-I of local failures from PC showed promising overall survival and biochemical control rates with a safe toxicity profile, independently by the analyzed variables (study design, period of the study, radiotherapy techniques performed, androgen deprivation therapy) and despite the heterogeneity of studies included. Overall, patients with low risk, small prostate volume and long time-interval to Re-I could be the best candidates for Re-I when high conformal techniques, as BRT and SBRT, are used. Prospective studies or large real-world high-quality datasets are warranted to improve the level of evidence of data, to address the unanswered questions, to give recommendation and to help clinicians for patients selection that may benefit from such a strategy.

Informed consent

Not applicable.

CRediT authorship contribution statement

Fernando Munoz: Data curation, Visualization, Writing - original draft. **Francesco Fiorica:** Formal analysis, Investigation, Validation. **Luciana Caravatta:** Conceptualization, Methodology, Project administration, Visualization, Writing - original draft. **Consuelo Rosa:** Data curation, Visualization, Writing - original draft. **Letizia Ferella:** Data curation, Visualization, Writing - original draft. **Luca Boldrini:** Validation. **Bruno Fionda:** Validation. **Anna Rita Alitto:** Data curation. **Alessia Nardangeli:** Data curation. **Francesco Dionisi:** Data curation. **Stefano Arcangeli:** Supervision, Writing - review & editing. **Alessandro Di Marzo:** Supervision, Writing - review & editing. **Antonio Pontoriero:** Supervision, Writing - review & editing. **Vittorio Donato:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing. **Mariangela Massaccesi:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

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.

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Appendix A. Supplementary data

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):7–34. https://doi.org/10.3322/caac.21551.

[2] Loi M, Di Cataldo V, Simontacchi G, Detti B, Bonomo P, Masi L, et al. Robotic stereotactic retreatment for biochemical control in previously irradiated patients affected by recurrent prostate cancer. ClinOncol (R CollRadiol) 2018;30(2):93–100. https://doi.org/10.1016/j.clon.2017.11.007.

[3] Fuller DB, Wurzer J, Shirazi R, Bridge SS, Law J, Mardirossian G. High-dose-rate stereotactic body radiation therapy for post radiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. PractRadiatOncol 2015;5:e615–23. https://doi.org/10.1016/j.prro.2015.04.0094.

[4] Gontero P, Marra G, Alessio P, Filippini C, Oderda M, Munoz F, et al. Salvage radical prostatectomy for recurrent prostate cancer : morbidity and functional outcomes from a large multicenter series of open versus robotic approaches. J Urol 2019;202:725–31. https://doi.org/10.1097/JU.0000000000000327.

[5] Alongi F, De Bari B, Campostrini F, Arcangeli S, Matei DV, Lopci E, et al. Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: a review. Crit Rev OncolHematol 2013;88(3):550–63. https://doi.org/10.1016/j.critrevonc.2013.07.009.

[6] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)-Prostate Cancer, Version 2.2019 -April 17, 2019. NCCN.org.

[7] Zerini D, Jereczek-Fossa BA, Fodor C, Bazzani F, Maucieri A, Ronchi S, et al. Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer. Br J Radiol 2015;88(1052):20150197. https://doi.org/10.1259/bjr.20150197.

[8] Baumann BC, Baumann JC, Christodouleas JP, Soffen E. Salvage of locally recurrent prostate cancer after external beam radiation using reduced-dose brachytherapy with neoadjuvant plus adjuvant androgen deprivation. Brachytherapy 2017;16(2):291–8. https://doi.org/10.1016/j.brachy.2016.12.011.

[9] Abusaris H, Hoogeman M, Nuyttens JJ. Re-Irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. Technol Cancer Res Treat 2012;11(6):591–7. https://doi.org/10.7785/tcrt.2012.500261.

[10] Das S, Patro KC, Mukherji A. Recovery and tolerance of the organs at risk during re-irradiation. J CurrOncol 2018;1:23–8.

[11] Mbeutcha A, Chauveinc L, Bondiau P-Y, Chand M-E, Durand M, Chevallier D, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. RadiatOncol 2017;12(1). https://doi.org/10.1186/s13014-017-0789-9.

[12] Referred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement - Journal of Clinical Epidemiology. https://www.jclinepi.com/article/S0895-4356(09)00179-6/fulltext.

[13] Institute of Health Economics | About Methodology Development. https://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[14] D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74. https://doi.org/10.1001/jama.280.11.969.

[15] Julious SA. 17:857–872. Stat Med 2005;24(21):3383–4. https://doi.org/10.1002/sim.2164.

[16] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.

[17] Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693–708. https://doi.org/10.1002/(sici)1097-0258(19991030)18:20<2693::aid-sim235>3.0.co;2-v.

[18] Wong WW, Buskirk SJ, Schild SE, Prussak KA, Davis BJ. Combined prostate brachytherapy and short-term androgen deprivation therapy as salvage therapy for locally recurrent prostate cancer after external beam irradiation. J Urol 2006;176:2020–4. https://doi.org/10.1016/j.juro.2006.07.00816.

[19] Nguyen PL, Chen M-H, D'Amico AV, Tempany CM, Steele GS, Albert M, 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(7):1485–92. https://doi.org/10.1002/cncr.v110:710.1002/cncr.22934.

[20] Lahmer G, Lotter M, Kreppner S, Fietkau R, Strnad V. Protocol-based image-guided salvage brachytherapy: early results in patients with local failure of prostate cancer after radiation therapy. StrahlentherOnkol 2013;189:668–74. https://doi.org/10.1007/s00066-013-0373-718.

[21] Yamada Y, Kollmeier MA, Pei X, Kan CC, Cohen GN, Donat SM, 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(2):111–6. https://doi.org/10.1016/j.brachy.2013.11.005.

[22] Detti B, Bonomo P, Masi L, Doro R, Cipressi S, Iermano C, et al. CyberKnife stereotactic radiotherapy for isolated recurrence in the prostatic bed. World J Urol 2016;34(3):311–7. https://doi.org/10.1007/s00345-015-1613-5.

[23] Miszczyk L, Stąpór-Fudzińska M, Miszczyk M, Maciejewski B, Tukiendorf A. Salvage CyberKnife-Based Reirradiation of Patients With Recurrent Prostate Cancer: The Single-Center Experience. TechnolCancer Res Treat. 2018;17:1533033818785496. doi: 10.1177/1533033818785496.

[24] D'Agostino GR, Di Brina L, Mancosu P, Franzese C, Iftode C, Franceschini D, et al. Reirradiation of locally recurrent prostate cancer with volumetric modulated arc therapy. Int J RadiatOncolBiol Phys 2019;104(3):614–21. https://doi.org/10.1016/j.ijrobp.2019.02.041.

[25] Rutenberg MS, Meister M, Amin PP, Hussain A, Naslund MJ, Kwok Y. Salvage external beam radiotherapy for locally recurrent prostate cancer after definitive brachytherapy. Brachytherapy 2016;15(6):722–9. https://doi.org/10.1016/j.brachy.2016.08.004.

[26] Jo Y, Fujii T, Hara R, Yokoyama T, Miyaji Y, YodenEet al. Salvage High-Dose-Rate Brachytherapy for Local Prostate Cancer R Eecurrence After Radiotherapy - Preliminary Results. BJU Int. 2012;109:835-9. doi: 10.1111/j.1464-410X.2011.10519.x.

[27] Łyczek J, Kawczyńska MM, Garmol D, Kasprowicz A, Kulik A, Dąbkowski M, et al. HDR brachytherapy as a solution in recurrences of locally advanced prostate cancer. J Contemp Brachytherapy 2009;1:105–8.

[28] Maenhout Metha, Peters Max, van Vulpen Marco, Moerland Marinus A, Meijer Richard P, van den Bosch Maurice AAJ, et al. Focal MRI-guided salvage high-dose-rate brachytherapy in patients with radiorecurrent prostate cancer. Technol Cancer Res Treat 2017;16(6):1194–201. https://doi.org/10.1177/1533034617741797.

[29] Koutrouvelis Panos, Hendricks Fred, Lailas Niko, Gil-Montero Guillermo, Sehn James, Khawand Nabil, et al. Salvage reimplantation in patient with local recurrent prostate carcinoma after brachytherapy with three dimensional computed tomography-guided permanent pararectal implant. Technol Cancer Res Treat 2003;2(4):339–44. https://doi.org/10.1177/153303460300200409.

[30] Burri Ryan J, Stone Nelson N, Unger Pam, Stock Richard G. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J RadiatOncolBiol Phys. 2010;77(5):1338–44. https://doi.org/10.1016/j.ijrobp.2009.06.061.

[31] Lacy John M, Wilson William A, Bole Raevti, Chen Li, Meigooni Ali S, Rowland Randall G, et al. Salvage brachytherapy for biochemically recurrent prostate cancer following primary brachytherapy. Prostate Cancer 2016;2016:1–9. https://doi.org/10.1155/2016/9561494.

[32] Peters Max, Maenhout Metha, van der Voort van Zyp Jochem RN, Moerland Marinus A, Moman Maaike R, Steuten Lotte MG, et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. RadiotherOncol. 2014;112(1):77–82. https://doi.org/10.1016/j.radonc.2014.06.013.

[33] Vargas Carlos, Swartz Douglas, Vashi Apoorva, Blasser Marc, Kasraeian Ali, Cesaretti Jamie, et al. Salvage brachytherapy for recurrent prostate cancer. Brachytherapy 2014;13(1):53–8. https://doi.org/10.1016/j.brachy.2013.10.012.

[34] Allen Gregory W, Howard Andrew R, Jarrard David F, Ritter Mark A. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. Cancer 2007;110(7):1405–16. https://doi.org/10.1002/cncr.22940.

[35] Lee Brian, Shinohara Katsuto, Weinberg Vivian, Gottschalk Alexander R, Pouliot Jean, Roach Mack, 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 RadiatOncolBiol Phys 2007;67(4):1106–12. https://doi.org/10.1016/j.ijrobp.2006.10.012.

[36] Aaronson David S, Yamasaki Ichiro, Gottschalk Alexander, Speight Joycelyn, Hsu I-Chow, Pickett Barby, et al. Salvage permanent perineal radioactive-seed Implantation for Treating Recurrence of Localized Prostate Adenocarcinoma After External Beam Radiotherapy. BJU Int 2009;104(5):600–4. https://doi.org/10.1111/j.1464-410X.2009.08445.x.

[37] Chen Chien Peter, Weinberg Vivian, Shinohara Katsuto, Roach Mack, Nash Marc, Gottschalk Alexander, et al. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J RadiatOncolBiol Phys 2013;86(2):324–9. https://doi.org/10.1016/j.ijrobp.2013.01.027.

[38] 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. https://doi.org/10.1159/000346322.

[39] Kukiełka AM, Hetnał M, Dąbrowski T, Walasek T, Brandys P, Nahajowski D, et al. Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failureSalvage-HDR-Brachytherapie in Kombination mit interstitieller Hyperthermie bei Lokalrezidiv eines Prostatakarzinoms nach erfolgloser Strahlentherapie. StrahlentherOnkol 2014;190(2):165–70. https://doi.org/10.1007/s00066-013-0486-z.

[40] Barbera F, Triggiani L, Buglione M, Ghirardelli P, Vitali P, Caraffini B et al. Salvage Low Dose Rate Brachytherapy For Recurrent Prostate Cancer After External Beam Radiotherapy: Results From A Single Institution With Focus On Toxicity And Functional Outcomes. Clin Med Insights Oncol. 2017;11:1179554917738765. doi: 10.1177/1179554917738765.

[41] Kollmeier Marisa A, McBride Sean, Taggar Amandeep, Anderson Erik, Lin Mary, Pei Xin, et al. Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: a comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time.

Brachytherapy 2017;16(6):1091–8. https://doi.org/10.1016/j.brachy.2017.07.013.
[42] Moman Maaike R, van der Poel Henk G, Battermann Jan J, Moerland Marinus A, van Vulpen Marco. 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(2):119–25. https://doi.org/10.1016/j.brachy.2009.06.007.
[43] Hsu Charles C, Hsu Howard, Pickett Barby, Crehange Gilles, Hsu I-Chow Joe, Dea Ryan, et al. Feasibility of MR Imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for localized recurrence after initial PPI for prostate cancer. Int J RadiatOncolBiol Phys 2013;85(2):370–7. https://doi.org/10.1016/j.ijrobp.2012.04.028.
[44] Rose Jim N, Crook Juanita M, Pickles Tom, Keyes Mira, Morris W James. Salvage low-dose-rate permanent seed brachytherapy for locally recurrent prostate cancer: association between dose and late toxicity. Brachytherapy 2015;14(3):342–9. https://doi.org/10.1016/j.brachy.2015.01.002.
[45] Wojcieszek Piotr, Szlag Marta, Głowacki Grzegorz, Cholewka Agnieszka, Gawkowska-Suwińska Marzena, Kellas-Ślęczka Sylwia, et al. Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. RadiotherOncol 2016;119(3):405–10. https://doi.org/10.1016/j.radonc.2016.04.032.
[46] Zilli Thomas, Benz Eileen, Dipasquale Giovanna, Rouzaud Michel, Miralbell Raymond. Reirradiation of prostate cancer local failures after previous curative radiation therapy: long-term outcome and tolerance. Int J RadiatOncolBiol Phys 2016;96(2):318–22. https://doi.org/10.1016/j.ijrobp.2016.05.024.
[47] Janoray G, Reynaud-Bougnoux A, Ruffier-Loubière A, Bernadou G, Pointreau Y, Calais G. Stereotactic body re-irradiation therapy for locally recurrent prostate cancer after external-beam radiation therapy: Initial report. Cancer Radiother 2016;20(4):275–81. https://doi.org/10.1016/j.canrad.2016.03.005.
[48] Leroy T, Lacornerie T, Bogart E, Nickers P, Lartigau E, Pasquier D. Salvage robotic SBRT for local prostate cancer recurrence after radiotherapy: preliminary results of the Oscar Lambret Center. RadiatOncol 2017;12:95. https://doi.org/10.1186/s13014-017-0833-.
[49] Jereczek-Fossa Barbara Alicja, Rojas Damaris Patricia, Zerini Dario, Fodor Cristiana, Viola Anna, Fanetti Giuseppe, et al. Reirradiation for isolated local recurrence of prostate cancer: mono-institutional series of 64 patients treated with salvage stereotactic body radiotherapy (SBRT). Br J Radiol 2019;92(1094):20180494. https://doi.org/10.1259/bjr.20180494.
[50] Olivier Jonathan, Basson Laurent, Puech Philippe, Lacornerie Thomas, Villers Arnauld, Wallet Jennifer, et al. Stereotactic re-irradiation for local recurrence in the prostatic bed after prostatectomy: preliminary results. Front Oncol 2019;9. https://doi.org/10.3389/fonc.2019.00071.
[51] Nguyen Paul L, D'Amico Anthony V, Lee Andrew K, Warren Suh W. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure. Cancer 2007;110(7):1417–28. https://doi.org/10.1002/cncr.22941.
[52] Baty M, Créhange G, Pasquier D, Palard X, Deleuze A, Gnep K, et al. Salvage reirradiation for local prostate cancer recurrence after radiation therapy. For who? When? How? Cancer Radiother 2019;23(6-7):541–58. https://doi.org/10.1016/j.canrad.2019.07.125.
[53] Mendenhall WM, Henderson RH, Hoppe BS, Nichols RC, Mendenhall NP. Salvage of locally recurrent prostate cancer after definitive radiotherapy. Am J ClinOncol 2014;37:411–6. https://doi.org/10.1097/COC.0b013e31824be3b4.
[54] Ingrosso Gianluca, Becherini Carlotta, Lancia Andrea, Caini Saverio, Ost Piet, Francolini Giulio, et al. Nonsurgical salvage local therapies for radiorecurrent prostate cancer: a systematic review and meta-analysis. EurUrolOncol 2020;3(2):183–97. https://doi.org/10.1016/j.euo.2018.12.011.
[55] Tetreault-Laflamme Audrey, Crook Juanita. Options for salvage of radiation failures for prostate cancer. SeminRadiatOncol 2017;27(1):67–78. https://doi.org/10.1016/j.semradonc.2016.08.007.
[56] Schulz Robert J, Kagan A Robert. Dose escalation in the radiation therapy of prostate cance. Int J RadiatOncolBiol Phys 2011;80(5):1289–91. https://doi.org/10.1016/j.ijrobp.2011.04.012.
[57] Cuccia F, Nicosia L, Mazzola R, Figlia V, Giaj-Levra N, Ricchetti F, et al. Linac-based SBRT as a feasible salvage option for local recurrences in previously irradiated prostate cancer. StrahlentherOnkol 2020;196:628–36. https://doi.org/10.1007/s00066-020-01628-6.
[58] Quivrin M, Peignaux-Casasnovas K, Martin É, Rouffiac M, Thibouw D, Chevalier C et al. Salvage brachytherapy as a modern reirradiation technique for local cancer failure: The Phoenix is reborn from its ashes. Cancer Radiother. 2018;22:372-381. doi: 10.1016/j.canrad.2018.01.005.
[59] Chatzikonstantinou Georgios, Zamboglou Nikolaos, Rödel Claus, Zoga Eleni, Strouthos Iosif, Butt Saeed Ahmed, et al. High-dose-rate brachytherapy as salvage modality for locally recurrent prostate cancer after definitive radiotherapyHigh-Dose-Rate-Brachytherapie als Salvage-Modalität beim lokal rezidivierten Prostatakarzinom nach definitiver Strahlentherapie: Ein systematischer Review. StrahlentherOnkol 2017;193(9):683–91. https://doi.org/10.1007/s00066-017-1157-2.
[60] Evans JD, Jethwa KR, Ost P, Williams S, Kwon ED, Lowe VJ, et al. Prostate cancer–specific PET radiotracers: a review on the clinical utility in recurrent disease. PractRadiat Oncol 2018;8:28–39. https://doi.org/10.1016/j.prro.2017.07.011.
[61] Afshar-Oromieh Ali, Zechmann Christian M, Malcher Anna, Eder Matthias, Eisenhut Michael, Linhart Heinz G, et al. Comparison of PET imaging with a 68 Ga-labelled PSMA ligand and 18 F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J NuclMedMolImaging 2014;41(1):11–20. https://doi.org/10.1007/s00259-013-2525-5.
[62] Dionisi F, Fiorica F, D'Angelo E, Maddalo M, Giacomelli I, Tornari E, et al. Organs at risk ' s tolerance and dose limits for head and neck cancer re- irradiation: a literature review. Oral Oncol 2019;98:35–47. https://doi.org/10.1016/j.oraloncology.2019.08.017.
[63] Caravatta L, Fiorica F, Rosa C, Boldrini L, Alitto AR, Nardangeli A, et al. Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Role of upper abdominal reirradiation for gastrointestinal malignancies: a systematic review of cumulative dose, toxicity, and outcomes on behalf of the Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). StrahlentherOnkol 2020;196:1–14. https://doi.org/10.1007/s00066-019-01519-5.
[64] Crook Juanita M, Zhang Peixin, Pisansky Thomas M, Trabulsi Edouard J, Amin Mahul B, Bice William, et al. A Prospective phase 2 trial of transperineal ultrasound-guided brachytherapy for locally recurrent prostate cancer after external beam radiation therapy (NRG Oncology / RTOG-0526). Int J RadiatOncolBiol Phys 2019;103(2):335–43. https://doi.org/10.1016/j.ijrobp.2018.09.039.
[65] Dipasquale Giovanna, Zilli Thomas, Fiorino Claudio, Rouzaud Michel, Miralbell Raymond. Salvage reirradiation for local failure of prostate cancer after curative radiation therapy: association of rectal toxicity with dose distribution and normal-tissue complication probability models. AdvRadiatOncol 2018;3(4):673–81. https://doi.org/10.1016/j.adro.2018.06.001.
[66] Duijzentkunst DAS, Peters M, van der Voort van Zyp JR, Moerland MA, van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World J Urol 2016;34:1521-1531. doi: 10.1007/s00345-016-1811-9.
[67] Golbari NM, Katz AE. Salvage therapy options for local prostate cancer recurrence after primary radiotherapy: a literature review. CurrUrol Rep 2017;18:63. https://doi.org/10.1007/s11934-017-0709-4.
[68] 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. https://doi.org/10.1111/j.1464-410X.2009.08715.x.
[69] Ramey Stephen J, Marshall David T. Re-irradiation for salvage of prostate cancer failures after primary radiotherapy. World J Urol 2013;31(6):1339–45. https://doi.org/10.1007/s00345-012-0953-7.
[70] Cuccia Francesco, Mazzola Rosario, Nicosia Luca, Giaj-Levra Niccolò, Figlia Vanessa, Ricchetti Francesco, et al. Prostate re-irradiation: current concerns and future perspectives. Expert Rev Anticancer Ther 2020;20(11):947–56. https://doi.org/10.1080/14737140.2020.1822742.
[71] Oates Richard, Jones Daryl, Foroudi Farshad, Gill Suki, Ramachandran Prabhakar, Schneider Michal, et al. Geographical miss of the prostate during image-guided radiotherapy with a 6-mm posterior expansion margin. J Med Radiat Sci 2017;64(2):97–105. https://doi.org/10.1002/jmrs.186.
[72] Kaljouw Emmie, Pieters Bradley R, Kovács György, Hoskin Peter J. Prostate cancer A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study. RadiotherOncol 2016;118(1):122–30. https://doi.org/10.1016/j.radonc.2015.10.021.