PO-1382 A systematic review regarding outcomes and toxicities of re-irradiation for prostate cancer

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Purpose or Objective

The optimal management of local relapse after previously irradiated prostate cancer (PC) is not still standardized. Re-irradiation (Re-I) could be proposed in highly selected PC patients, even if high quality evidences are lacking. We conducted this study aiming to provide a literature review on efficacy and safety of prostatic Re-I.

Materials and Methods

On the behalf of the Re-I Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO), this systematic review was performed following PRISMA recommendations. We considered only studies where Re-I field overlaps with previous radiotherapy (P-RT). A meta-analysis over single arm study was performed to determine the pooled 2 and 4 years overall mortality (OM), 2 and 4 years biochemical failure (BF) and acute and late G≥3 toxicities rate. Heterogeneity was examined by the Cochrane Q chi-square test and the I2 statistic.

Results

The literature search yielded 73 citations: 38 studies, published between 2003 and 2019 with 1194 patients, met inclusion criteria (table 1). P-RT was delivered in 18 studies with External Beam Radiation Therapy (EBRT), in 4 studies with exclusive Brachytherapy (BRT) and in the remaining 16 studies with a combination of EBRT and BRT. In all studies, the median prior radiation dose was 72.5 Gy (52-145 Gy). The mean time between P-RT and Re-I was 69 months (30-150 months). Median follow-up from Re-I was 30 months (10-94 months). Twenty-seven studies used BRT as Re-I technique, followed by 9 studies using Stereotactic Body Radiotherapy (SBRT) and 2 using EBRT. Re-I prescription ranged from 19 Gy in single HDR fraction to 145 Gy (interstitial BRT). Twenty-five studies stated dose-constraints of OARs; constraints were always reported as not-cumulative dose, from previous RT and the Re-I (table 2).

The pooled 2 and 4years 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). Globally, acute and late G≥3 toxicity was observed in 148 patients (12.1%). Twenty-five acute G≥3 acute events were reported, with a pooled result of G≥3 acute toxicity of 1.4% (95%CI: 0.7–3%, P < 0.001). One hundred and three G≥3 late events were reported, with a pooled result of G≥3 late toxicity of 8.7% (95%CI: 5.8–13%, P < 0.001).

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 (15-77)	-	BRT: 125I BRT: 103Pd	126
Allen et al. 2007	R	12	70 (59.4-70.2)	45 (11-64)	69.12 (39.96-309.2)	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 (15-65)	49 (26-109)	BRT: 125I BRT: 103Pd	72 (65-80)
Lycick 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
Momen 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 (144-360); 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 + HDR24; HDR-BT: 37.5; Proton: 74	29 (18-41)	41.5	HDR-BRT	22
Lehmet et al. 2013	P	18	69.3 (49.9-73.8)	21 (8-77)	64.5 (27-271)	PDR-BRT, 1x192	60
Peters et al. 2014	R	20	125I: 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	52
Vargas et al. 2014	R	66	68.4	60	150	BRT	100
Rose et al. 2015	R	19	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	35	45.5	BRT	144
Fuller et al. 2015	P	29	73.8 (64.8-81)	24 (3-60)	86 (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	26.3 (1-53.6)	49 (13-136)	IMRT/3D-CRT	70.2 (64.8-75.6)
Jereczek 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)	75 (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; 192: 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	33	73.6 (70-73.6)	22.6 (6-40)	65 (28-150)	SBRT (Cyberknife)	36
Miszczyk et al. 2018	P	38	76 (45-78); BRT: 30-30-36	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 (37-79)	SBRT (Cyberknife)	35
D'Agostino et al. 2018	P	23	-	35	90	SBRT	25
Jereczek-Fossa et al. 2019	R	64	70.2 (45-145)	26.1 (5.1-82.4)	100 (23-308)	SBRT	30
Olivier et al. 2019	R	12	66	34.2 (5.5-64.4)	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.

Table 2. Twenty-five studies reporting dose parameters for Re-I.

Authors and years	Re-I technique	Dosimetric parameters as not-cumulative doses							
		CTV	Prostate	Urethra	Rectum	Femoral heads	Bladder	Penile Bulb	Small intestine
Burri et al. 2010	BRT	-	D_{50}:122 Gy (44-166)	-	-	-	-	-	-
Moman et al. 2010	BRT	-	$V_{100\%}$>95% $V_{90\%}$<150% $V_{10\%}$<200%	D_{max}≤200%	D_{max}<100%	-	-	-	-
Hsu et al. 2012	BRT: 125I BRT: 103Pd EBRT	D_{90}=142Gy*	D_{90}=37Gy*	Mean V_{100}=32% V_{150}=0.3 cc*	Mean V_{100}=0.5% V_{150}=0.07 cc*	-	-	-	-
Lahmer et al. 2013	PDR-BRT, Ir192	V_{100}=90-95% D_{90}>100%	-	$D_{0.1cc}$<130%	$D_{0.1cc}$<50%	-	-	-	-
Patans et al. 2014	BRT: 125I	-	-	D_{0}< 150% $D_{10\%}$<216Gy	$D_{0.1cc}$< 100% $D_{0.1cc}$<144 Gy $D_{0.1cc}$<200 Gy	-	-	-	-
Kukielka et al. 2014	BRT: 192Ir	D_{90}>95%[§]	-	D_{max}<120%	D_{max}<80%	-	-	-	-
Yamada et al. 2014	HDR-BRT	-	-	D_{max}<120%	D_{max}<100%	-	-	-	-
Vargas et al. 2014	BRT	-	$D_{90\%}$>100 Gy*	$D_{0.01\ cc,\ max}$<0 D_{max}<0.42*	$D_{0.01\ cc,\ max}$<0 D_{max}<0.59*	-	-	-	-
Rose et al. 2015	BRT: 125I	-	D_{90}: 134 Gy (105-165) V_{150}: 39%(23-55) V_{200}: 14%(0-20)*	-	V_{max}: 0.21cc (0-1)*	-	-	-	-
Detti et al. 2015	SBRT	-	-	D_{max}<33.70Gy $D_{0.01cc}$<31 Gy	$V_{18.1Gy}$<30% V_{30Gy}<60%	$V_{18.1Gy}$<5 %	$V_{18.1Gy}$<40% $V_{30.6Gy}$<50%	$V_{30.6Gy}$<50%	-
Shimbo et al. 2015	BRT	-	$D_{median\ dose}$: 159.5 Gy (124.3–184.1)*	V_{100}=0.45ml (0.17–1.3) V_{median}: 18.7ml (11.9–33.9)*	V_{100}=0.29ml (0.01–0.93) -	-	-	-	-
Fuller et al. 2015	SBRT (Cyberknife)	-	-	D_{max}<120% D_{50}< 105%	D_{max}<160%[@] D_{max}<75%[¥]	-	D_{max}<100%[^]	-	-
Wojcieszek et al. 2016	HDR BRT: 192Ir	-	-	D_{50} ≤120%	D_{50} ≤70%	-	D_{50} ≤70%	-	-
Janoray et al. 2016	SBRT (Cyberknife)	-	-	-	$V_{18.1Gy}$<50% V_{30Gy}<20% V_{36Gy}<1cm³	$V_{18.1Gy}$< 5%	$V_{18.1Gy}$<40% V_{30Gy}<10cm³	-	-
Baumann et al. 2017	BRT: 103Pd BRT: 192Ir	-	-	V_{150}=0	-	-	-	-	-
Barbera et al. 2017	BRT: 125I	$V_{100\%}$ ≥ 100% $V_{150\%}$ ≤ 60% $D_{98\%}$ ≥ 100%[§]	-	D_{max}≤130% $D_{10\%}$<150%*	$D_{0.1cc}$≤100%	-	-	-	-
Maenhout et al. 2017	BRT	-	-	$D_{10\%}$<17.7Gy	$D_{0.1cc}$<12Gy	-	$D_{0.1cc}$<12 Gy	-	-
Kollmeier et al. 2017	LDR-BRT HDR-BRT	-	D90 ≥ 90%	D_{05}<120%	$D_{0.1cc}$<100%[@]	-	-	-	-
Lai et al. 2017	SBRT (Cyberknife)	-	-	D_{max}<120% Median D_{max}: 33.6Gy*	D_{max}<100% Median D_{max}: 30Gy*	-	D_{max}<120% Median D_{max}: 34Gy*	-	$D_{max(0.5cc)}$<21 Gy
Leroy et al. 2017	SBRT (Cyberknife)	V_{100}>90%[§]	-	V_{30}<30% V_{36}<1cc*	V_{30}<2cc V_{36}<20%	-	V_{30}<5cc V_{36}<35%	-	-
Mbeutcha* et al. 2017 (BRT)	HDR-BRT	V_{100}≥95% V_{150}<30% V_{200}<32%	-	V_{150}<1%	V_{80}<1%	-	-	-	-
Mbeutcha* et al. 2017 (SBRT)	SBRT (Cyberknife)	V_{100}≥95% V_{150}<30% V_{200}<32%	-	V_{150}<1%	V_{80}<1%	-	-	-	Mean dose= 371-428 cGy*
D'Agostino et al. 2018	SBRT	V98%> 98%	-	-	V_{30Gy}<40% V_{36Gy}<20%	V_{30}< 10%	V_{30Gy}<25% V_{36Gy}< 15%	V_{30}< 50%	V_{36}<5cm³
Jeruzek-Fossa et al. 2019	SBRT	-	-	-	$V_{11.5Gy}$<30% $V_{18.1Gy}$<60%	-	$V_{18.1Gy}$<30%	-	-
Olivier et al. 2019	SBRT (CyberKnife)	-	-	-	V_{30}<20% V_{36}< 2cc	-	V_{30}<15% V_{36}< 5cc	-	-

Legend: Re-I=re-irradiation; BRT=Brachytherapy; EBRT= External Beam Radiotherapy; LDR-BRT= low dose rate Brachytherapy; HDR-BRT= high dose rate Brachytherapy; PDR-BRT= pulse dose rate Brachytherapy; SBRT= Stereotactic Body Radiotherapy; *: study comparing salvage prostate Re-I using HDR-BRT and SBRT, both arms was analyzed as single study; +no extra-capsular extension or seminal vesicle involvement; ^: bilateral relapse+ extra-capsular invasion; †: PTV; °: obtained; #: cumulative dose; ^: prostatic/intraprostatic urethra; @: rectal wall; ¥: rectal mucosa; ^: bladder wall

Conclusion

Re-I of local failures from PC showed promising OM and BF rates with a safe toxicity profile, independently by study design, period of the study, radiotherapy techniques, androgen deprivation therapy and despite the heterogeneity of studies. Low risk patients with small prostate and long time-interval to Re-I could be the best candidates for Re-I using BRT and SBRT. Prospective studies or large high-quality datasets are necessary to give recommendation, helping clinicians for patients selection that may benefit from Re-I and to address the unanswered questions.

PO-1383 Radiation therapy with curative intention in men with de novo metastatic prostate carcinoma

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Purpose or Objective

To evaluate feasibility and tolerance of radiotherapy of both primary tumor and secondary lesions as a radical alternative for selected prostate cancer patients with de novo oligometastases.

Materials and Methods

Between 2015-2020, 26 patients (median age 69.5 years, range 52-84) with de novo prostate carcinoma with bone or lymph node metastases were retrospectively reviewed. Eighteen patients (69%) presented lymph node metastases, 4 (15.5%) bone metastases and 4 (15.5%) both lymph node and bone metastases. Mean and median number of metastases per patient were 2.1 and 1.5 respectively.Twenty-six per cent of the lymphatic metastases were located in the obturator nodes and 19% in the common iliac, external iliac and internal iliac nodes respectively (Fig.1). The bone metastases settled mainly on the pelvic girdle, 30% in the sacroiliac region. Only in one case the existence of bone metastases was observed in the spine outside the pelvis. Number and location of lymph node and bone metastases are detailed in Fig.1. All patients received moderate hypofractionated IMRT/VMAT up to 63 Gy in 21 daily fractions of 3 Gy to prostate and metastases with neoadjuvant and concurrent androgen deprivation therapy (ADT). According to known advances some patients also received abiraterone, enzalutamide, or docetaxel.
Fig. 1: Number and location of lymph node and bone oligometastases