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Review

Postoperative Hypofractionated Radiation Therapy in Prostate Carcinoma: A Systematic Review

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Abstract. *Background/Aim: A systematic review on toxicity, local control (LC), overall survival (OS), and biochemical relapse-free survival (bRFS) after postoperative hypofractionated radiotherapy (HFRT) on prostate cancer (PCa) was performed. Materials and Methods: Based on the PRISMA methodology, studies reporting clinical results after adjuvant or salvage HFRT were included. Results: A total of 1,208 patients from 17 eligible studies were included. Median follow-up was 30 months. No case of severe acute gastrointestinal (GI) toxicity was recorded. Grade ≥3 acute genitourinary (GU) toxicity ranged between 0% and 3%. Different rates of grade ≥2 late GI (range=0-8.7%) and GU (range=0-66%) toxicity were recorded. Encouraging results on LC, OS, and bRFS were reported. Conclusion: Acute toxicity does not seem to be increased in patients receiving postoperative HFRT, but the results of late-GU toxicity are conflicting. Further prospective studies are needed before including postoperative HFRT in clinical practice.*

This article is freely accessible online.

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Prostate cancer (PCa) is the most common non-skin cancer in males older than 70 years in Europe (1). Radical prostatectomy (RP) is a treatment option in patients with life expectancy longer than 10 years and organ-confined disease (1-2). Patients with adverse pathological features show 50-75% 5-year biochemical failure rates after RP (3). Negative prognostic factors are extracapsular extension, seminal vesicles invasion, positive surgical margins, higher Gleason score and higher preoperative prostate-specific antigen (PSA) (4).

The efficacy of postoperative radiotherapy (RT) was demonstrated by three randomized clinical trials: Southwest Oncology Group (SWOG) 8794 (5), European Organisation for Research and Treatment of Cancer (EORTC) 22911 (6), and German Cancer Society (ARO) 96-02 (7). These studies showed that adjuvant RT significantly improves 10-year biochemical recurrence-free survival (bRFS), local control (LC) and disease-free survival (DFS).

Available literature data do not define the optimal dose and fractionation for adjuvant and salvage RT. The three randomized trials mentioned above used a lower total dose (60-64 Gy with conventional fractionation) compared to other retrospective and prospective non-randomized studies (8-10).

Radiobiological analyses suggest that PCa α/β ratio is approximately 1.5 and thus lower compared to bladder and rectum (11). Therefore, the choice to prescribe a

Table I. *Patients characteristics*.

Reference, year	Institution	Study design	N° pts	% setting	Median follow-up, months (range)	GS ≥7, %	Positive surgical margin, %	Median PSA at diagnosis, ng/ml (range)	Median PSA before RT, ng/ml (range)
Syndikus I *et al*. 1996 (19)	British Columbia; Canada	Prospective Phase 2	115	adj: 77.4 salv: 22.6	adj: 87 (59-121), salv: 111 (46-146)	NR	85.0	12 (2-70) *	2 (0.1-21) *
Lee LW *et al*. 2004 (20)	Manchester; UK	Retrospective	37	salv: 100	36 (20-85)	30.0	73.0	11.2 (5.6-60)	2.9 (0.5-11.4)
Cozzarini C *et al*. 2007 (21)	Milan; Italy	Prospective Phase 1-2	23	adj: 78.3 salv: 21.7	11.5 (3.4-25.7)	NR	NR	NR	NR
Cozzarini C *et al*. 2008 (22)	Milan; Italy	Prospective Phase 1-2	50	adj:100	25 (15.5-31.6)	NR	54.0	6.9	0.02
Wong G *et al*. 2008 (23)	Madison; USA	Retrospective	50	salv: 100	18.9 (5.3-35.9)	58.0	70.0	6.6 (3-21.1)	0.5 (0.2-9.5)
Alongi F *et al*. 2009 (24)	Milan; Italy	Retrospective	43	NE	NR	NE	NR	NE	NE
Kruser TJ *et al*. 2011 (25)	Madison; USA	Retrospective	108	salv: 100	32.4 (5.8-70.5)	64.0†	69.0‡	6.79 (2.2-38.5)§	0.44 (0.05-9.5)
Koukourakis M *et al*. 2012 (26)	Alexandroupolis; Greece	Prospective Phase 1-2	48	adj: 43.8 salv: 56.2	41 (12-84)	54.2	20.8	NR	adj: 0.18‖ (0.03-1.6) salv: 2.2‖ (0-31)
Alongi F *et al*. 2013 (27)	Milan; Italy and Bellin zona, Switzerland	Retrospective	39	adj: 76.9 salv:23.1	22.8 (9-28)	NE	NR	NR	0.32 (0.01-3.25)
Ippolito E *et al*. 2013 (28)	Campobasso & Rome; Italy	Prospective Phase 1	25	adj: 100	19 (6-36)	76.0	72.0	12.45 (3.80-54.0)	0.10 (0.00-0.13)
Massaccesi M *et al*. 2013 (29)	Campobasso & Rome; Italy	Prospective Phase 2	49	adj: 79.6 salv: 20.4	NR	55.8¶	57.1	10.2**	adj: 0.27‖ salv: 1.25‖
Cozzarini C *et al*. 2014 (30)	Milan; Italy	Retrospective	247	adj: 67.6 salv: 32.4	68 (54-81)	34.4	57.0	8 (5.6-12.7)	0.03 (0.01-0.06)††
Katayama S *et al*. 2014 (31)	Heidelberg, Germany	Prospective Phase 2	39	adj: 28.2 salv: 71.8	NR	NR	NR	NR	0.24 (0.02-2.18)
Gladwish A *et al*. 2015 (32)	Toronto; Canada	Prospective Phase 1-2	30	adj: 13.3 salv: 86.7	24 (18-42)	93.0	67.0	NR	0.12 (0.01-1.42)
Lewis S.L *et al*. 2016 (33)	North Carolina; USA	Prospective Phase 2	56	adj: 23.2 salv: 76.8	48 (21-67)	85.0	76.0	8.5 (3.7-154.8)	1.14 (0.01-40.3)
Fersino S *et al*. 2017 (34)	Negrar-Verona; Italy	Retrospective	125	adj: 51.2 salv: 48.8	18 (6-53)	NR	46.4	NR	adj: 0.035 (0-0.2) salv 0.45 (0.2-5.1)
Macchia G *et al*. 2017 (35)	Campobasso; Italy	Prospective Phase 1-2	124	adj: 85.5 salv: 14.5	30 (13-92)	78.2	84.7	7.6 (0.1-80.8)	NR

Adj: Adjuvant; GS: Gleason score; NE: not evaluable; NR: not reported; pts: patients; salv: salvage; *setting adjuvant; †only 106 pts; ‡only 105 pts; §only 103 pts; ‖mean; ¶GS > 7; **setting adjuvant; ††interquartile range.

hypofractionated radiotherapy (HFRT) seems justified. Results from randomized and non-randomized trials evaluating feasibility and safety of this therapeutic approach are available for radical HFRT in non-resected PCa (12-14), but only few non-randomized studies have been published and no systematic review or meta-analyses are available about postoperative HFRT.

Therefore, the purpose of this systematic review is to analyse acute and late treatment-related sequelae of postoperative HFRT in PCa patients. Secondary endpoints of this trial are LC, overall survival (OS), and bRFS.

Materials and Methods

Inclusion criteria

Type of studies. In this review all clinical studies reporting toxicity in patients treated with postoperative HFRT were included, excluding case reports and reviews. Only studies published in English were included.

Type of participants. Only trials enrolling patients with resected non-metastatic PCa were included in this analysis (Table I).

Type of interventions. Eligible intervention included postoperative hypofractionated external beam RT independently by technique,

Table II. *Treatment characteristics*.

Reference, year	Technique	Dose, Gy (median)	Dose per fraction, Gy (median)	Image guidance	EQD2 (α/β=1.5)*	EQD2 (α/β=3)*	Patients receiving HT, %
Syndikus I *et al*. 1996 (19)	NR	PB: 50.0-55.0 (52†)	PB: 2.0-3.1 (2.76†)	NR	63.3	59.9	15.6
Lee LW *et al*. 2004 (20)	3DCRT	PB: 50.0-52.5 (50)	PB: 2.5-2.6 (2.5)	NR	57.1-61.5	55.0-58.8	NR
Cozzarini C *et al*. 2007 (21)	IMRT-SIB-HTT	PB: 64.4-72.0 (72.0) PNI: 50.4-54.0 (52.0)	PB: 2.2-2.6 PNI: 1.5-1.9	MVCT	68.1-84.3	66.9-80.6	NR
Cozzarini C *et al*. 2008 (22)	IMRT	PB: 58.0	PB: 2.9	MVCT	73.0	68.0	NR
Wong GW *et al*. 2008 (23)	IMRT	PB: 65.0-70.0 PNI: 54.0-56.0‡	PB: 2.5 PNI: 2.0	MVCT; U/S	74.3-80.0	71.5-77.0	8.0
Alongi F *et al*. 2009 (24)	IMRT	PB: 64.4-70.0 PNI: 50.4-54 .0 (51.8)	PB: 2-2.6 (2.35) PNI: 1.8-2 (1.85)	NR	68.1-82.0	67.0-78.4	NE
Kruser TJ *et al*. 2011 (25)	IMRT	PB: 65.0-70.0 PNI: 52.0-56.0§	PB: 2.5 PNI: 2.0	MVCT; U/S	74.3-80.0	71.5-77.0	17.0
Koukourakis M *et al*. 2012 (26)	3DCRT‖	PB: 51.0 PNI: 37.8	PB: 3.4 PNI: 2.7	NR	71.4	65.3	47.9
Alongi F *et al*. 2013 (27)	VMAT	PB: 70.0-71.4 (70)	PB:2.5-2.55	CB-CT	80.0-82.6	77.0-79.2	NR
Ippolito E *et al*. 2013 (28)	IMRT-SIB	PB: 56.75, 59.75, 61.25, 62.5¶ PNI: 45.0	PB: 2.27, 2.39, 2.45, 2.50 PNI: 1.8	NR	61.1-66.4-69.1-71.4	59.8-64.4-66.7-68.7	NR
Massaccesi M *et al*. 2013 (29)	IMRT-SIB	PB: 62.5 PNI: 45.0	PB: 2.5 PNI: 1.8	NR	71.4	68.75	73.4
Cozzarini C *et al*. 2014 (30)	IMRT-SIB	PB: 58.0-72.8 (71.4) PNI: 50.0-52.0	PB: 2.35-2.90 (2.50) PNI: (1.8)	IGRT	72.4-72.9	70.4-68.4	54.0
Katayama S *et al*. 2014 (31)	IMRT	PB: 54.0	PB: 3.0	MVCT	69.4	64.8	12.8
Gladwish A *et al*. 2015 (32)	IMRT	PB: 51.0	PB: 3.0	IGRT	65.6	61.2	13.0
Lewis SL *et al*. 2016 (33)	IMRT	PB: 57.5-65 .0(65.0)	PB: 2.5	IGRT	65.7-74.3	63.2-71.5	17.8
Fersino S *et al*. 2017 (34)	VMAT	PB: 65.5-71.4 (66.0) PNI: 50.4-54 .0(52.5)	PB: 2.2-2.4 PNI: 1.8-2.0	CB-CT	69.2-79.6	68.1-77.1	NR
Macchia G *et al*. 2017 (35)	IMRT-SIB	PB: 62.5 PNI: 45.0	PB: 2.5 PNI: 1.8	NR	71.4	68.7	79.8

3DCRT: 3D Conformal Radiotherapy; adj: adjuvant; CB-CT: cone beam CT; conc: concomitant; EQD2: equivalent dose in 2 Gy fractions; GS: Gleason score; HT: hormone therapy; HTT: Helical Tomotherapy; IGRT: image guided radiotherapy; IMRT: intensity modulated radiation therapy; MVCT: Megavoltage CT; neoadj : neoadjuvant; NE: not evaluable; NR: not reported; PB: prostate bed; pts: patients; PNI: prophylactic nodal irradiation; SIB: simultaneous Integrated Boost; VMAT: Volumetric Modulated Arc Therapy. *prostate bed dose; †mean; ‡only 4 pts; §only in 14 pts; ‖amifostine cytoprotection in association; ¶dose escalation.

total dose and treatment intent (adjuvant or salvage) after RP with or without lymphadenectomy. Additional treatments (neoadjuvant and/or concurrent and/or adjuvant hormone therapy) and supportive care were not exclusion criteria (Table II).

Type of outcome measures. Primary endpoint of the analysis was treatment-related toxicity after HFRT in postoperative setting and secondary endpoints were LC, OS, and bRFS (Table III).

Literature search strategy. Trials were independently selected by two different authors (GS and MB) and a third author resolved potential discrepancies (AGM). The same two authors (GS and MB) extracted data independently with resolution of all differences by the third author (AGM). Based on the PRISMA methodology, a bibliographic search was performed using the PubMed database. The search algorithm was “prostate” (MeSH) AND “hypofractionated” (MeSH) AND “postoperative” (MeSH). There were no time limits in the literature search. We included only studies in English language and we excluded reviews, case reports and study protocols. Studies including radical RT, conventional fractionation or palliative treatments were also excluded in the review process.

Results

Characteristics of included studies. Through the literature research, performed as previously reported, 21 records were identified. Figure 1 shows the selection process of trials included in this review. Four papers were excluded: two were not pertinent (15, 16), one was a case report (17), and the other was a study protocol (18). A total of 17 studies fulfilled all the inclusion criteria reporting data on 1208 patients. Among the selected trials, 12 were performed in European centers, 3 in USA, and 2 in Canada. Seven studies had a retrospective design, one was a phase 1 trial, four were phase 2 trials, and five were phase 1-2 trails.

Table III. *Results*.

Reference, year	Acute toxicity G ≥3, % (Scale)	Late toxicity G ≥2, %* (Scale)	LC, %	OS, %	bRFS, %	Main findings
Syndikus I *et al*. 1996 (19)	NR	GI: 8.7; GU:46.1 (RTOG/EORTC)	5-y: 69.0† 10-y: 54.0†	10-y: 91.0‡	NR	early post-operative RT <local recurrence rates
Lee LW *et al*. 2004 (20)	GI: 0; GU: 0 (RTOG)	GI: 3.0; GU:0 (RTOG/EORTC)	NR	100*	1-y: 92.0 2-y: 83.0 3-y: 74.0	Salv RT in PSA <2 ng/mL improves biochemical control
Cozzarini C *et al*. 2007 (21)	GI: 0; GU: 0 (RTOG)	NR	NR	NR	NR	Efficient sparing of intestinal cavity with HTT compared to IMRT
Cozzarini C. *et al*. 2008 (22)	GI: 0; GU: 2.0 (RTOG)	GI: 0; GU: 12.0 (RTOG/EORTC)	NR	NR	100*	Acute toxicity and late toxicity outcomes, excellent with HTT post RP
Wong GW *et al*. 2008 (23)	GI: 0; GU: 0 (RTOG)	GI: 4.0; GU: 4.0 (RTOG/EORTC)§	NR	98.0*	1-y: 83.7 2-y: 72.9	Biochemical control rates significantly improved in pts with PSA level <0.4
Alongi F *et al*. 2009 (24)	GI:0; GU:0 (RTOG)	NR	NR	NR	NR	Excellent profile of acute toxicity in WPRT in adju/salv post-operative ≥70 Gy
Kruser TJ *et al*. 2011 (25)	GI: 0; GU: 1.0 (RTOG)	GI: 4.0; GU: 15.0 (RTOG/EORTC)§	NR	99.1*	4-y: 67.0	Reduced treatment time; low rates of toxicity
Koukourakis M *et al*. 2012 (26)	GI: 0; GU: 0; (CTCAE)	GI: 0; GU: 0 (CTCAE/EORTC)	93.7*	NR	85.4*	Better pts outcome with high dose of amifostine (1000 mg); low incidence of late radiation events
Alongi F *et al*. 2013 (27)	GI: 0; GU: 0 (RTOG)	GI: 0; GU: 11.0 (RTOG/EORTC)	NR	NR	NR	Better late rectal toxicity profile with VMAT; good bladder and rectum sparing
Ippolito E *et al*. 2013 (28)	GI: 0; GU: 0 (RTOG)	NR	NR	NR	NR	Total dose of 62.5 (2.5) Gy is feasible in terms of acute toxicity and overall treatment time reduction
Massaccesi M *et al*. 2013 (29)	GI: 0; GU: 1.9 (RTOG)	NR	NR	NR	NR	62.5 (2.5) Gy compares favourably with that of 3DCRT high doses
Cozzarini C *et al*. 2014 (30)	NR	GI: NR; GU: 16.5**; 5-y: 18.1 (CTCAE 4.0)	NR	NR	NR	The toxicity increased when the median dose per fraction was increased from 1.8 Gy to 2.35 to 2.55
Katayama S *et al*. 2014 (31)	GI: 0; GU: 0 (CTCAE 4.0)	NR	NR	NR	NR	Hyp IMRT of PB is well tolerated with severe acute side effects
Gladwish A *et al*. 2015 (32)	GI: 0; GU: 3.0 (CTCAE 3.0)	GI: 6.0; GU: 3.0 (CTCAE 3.0)	NR	NR	83.0*	Well tolerate hyp in terms of toxicity and QoL
Lewis SL *et al*. 2016 (33)	GI: 0; GU: 0 (CTCAE 4.0)	GI: 3.6; GU: 66.1‡‡ (CTCAE 4.0)	NR	96.4*	4-y: 75.0	Late grade 3 GU toxicity was higher than anticipated with hyp of 65 Gy
Fersino S *et al*. 2017 (34)	GI: 0; GU: 0.8 (CTCAE 4.0)	GI: 8; GU: 12.0‡‡ (CTCAE 4.0)	NR	NR	3-y: 94 .0 (adj) 3-y: 77.0 (salv)	Moderate hypofractionated postoperative RT with VMAT was feasible and safe
Macchia G *et al*. 2017 (35)	GI: 0; GU: 0.8 (RTOG)	5-y GI: 1.1; 5-y GU: 7.3 (RTOG/EORTC)	3-y: 99.9 5-y: 94.9	3-y: 100 5-y: 100	3-y: 91.1 5-y: 86.5	Hyp IMRT-SIB provides excellent Long-term bRFS with minimal rate of late complications when combined with HT;

ADJ: Adjuvant; bPFS: biochemical progression-free survival; bRFS: biochemical relapse free survival; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; FU: follow-up; hyp: hypofractionated; IMRT: intensity modulated radiation therapy; GI: gastrointestinal; GU: genitourinary; HTT: Helical Tomotherapy; LC: local control; mo: months; NR: not reported; OS: overall survival; PB: prostate bed; pts: patients; RT: radiotherapy; salv: salvage; *crude; †salvage group; ‡adjuvant group; §RTOG/EORTC modified; ¶bPFS, **G3/G4 toxicity; ††only 19 pts; ‡‡4-y grade 3 late toxicity was 28%.

Literature review. The first report on postoperative HFRT for PCa was published in 1996. In this study Syndikus and colleagues enrolled a total of 203 patients: 88 were treated with RP alone, 89 underwent early postoperative RT, generally because of pT3 stage, and 26 received salvage RT for local recurrence (postoperative RT: 115 patients). The aim of the analysis was to evaluate the impact of RT using a total dose to the prostate bed of 50-55 Gy with 2.0-3.1 Gy daily fractions. Late toxicity was scored with the RTOG/EORTC scale. Five- and 10-year LC were 69.0% and 54.0% in patients treated for local recurrence, respectively. Actuarial 10-year OS for early postoperative RT group was

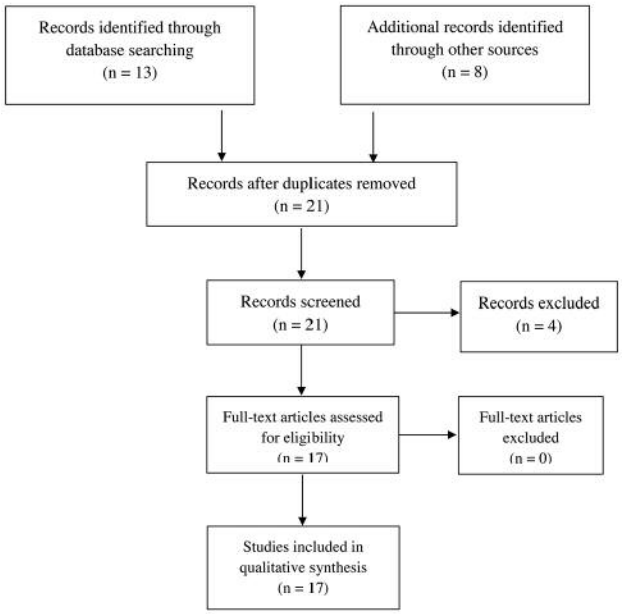

Figure 1. *Flow diagram of study identification and selection.*

91.0%. Grade ≥ 2 late gastrointestinal (GI) and genitourinary (GU) toxicity rates in adjuvant setting were 10.0% and 44.0%, respectively, and in salvage setting they were 4.0% and 54.0%, respectively. Based on these results, the authors concluded that local RT in pT3 stage has a positive impact on LC but not on OS. Because of the high rate of severe late urinary complications, they suggested to treat in the adjuvant setting only patients with a high risk of local recurrence (19).

In their retrospective analysis, Lee and co-workers included 37 patients with biochemical relapse after RP. Patients underwent salvage HFRT using 50.0-52.2 Gy in 20 fractions (2.5-2.6 Gy daily fractions). Acute and late toxicity was evaluated with RTOG and RTOG/EORTC scales, respectively. No patients died due to PCa or developed distant metastases. One-, 2- and 3-year bRFS was 92.0%, 83.0%, and 74.0%, respectively. No case of grade ≥3 acute and late toxicity was reported. Only 3.0% grade ≥2 late GI toxicity crude rate was recorded. The authors concluded that this RT regimen achieved prolonged biochemical control with good tolerance (20).

The first Italian phase 1-2 trial was published in 2007. Cozzarini and colleagues, using helical tomotherapy based postoperative HFRT, reported acute toxicity in 23 patients (78.3% and 21.7% treated with adjuvant and salvage intent, respectively). With a median dose of 74.2 Gy on surgical bed and moderately hypofractionated regimen, no patient developed grade ≥3 acute toxicity according to the RTOG scale (21).

One year later, the same group published the results of a case series of 50 patients with high risk disease treated with adjuvant dose of 58.0 Gy in 2.9 Gy per fraction on prostatic fossa using helical tomotherapy. No grade ≥3 acute and grade ≥2 late GI toxicity was recorded, without differences compared to patients treated with three-dimensional conformal radiotherapy (3D-CRT) and a conventionally fractionated dose. Only 2.0% developed grade ≥3 acute GU toxicity and 12.0% grade ≥2 late GU toxicity according to the RTOG and RTOG/EORTC scale, respectively. In addition, bRFS was 100% with a median follow-up of 25 months (22).

Wong and his group reported the results of salvage HFRT in a retrospective analysis on 50 patients with biochemical relapse. On the surgical bed 2.5 Gy were delivered daily for 26-28 fraction (total dose=65-70 Gy). Based on RTOG and RTOG/EORTC scales, no grade ≥3 acute GI and GU toxicity was reported and only 4.0% of patients showed grade ≥2 late GI and GU toxicity. One- and 2-year bRFS was 83.7% and 72.9%, respectively, with biochemical control rates significantly better in patients with PSA level <0.4 ng/ml (p=0.018) (23).

Alongi and co-workers used IMRT-based postoperative RT in 43 patients with a total dose of 64.4-70.0 Gy (2.0-2.6 Gy) on the prostate surgical bed and 50.4-54.0 Gy (1.8-2.0 Gy) to the pelvis. Despite the use of whole-pelvic irradiation, no patient showed any grade ≥3 acute toxicity according to the RTOG scale (24).

Kruser and colleagues published their experience on HFRT (65-70 Gy in 2.5 Gy fractions in about 5 weeks) in 108 patients with post-prostatectomy biochemical recurrence. GI and GU grade ≥3 acute toxicity rates were 0% and 1.0%, respectively. GI and GU late toxicity were 4.0% and 15.0%, respectively. Four-year bRFS was 67.0% and only one patient died from hormonal refractory PCa with a median follow up of 32.4 months. The authors concluded that salvage HFRT is safe and effective (25).

The Greek group coordinated by Koukourakis enrolled 48 patients with high-risk disease or recurrent PCa. HFRT was delivered on prostatic bed (51.0 Gy in 3.4 Gy per fraction) and pelvic nodes (37.8 Gy in 2.7 Gy per fraction) with amifostine cytoprotection. With a median follow up of 41.0 months, no GI and GU toxicity was reported and 14.6% of patients showed PSA biochemical failure with 6.3% local relapse rate. Based on the low toxicity rate the authors considered this treatment as feasible (26).

Alongi and co-workers published in 2013 the results of post-operative HFRT (adjuvant/salvage) delivered with Volumetric Modulated Arc Therapy (VMAT). Thirty-nine patients were enrolled, 76.9% and 23.1% for adjuvant and salvage RT, respectively. They were treated with 70.0 Gy median dose to the prostatic bed (2.5-2.55 Gy per fraction). Based on RTOG-EORTC scale, 11.0% of patients showed grade ≥2 late GU toxicity with a median follow up of 22.8

months. The authors observed a lower rate of late rectal toxicity with VMAT technique (27).

In the same year two other Italian studies were published. Ippolito and colleagues enrolled 25 patients undergoing adjuvant RT for high risk PCa in a phase 1 trial on post-operative Intensity Modulated Radiation Therapy with simultaneous integrated boost (IMRT-SIB). A dose-escalation (4 levels) was performed only on the surgical bed. The recommended dose was 62.5 Gy in 2.5 Gy per fraction based on the low acute toxicity rate (0% grade ≥3 acute GI and GU toxicity, RTOG scale) (28).

Massaccesi and co-workers enrolled 49 patients after RP in a phase 2 trial. From this cohort of patients, 79.6% and 20.4% were treated with adjuvant and salvage intent, respectively. IMRT-SIB was prescribed to the whole pelvis (45 Gy in 1.8 Gy per fraction) and to the prostatic bed (62.5 Gy in 2.5 Gy per fraction). Only 1.9% of patients showed grade ≥3 acute GU toxicity according to RTOG criteria. No cases of grade ≥3 acute GI toxicity were recorded. The authors concluded that hypofractionated IMRT-SIB reduces the overall treatment time and shows an acute toxicity profile which compares favourably with 3D-CRT (29).

Cozzarini and colleagues reported late toxicity rates from a group of 247 patients (67.6% and 32.4% treated with adjuvant and salvage intent, respectively) undergoing HFRT (median dose: 71.4 Gy; median dose per fraction: 2.5 Gy). Five-year grade 3-4 late GU toxicity was recorded in 18.1% of patients (CTCAE 4.0). The toxicity rate progressively worsened with the dose per fraction increasing from 1.8 Gy to 2.55 Gy. The authors observed that this risk of urinary effects must be considered in the benefit-risk ratio (30).

Katayama and co-workers in the PRIAMOS-1 phase 2 trial evaluated the safety and toxicity of hypofractionated IMRT on the prostate bed (54 Gy in 3 Gy per fraction). No patient developed grade ≥3 acute GI and/or GU toxicity based on CTCAE 4.0 (31).

Gladwish and colleagues tested adjuvant and salvage HFRT in a prospective phase 1-2 study. Thirty men treated with 51.0 Gy in 3 Gy per fraction showed 0% and 3.0% grade ≥3 acute GI and GU toxicity, respectively. Grade ≥2 late GI and GU adverse effects were reported in 3.0% and 6.0% of patients, respectively, based on CTCAE 3.0 criteria. Crude rate of bRFS was recorded in 83.0% of patients. The authors concluded that treatment tolerance and biochemical control of the disease were encouraging (32).

In Lewis and colleagues trial, 56 IMRT hypofractionated adjuvant or salvage treatments were performed delivering 57.5-65.0 Gy in 2.5 Gy per fraction on the prostate bed. With a median follow up of 48 months, grade ≥2 late GI and GU toxicity rates were 3.6% and 66.1%, respectively, based on CTCAE 4.0. No cases of grade ≥3 acute GI and GU toxicity. Crude OS was 96.4% and actuarial 4-year bRFS was 75.0% (33).

Fersino and co-workers trial (34) retrospectively analyzed 125 patients previously treated with moderate adjuvant or salvage HFRT. Based on CTCAE 4.0, grade ≥ 3 acute GI and GU toxicity rates were 0% and 0.8%, respectively. Grade ≥ 2 late GI and GU were observed in 8.0% and 12.0%, respectively. Actuarial 3-year bRFS in adjuvant and salvage setting was 94.0% and 77.0%, respectively.

The last published study on postoperative HFRT was the Macchia and collegues trail (35). This Italian group in a prospective phase 1-2 study enrolled 124 patients: 85.5% and 14.5% for adjuvant and salvage RT, respectively. Using IMRT-SIB (62.5 Gy and 45 Gy in 25 fractions to the prostate bed and pelvic nodes) grade ≥3 acute GI and GU toxicity was reported in 0% and 0.8% of patients, respectively. Five-year grade ≥2 late GI and GU was 1.1% and 7.3% based on RTOG/EORTC scale. Three- and 5-year LC, OS, and bRFS were 99.9% and 94.9%, 100% and 100%, and 91.1% and 86.5%, respectively.

Literature analysis. Seventeen eligible studies were included. (19-35) These retrospective (20, 23-25, 27, 30, 34) [7] and prospective (19, 21, 22, 26, 28, 29, 31-33, 35) [10] trials had heterogeneous characteristics in terms of dose, target definition and combination with hormonal therapy. Median follow-up ranged between 11.5 and 111.0 months (median: 30.0 months).

Patients characteristics. A total of 1208 patients were included. Patients treated for adjuvant and salvage setting in the different studies ranged between 13.3% and 100% (median: 76.9%), and between 14.5% and 100% (median: 52.5%), respectively. One trial did not report the specific percentage of patients treated with adjuvant and salvage HFRT (24). Gleason grading was reported in ten trials (20, 23, 25, 26, 28-30, 32, 33, 35). Range and median of pathological Gleason score ≥7 were 30.0-93.0% and 61.0%, respectively. Thirteen authors (19, 20, 22, 23, 25, 26, 28-30, 32-35) reported data on positive surgical margins with a median value of 69.0% (range=21.0-85.0%). PSA at diagnosis and before RT, were reported in ten (19, 20, 22, 23, 25, 28-30, 33, 35) and fourteen (19, 20, 22, 23, 25-34) trials (median: 8.25 ng/ml and 0.32 ng/ml, respectively).

Treatment characteristics. In all trials, the RT technique was specified except in one (19). Most (12 trials) were performed with IMRT (21-25, 28-33, 35) and 5 of these used an IMRT-SIB approach (21, 28-30, 35). VMAT technique was used in two series (27, 34) and 3DCRT in two trials (20, 26).

Clinical targets volumes definitions were: prostate bed alone in 7 studies (19, 20, 22, 27, 31-33) and prostate bed and pelvic lymph nodes in 10 (21, 23-26, 28-30, 34, 35) trials. The delivered dose to prostate bed and pelvic nodes was 50.0-74.2 Gy and 37.8-56.0 Gy, respectively. Fractionation ranged between 2.0 and 3.4 Gy and between 1.8 and 2.7 Gy for prostate bed and pelvic nodes, respectively.

Some form of image guidance was used in 10 trials (21-23, 25, 27, 30-34) while in 6 reports (19, 20, 24, 26, 28, 29, 35) this information was not available.

EQD2 calculated with α/β=1.5 and α/β=3 ranged between 57.1 and 82.6 Gy and between 55 and 79.2 Gy, respectively, with this value not evaluable in 1 trial (21).

Data on androgen deprivation therapy were reported in 10 series (19, 23, 25, 26, 29-33, 35) with 17.4% median percentage of patients receiving this systemic treatment (range=8.0-79.8%).

Results

No case of Grade ≥3 acute GI toxicity was recorded. Grade ≥3 acute GU toxicity ranged between 0% and 3.0% (median: 0%).

Crude rates of Grade ≥2 late GI toxicity were 0-8.7% (median: 3.6%) and crude rates of grade ≥2 late GU toxicity were 0-66.0% (median: 12.0%). Five-year grade ≥2 late GU toxicity ranged between 7.3% and 18.1%. LC was reported only in three studies: 93.7% (26) (crude rate), and 69.0% (19) and 94.9% (35) at 5-years, respectively. Crude rate of OS ranged between 96.4% and 100% (median: 98.5%). Actuarial rates of OS were 100% (35) at 3 and 5 years and 91.0% (19) at 10 years. Crude rate of bRFS was 83.0% (32), 85.4% (26), and 100% (22) in three studies, respectively. Actuarial rates of bRFS ranged between 83.7% and 92.0% at 1 year, 72.9% and 83.0% at 2 years, and 74.0% and 94.0% (median: 84.0%), 67.0% and 75.0%, 86.5% at 3, 4 and 5 years, respectively (data reported in 6 trails).

Discussion

RP is one of the standard treatment options for patients with localized PCa and life expectancy longer than 10 years, regardless of risk category (1, 2). However, up to 30% of patients treated with surgery require postoperative RT for high-risk pathological features or for biochemical failure (35-38). PCa is a relatively radio-resistant tumor, with a strong dose-response relationship. In fact, there is evidence that biochemical control of disease improves by increasing the delivered RT dose. Prospective phase 1-2 trials have shown the efficacy and safety of postoperative treatment with total doses ≥70 Gy and standard fractionation on surgical bed, with improved bRFS without significant worsening of toxicity (10, 39, 40). Based on PCa low α/β ratio, several trials tested HFRT in a curative setting (12-14). However high-level evidence in the adjuvant and salvage setting are currently lacking.

This is the first systematic analysis comparing published trials on postoperative HFRT in patients with PCa, without time limits. In our analysis no randomized trials were found, and most studies (eleven out of seventeen) enrolled a small number of patients (≤50) with a short follow-up duration. Furthermore, the different studies were heterogeneous in terms of pathological features of disease, dose, radiotherapy aim, target volume and concomitant systemic therapy.

Within these limits, preliminary results on HFRT in this setting showed an acceptable disease control with reasonable radiotherapy-induced toxicity profile.

Comparing the seventeen selected trials there are different results about late radiation-induced effects (grade ≥2 late GU toxicity: 0-66.1%, median: 12.0%).

Cozzarini and colleagues reported a high rate (5-year: 18.1%) of grade ≥3 late GU toxicity, significantly higher compared to a cohort of patients receiving conventionally fractionated RT (5-year: 6.9%) (30). In multivariate analysis, acute grade ≥2 and dose per fraction independently predicted late GU toxicity. The highest percentage of crude toxicity (grade ≥2 late GU: 66.1%) with a median follow-up of 48.0 months (range=21-67 months) was reported by Lewis's group (33). The reason of this unexpected outcome is unclear because the authors used an IG-IMRT technique delivering a similar total dose and dose per fraction compared to other studies (median dose: 65.0 Gy in 2.5 Gy per fraction). Even the low percentage of patients receiving hormone suppressive therapy (17.8%) as well as RT target (prostatic fossa only) cannot explain this result. The authors of this analysis suggested some explanation in a subsequent publication (41). All their patients were treated and followed based on a detailed electronic medical record system. This could have given the opportunity to capture intermittent events normally not detected with a standard follow-up modality. Also, 60.0% of their patients were receiving anticoagulants which could have contributed to the incidence of gross hematuria. Finally, the authors stressed that the use of Radiation Therapy Oncology Group consensus guidelines could have led to the irradiation of larger bladder volumes, compared to other series.

A reasonable explanation about high late GU toxicity rate (grade ≥2: 46.1%) shown by Syndikus and colleagues (19) may be due to the use of obsolete technique (60cobalt machine) as well as dose per fraction up to 3.1 Gy (mean: 2.76 Gy).

In three studies, the percentages of severe late GU toxicity were comparable (11.0-15.0%) (22, 25, 27). All these authors prescribed in both adjuvant and salvage treatments a daily dose lower than 3.0 Gy on the prostate bed (range=2.5-2.9 Gy) using advanced treatment techniques such as IG-IMRT or VMAT with cone beam CT. The data on late toxicity reported by the other four studies was very encouraging, with a late GU toxicity rate ranging between 0% and 7.0% (20, 23, 26, 32, 35). The results achieved by Koukourakis and colleagues and Gladwish and co-workers are particularly interesting (26, 32). Despite the delivery of 3.4 and 3.0 Gy per fraction, respectively, late grade ≥2 GU toxicity rates were only 0% and 3.0%. It should be noted that the Greek group (26) used a 3D-CRT technique, while all the other studies used IMRT.

Probably, in this latter trial, the high-dose of amifostine positively impacted the results in terms of treatment tolerability.

About grade ≥2 late GI toxicity, all studies showed a low incidence (0-9.0%). The highest rate of this toxicity occurred in the study of Syndikus and his group (19) despite it not including irradiation of pelvic lymph nodes in the treatment field. These results are probably due to the RT technique, as mentioned above.

Homogeneous results were also observed for acute toxicity. In fact, grade ≥ 3 acute GI and GU toxicity were recorded in 0% and 0-3% of patients, respectively. Based on these homogeneous results, it seems that prophylactic lymph nodes irradiation as well as concomitant androgen suppressive therapy did not worsen short term toxicity.

LC rate was reported by 3 trials (19, 26, 35). The higher LC rate (3-year: 99.9% and 5-year: 94.9%) was observed in Macchia and co-workers study despite the high percentage of patients with high-risk features (GS ≥7: 78.2%; R1 resection: 84.7%) enrolled in the trial and non-negligible percentage of patients with biochemical or local failure (salvage RT: 14.5%) (35). An explanation of this excellent result may be the choice of administering a prophylactic irradiation on pelvic nodes combined with hormonal therapy in 80% of patients. Another excellent result was reported in Koukourakis and colleagues trial (26) despite the high percentage of patients with disease failure (salvage RT: 56.2%) and high-risk Pca (GS ≥7: 54.2%; R1 resection: 20.8%) enrolled in the study. This result may be due to the higher dose per fraction (3.4 Gy in 15 fractions) compared to other studies, or irradiation of pelvic lymph nodes with HFRT (2.7 Gy/fraction) and combination with hormonal therapy in 47.9% of patients. Actuarial 5- and 10-year LC in Syndikus and colleagues trial were 69.0% and 54.0%, respectively (19). This result was reported only for patients with local recurrence while data on patients treated with early RT were not reported. Also for this study, the use of a high dose per fraction (2.76 Gy) and combination with hormonal therapy could explain the high local control rate.

Actuarial long-term OS was reported in Syndikus and Macchia trials: 91.0% at 10 years (19) and 100% at 3 and 5 years (35), respectively. Four other trials with median follow-up 36.0 (20), 18.9 (23), 32.4 (25), and 48.0 months (32) reported excellent crude OS rates (100%, 98.0%, 99.1%, and 96.4%, respectively). Delivery of a daily minimum dose of 2.5 Gy on the prostate bed and the choice to irradiate regional lymph nodes (as done in two of these trials (23, 25, 35)) in patients with high-risk disease and biochemical relapse could probably have had a positive impact on OS.

In the salvage setting, two studies reported 83.7-92.0% and 72.9-83.0% 1- and 2-year bRFS, respectively (20, 23). The better results recorded by Wong and colleagues (23) compared to Lee and co-workers (20) could be explained by the higher pathological tumor grade in the latter series (GS ≥7: 58.0% *vs*. 30.0%, respectively). Three studies reported 3-year bRFS ranging between 74.0% and 94.0% (20, 34, 35). As expected, the results were better in the adjuvant setting (94.0%) (34) compared to the salvage setting (74.0-77.0%) (20, 34). Four-year bRFS was reported in two studies ranging between 67.0% and 75.0% (25, 33). This difference can by justified by the inclusion in the Kruser and colleagues' studies, of only patients treated for biochemical relapse (25). In a series of patients undergoing adjuvant (85.5%) and salvage (14.5%) RT, 86.5% bRFS at 5-year was shown (35).

Other authors reported only crude bRFS rates (83.0% (32), 85.4% (26), 100% (22)) with a median follow up of 25.0, 41.0, and 24.0 months, respectively (22, 26, 32). The highest percentage of biochemical control was reported by Cozzarini and colleagues (22). It should be noted that their series was the one with the lowest median PSA before HFRT (0.02 ng/ml) compared to the other two trials (26, 32).

Considering the follow-up duration, also the results of Koukourakis and co-workers (26) seem positive, with 85.4% bRFS at median follow-up of 41 months. The high dose per fraction on the surgical bed (3.4 Gy per fraction) and the choice of an hypofractionated regimen to the pelvic lymph nodes (2.7 Gy per fraction) could have produced a positive impact on biochemical control, as previously mentioned for LC.

In conclusion, postoperative HFRT seems feasible and relatively well tolerated based on most published trials. However, it should be noted that: i) one trial showed a high 5-year grade ≥3 late GU toxicity (18.1%) (30), ii) two trials showed a high incidence of grade ≥2 late GU toxicity (46.1% and 66.1%) (19, 33), iii) median follow-up between the analysed series was short (median: 30.0 months), iv) most series reported only crude data on late toxicity with a relevant risk of underestimating these effects. Therefore, in absence of clear data on radiation induced toxicity, in accordance with Hegemann and colleagues (42) and Höcht and coworkers (43) opinions, HFRT following radical prostatectomy should be used only in clinical trials. Randomized trials comparing postoperative RT with standard fractionation versus HFRT seem justified.

Conflicts of Interest

No actual or potential conflicts of interest exist regarding this paper.

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