International Journal of Radiation Oncology biology • physics

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Critical Review

Conventional Versus Hypofractionated Radiation Therapy for Localized or Locally Advanced Prostate Cancer: A Systematic Review and Meta-analysis along with Therapeutic Implications

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Received May 30, 2017, and in revised form Jul 14, 2017. Accepted for publication Jul 18, 2017.

Purpose: A systematic review and meta-analysis were conducted to evaluate the therapeutic outcomes of conventional radiation therapy (CRT) and hypofractionated radiation therapy (HRT) for localized or locally advanced prostate cancer (LLPCa).

Methods and Materials: A total of 599 abstracts were extracted from 5 databases and screened in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Only phase III trials randomized between CRT and HRT in LLPCa with a minimum of 5 years of follow-up data were considered. The evaluated endpoints were biochemical failure, biochemical and/or clinical failure, overall mortality, prostate cancer-specific mortality, and both acute and late gastrointestinal (GI) and genitourinary (GU) (grade $\geq$2) toxicity.

Results: Ten trials from 9 studies, with a total of 8146 patients (CRT, 3520; HRT, 4626; 1 study compared 2 HRT schedules with a common CRT regimen), were included in the evaluation. No significant differences were found in the patient characteristics between the 2 arms. However, the RT parameters differed significantly between CRT and HRT ($P<.001$ for all). The use of androgen deprivation therapy varied from 0% to 100% in both groups (mean $\pm$ standard deviation 43.3% $\pm$ 43.6% for CRT vs HRT; P=NS). The odds ratio, risk ratio, and risk difference (RD) between CRT and HRT for biochemical failure, biochemical and/or clinical failure, overall mortality, prostate cancer-specific mortality, acute GU toxicity, and late GU and GI toxicities were all nonsignificant. Nevertheless, the incidence of acute GI toxicity was 9.1% less with CRT (RD 0.091; odds ratio 1.687; risk ratio 1.470; $P<.001$ for all). On subgroup analysis, the patient groups with $\leq$66.8% versus >66.8% androgen deprivation therapy (RD 0.052 vs 0.136; $P=.008$) and <76% versus $\geq$76% full seminal vesicles in the clinical target volume (RD 0.034 vs 0.108; $P<.001$) were found to significantly influence the incidence of acute GI toxicity with HRT.

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Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Acknowledgments—The authors acknowledge Nicci Lomax, Physicist, Kantonsspital Aarau, Switzerland for reviewing the rectal dose–volume constraints and Professor Michael Borenstein, Biostat, USA for his input on the meta-analysis. Partial fundings by Kelm Stiftung and Forschungsrat KSA, Switzerland is also acknowledged.

Int J Radiation Oncol Biol Phys, Vol. 99, No. 3, pp. 573–589, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.07.021

Conclusions: HRT provides similar therapeutic outcomes to CRT in LLPCa, except for a significantly greater risk of acute GI toxicity. HRT enables a reduction in the overall treatment time and offers patient convenience. However, the variables contributing to an increased risk of acute GI toxicity require careful consideration.

Introduction

Hypofractionated radiation therapy (HRT) regimens for localized or locally advanced prostate cancer (LLPCa) have been compared with conventional radiation therapy (CRT) in a number of prospective phase III randomized clinical trials (1-10). The feasibility of exploring HRT regimens for LLPCa has been of interest, because these tumors are considered to have a fractionation sensitivity with low α/β values, similar to those of late-responding normal tissues. The α/β values for prostate cancer have been estimated by several investigators to range from 1 to 1.8 Gy, even lower than the adjacent late-responding normal structures, such as the rectum and bladder ($\alpha/\beta \approx$ 3-5 Gy) (11-15).

HRT would, therefore, be expected to result in improved therapeutic outcomes compared with CRT. Fewer hospital visits for HRT would not only make it more convenient, especially for elderly patients, but also economically attractive (16). However, before HRT can be adopted as a standard of care for LLPCa, it is mandatory to assess the long-term therapeutic outcomes in terms of both the efficacy and the incidence of acute and late toxicity compared with CRT protocols.

To address this issue, a number of randomized trials between HRT and CRT have been performed either as single-institution or multicenter trials. Some of these studies were designed as noninferiority trials (1, 3, 4) and have now been reported with a minimum of 5 years of follow-up data (1-9). Although all these studies included LLPCa, differences were present in the patient population in terms of the T stage, Gleason score, pretreatment prostate-specific antigen level, risk category, use of androgen deprivation therapy (ADT), irradiated portals, and radiation therapy (RT) schedules (ie, total dose, dose/fraction, number of fractions, and overall treatment time [OTT]) in both regimens. The outcomes are usually reported as biochemical failure (BF), biochemical and/or clinical failure (BCF), overall survival, prostate cancer-specific survival, and early and late gastrointestinal (GI) and genitourinary (GU) toxicity.

It was desirable to synthesize the multiple studies to examine the therapeutic potential of HRT in LLPCa. The relatively large patient population enrolled in these trials, with a wide range of both patient characteristics and RT schedules, also provides an opportunity to explore possible predictive covariates that could significantly influence the clinical outcomes. The present study was performed to address these issues through a systematic review and meta-analysis of randomized trials between HRT and CRT for LLPCa.

Methods and Materials

Search strategy

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (17) (Fig. 1). Five databases (ie, PubMed, Embase, Scopus, Web of Science, and the Cochrane library) were searched. The terms used were "prostatic neoplasms" (MeSH terms)" AND "radiotherapy" (MeSH terms) AND "hypofractionated" (all fields) AND "randomized controlled trial" (ptyp). The search was not limited to any date. The last search was performed on March 30, 2017. Additional reports and abstracts of presentations at key radiation oncology conferences were retrieved through a manual search. The lead authors of the reports were contacted for updates and clarifications when required.

Inclusion criteria

The study inclusion criteria were prospective randomized clinical trials of HRT and CRT for LLPaC; a minimum follow-up period of 5 years; studies that treated patients exclusively with external beam photon RT; and reports in the English language. In the case of multiple reports from the primary study, all updates of the treatment outcomes reported were considered.

Study selection

From a total of 599 citations, 387 reports remained after removing the duplicates. An additional 316 studies were omitted on the basis of their title and/or abstract (Fig. 1). Finally, 71 reports were subjected to a full text review to assess their suitability according to the stated inclusion criteria. The following studies were excluded after a full review: nonrandomized or retrospective studies; studies of RT dose escalation; studies including the use of protons or brachytherapy as part or full treatment; reports from shortlisted trials that were subsequently updated by the trial group; and studies with $<$5 years of follow-up data. Thus, 19 reports from 9 randomized studies were considered for the final meta-analysis.

Data extraction, quality assessment, and critical appraisal

The endpoints for evaluation were BF, BCF, overall mortality (OM), prostate cancer-specific mortality (PCaSM), GI

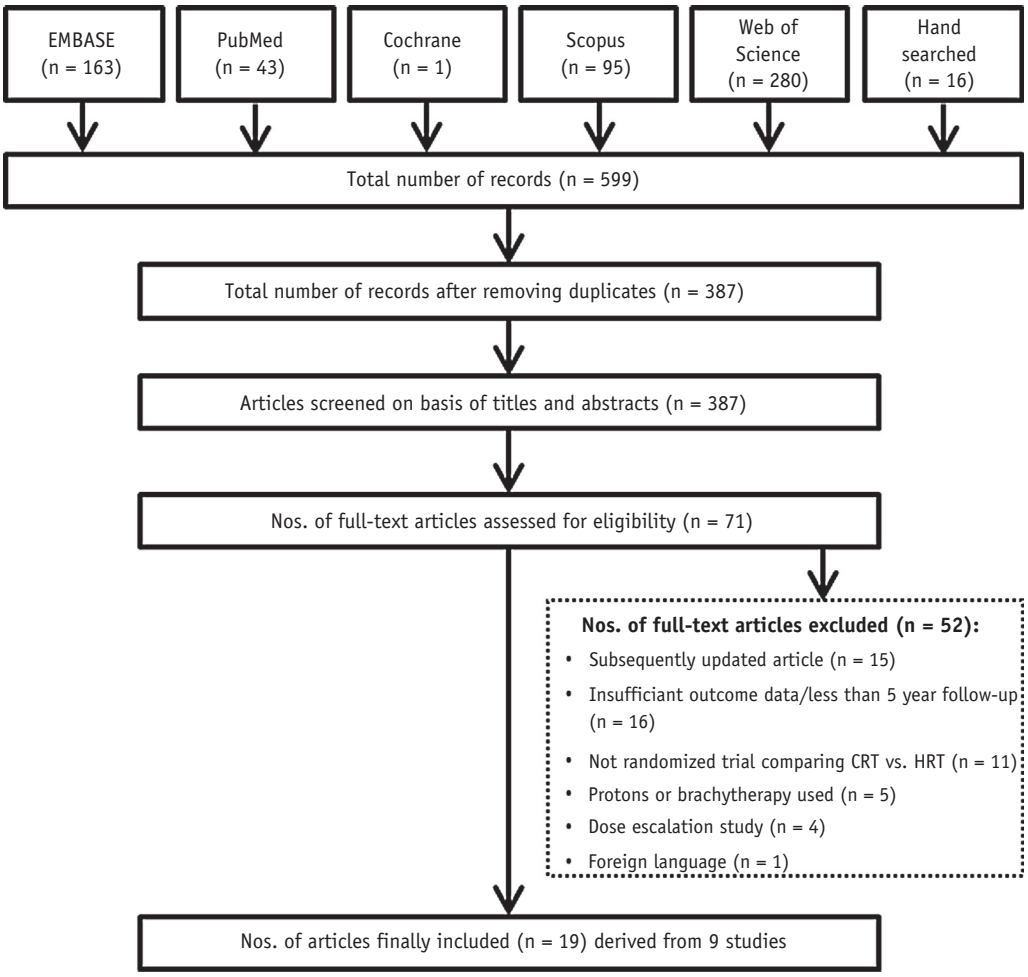


Fig. 1. Flow chart showing the study selection procedure for shortlisting the 9 randomized trials of hypofractionated (HRT) and conventional radiation therapy (CRT) for localized and/or locally advanced prostate cancer. One of the trials (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer trial) had 3 treatment arms.

and GU acute and late grade ≥2 toxicity. All studies were extracted independently by 2 of us (N.R.D., E.S.) and critically reviewed. In the case of any discrepancies, a consensus was reached by discussion with the other co-authors (S.R., S.B.). The risk of bias was assessed using the Cochrane collaboration tool (18). The shortlisted studies were reviewed further by all co-authors to ascertain the correctness of all entries.

Most of the studies reported their outcomes through serial publications at different periods. Thus, all studies were listed in the forest plots using the acronym of the trials or name of the institution or the lead author. The most recent results were used whenever possible to compute the effect measures. The details from the several reports of the individual studies were collated to extract all the possible information. The trials included were: (*1*) Prostate Fractionated Irradiation Trial (PROFIT; 27 centers across Canada, Australia, and France; n = 1206) (1); (*2*) Regina Elena National Cancer Institute trial (IRE; Rome, Italy; n = 168) (2, 19, 20); (*3*) Radiation Therapy Oncology Group (RTOG) 0415 study (308 participating centers, United States; n = 1092) (3); (*4*) Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP; 71 centers; United Kingdom; n = 3216 in 3 arms) (4); (*5*) Hypofractionated Irradiation for Prostate Cancer (HYPRO; 7 Dutch centers; n = 804) (5, 21, 22); (*6*) Fox Chase Cancer Center (FCCC; United States; n = 303) (6, 23, 24); (*7*) Royal Adelaide Hospital (RAH; Australia; n = 217) (7, 25-27); (*8*) MD Anderson Cancer Center (MDACC; United States; n = 204) (8, 28); and (*9*) Lukka et al (16 Canadian centers; n = 936) (9, 26). The various outcomes reported in the different trials were as follows: BF (1-3, 5, 7-9), BCF (1, 4-6, 8, 9), OM (1-7, 9), PCaSM (1-3, 5-9), acute GI toxicity (1-6, 9), late GI toxicity (1-6, 8, 9), acute GU toxicity (1-6, 9), and late GU toxicity (1-6, 8, 9). All GI and GU toxicities evaluated pertain only to grade ≥2.

Estimation of biologically effective dose

The biologically effective dose (BED) for prostate cancer was computed for each of the individual CRT and HRT schedules using the expression: BED = $nd(1+d/[\alpha/\beta])$,

Table 1 Summary of randomized trials between hypofractionated and conventional fractionated radiation therapy included in the meta-analysis

Study	Arm	Total (n)	T stage	GS	PSA (ng/mL)	Risk category (%)			ADT (%)
						L	I	H	
PROFIT (1)	CRT	598	T1-T2	≤7	≤20	0	100	0	5.1
	HRT	608	T1-T2	≤7	≤20	0	100	0	6.0
IRE (2, 19, 20)	CRT	85	T1-T3	≤10	≤100	0	0	100	100
	HRT	83	T1-T3	≤10	≤100	0	0	100	100
RTOG 0415 (3)	CRT	542	T1-T2	≤6	<10	100	0	0	0
	HRT	550	T1-T2	≤6	<10	100	0	0	0
CHHiP (HRT_{60}) (4)	CRT	1065	T1-T3	≤8	<40	15	73	12	97.3
	HRT	1074	T1-T3	≤8	<40	15	73	12	97.5
CHHiP (HRT_{57}) (4)	CRT	1065	T1-T3	≤8	<40	15	73	12	97.3
	HRT	1077	T1-T3	≤8	<40	15	73	12	96.8
HYPRO (5, 21, 22)	CRT	397	T1-T4	≤10	≤60	0	27	73	67.2
	HRT	407	T1-T4	≤10	≤60	0	26	74	66.3
FCCC (6, 23, 24)	CRT	152	T1-T3	≤10	≤80	15.8	55.9	28.3	46.7
	HRT	151	T1-T3	≤10	≤80	14.6	57	28.5	45
RAH (7, 25-27)	CRT	109	T1-T2	≤10	≤80	31.2	57.8	11	0
	HRT	108	T1-T2	≤10	≤80	24.1	52.8	23.1	0
MDACC (8, 28)	CRT	102	T1-T2	≤8	≤20	29	71	1	19.6
	HRT	102	T1-T2	≤8	≤20	27	72	1	22.5
Lukka et al (9, 26)	CRT	470	T1-T2	≤9	≤40	24	59.1	16.8	0
	HRT	466	T1-T2	≤9	≤40	24.2	56.9	75.8	0

Abbreviations: ↑ = increased with treatment modality; ADT = androgen deprivation therapy; BCF = biochemical and/or clinical failure; BF = biochemical failure; CRT = conventional radiation therapy; D = dose; FU = follow-up; Fx = fraction; GI = gastrointestinal; GS = Gleason score; GU = genitourinary; H = high; HRT = hypofractionated radiation therapy; I = intermediate; L = low; NA = not available; OM = overall mortality; OTT = overall treatment time; PCaSM = prostate cancer-specific mortality; PSA = prostate-specific antigen; RT = radiation therapy; TD = total dose.

* *P* values provided if reported and statistically significant.

† Follow-up time for late toxicity.

‡ Four fractions per week.

§ Three fractions per week.

‖ As stated in Yeoh et al (7): late toxicity in GI/GU not classified as grades 1 to 4.

¶ As per the American Society for Radiation Oncology definition.

As stated by Lukka et al (9).

** Acute and late toxicity reported as grade ≥3.

where "n" is the number of RT fractions and "d" is the dose per fraction and assuming an α/β of 1.5 Gy (11, 14). No time factor correction was used.

The BED for acute GI effects for each of the fractionation arms was computed with a time factor correction using $BED = nd(1+d/[\alpha/\beta]) - \log_e 2\,(T - T_k)/\alpha T_p$, where T is the

Table 1 Summary of randomized trials between hypofractionated and conventional fractionated radiation therapy included in the meta-analysis *(continued)*

RT schedule					Differences in reported outcomes (CRT vs HRT)*	
TD (Gy)	D/Fx (Gy)	Fx (n)	OTT (d)	FU (y)	BF, BCF, OM, PCaSM	GI, GU toxicities (grade ≥2)
78.0	2.0	39	53	5	BF, NS	Acute GU, NS
60.0	3.0	20	26		BCF, HRT noninferior	Late GU, NS
					OM, NS	Acute GI, ↑HRT ($P=.003$)
					PCaSM, NS	Late GI, ↑CRT ($P=.006$)
80.0	2.0	40	54	10; 9†	BF, NS	Acute GU, NS
62.0	3.1‡	20	33		BCF, NA	Late GU, NS
					OM, NS	Acute GI, NS
					PCaSM, NS	Late GI, NS
73.8	1.8	41	57	5	BF, HRT noninferior	Acute GU, NS
60.0	2.5	24	38		BCF, NA	Late GU, ↑HRT ($P=.009$)
					OM, HRT noninferior	Acute GI, NS
					PCaSM, NS	Late GI, ↑HRT ($P=.005$)
74.0	2.0	37	51	5	BF, NA	Acute GU, NS
60.0	3.0	20	26		BCF, HRT noninferior	Late GU, ↑HRT ($P=.07$)
					OM, NS	Acute GI, ↑HRT ($P<.0001$)
					PCaSM, NA	Late GI, NS
74.0	2.0	37	51	5	BF, NA	Acute GU, NS
57.0	3.0	19	25		BCF, HRT inferior	Late GU, NS
					OM, NS	Acute GI, ↑HRT ($P<.0001$)
					PCaSM, NA	Late GI, NS
78.0	2.0	39	53	5; 3†	BF, NS	Acute GU, NS
64.6	3.4§	19	43		BCF, HRT not superior	Late GU, NS
					OM, NS	Acute GI, ↑HRT ($P=.0015$)
					PCaSM, NS	Late GI, NS
76.0	2.0	38	52	5	BF: NA	Acute GU, NS
70.2	2.7	26	36		BCF, NS	Late GU, NS
					OM, NS	Acute GI, NS
					PCaSM, NS	Late GI, NS
64.0	2.0	32	44	7.5; 5†	BF, HRT better ($P<.05$)	Acute GU, NA
55.0	2.75	20	26		BCF, NA	Late GU, NS‖
					OM, NS	Acute GI, NA
					PCaSM, NS	Late GI, NS‖
75.6	1.8	42	58	5	BF, NS	Acute GU, NA
72.0	2.4	30	40		BCF, NS	Late GU, NS
					OM, NS	Acute GI, NA
					PCaSM, NS	Late GI, NS
66.0	2.0	33	45	5	BF¶,#, HRT might be inferior	Acute GU**, ↑HRT (significant)
52.5	2.62	20	26		BCF¶,#, HRT might be inferior	Late GU**, NS
					OM, NS	Acute GI**, NS
					PCaSM, NS	Late GI**, NS

OTT (in days), T_k, the kick-off time (7 days), T_p, the average doubling time (2.5 days), α is 0.35/Gy, and α/β is 10 Gy (14). For late GI effects, the BED was computed assuming α/β as 3 Gy without any time factor correction (14).

Statistical analysis

Comprehensive Meta-analysis Software, version 3.0, was used to perform the meta-analysis (29). Effect measures

were computed for all dichotomous outcomes and were scored as events related to BF, BCF, OM, and PCaSM. With regard to toxicity, all acute and late toxicities (grade $\geq$2) were considered as an event. The odds ratio (OR), risk ratio (RR), and risk difference (RD) for each of the desired endpoints were computed, and results are given by the point estimate, 95% confidence interval (CI), Z value, and *P* value. Heterogeneity was assessed using the I^2 statistic, which represents the estimated proportion of unexplained interstudy variance before pooling the data from the studies. An I^2 of $\leq$40% was considered to indicate the absence of any substantial heterogeneity (30). A fixed-effect model was used for outcomes with nonsignificant heterogeneity in the estimated effect measure. In the case of significant heterogeneity, a random-effects model was used. Potential publication bias was evaluated through funnel plots and rank correlation tests using Kendall's tau (31). Subgroup analyses were performed of the RD using a mixed-effects model. The random-effects model was used to combine studies within each subgroup, and a fixed-effect model was used to combine the subgroups and yield the overall effect. The Q value, degrees of freedom, and *P* value were computed for each of the subgroups evaluated. All statistical analyses were performed by the corresponding author, who can be contacted for any clarifications related to the analyses.

Results

Study inclusion

A total of 9 randomized trials reported from 2005 to 2017 were finally considered (1-9). The CHHiP study (4) used 2 different HRT schedules (HRT_{60}, 60 Gy/20 fractions; and HRT_{57}, 57 Gy/19 fractions). These were compared against a common CRT arm (74 Gy/37 fractions). These 2 HRT arms (CHHiP HRT_{60} and CHHiP HRT_{57}) were compared individually with the CRT arm in the present meta-analysis. Thus, 10 randomized comparative study arms between HRT and CRT were available for evaluation (Table 1).

A total of 8146 patients were included in these 9 studies (CRT, n=3520; HRT, n=4626). In 3 studies, the patients were treated with 2-dimensional (2D) or 3-dimensional conformal RT (3D-CRT) (2, 7, 9). Intensity modulated RT (IMRT) was used exclusively in 3 studies (4, 6, 8). In the remaining studies, treatment was undertaken using both 3D-CRT and IMRT, with most patients undergoing IMRT (1, 3, 5).

Patient demographic data and treatment schedules in CRT and HRT studies

No significant differences were found in the demographic data of the patients included in the 2 arms with respect to T stage, Gleason score, pretreatment prostate-specific antigen, and risk category (Table 2). Five studies included varying proportions of patients in the low-, intermediate-, and high-risk groups (4, 6-9). One study each included patients exclusively in the low-risk (3), intermediate-risk (1), and high-risk (2) categories, and one had included only intermediate- and high-risk patients (5).

ADT was initiated with RT in approximately 43% of both CRT and HRT patients (range 0%-100%; *P*=NS; Table 2). Each of the 10 comparative arms used a different RT schedule and OTT for CRT versus HRT, and the differences for each of these parameters were statistically significant. Consequently, the BED computed for prostate and acute GI effects were significantly different in the 2 groups (Table 2).

Effect measures for various outcomes: HRT versus CRT

The endpoints evaluated were BF, BCF, OM, PCaSM, and both acute and late GI and GU (grade $\geq$2) toxicity. Of the 10 comparative arms, BF, BCF, OM, and PCaSM were available for effect measures in 7, 7, 9, and 8 trials, respectively. Acute GI and GU toxicities were estimated from 7 randomized comparisons, and late GI and GU toxicities were estimated from 8 of the 10 study arms. Lukka et al (9) reported only grade $\geq$3 toxicities; thus, their study was not considered for the effect measures because the remaining studies pertained only to grade $\geq$2 toxicities. Because the studies were updated in subsequent reports by the respective study groups, the most recent outcomes were considered for each of these endpoints. Additional information was also obtained from an update of the studies listed in the report by Miralbell et al (26). All studies had a minimum follow-up period of 5 years.

BF was mostly assessed using the Phoenix criteria (32). Lukka et al (9) reported BF and BCF using the American Society for Radiation Oncology guidelines (33) in 2005; the Phoenix criteria were reported in 2006. Considering all trials, 20.6% of the HRT and 22.1% of the CRT patients experienced BF and 18.0% and 17.8% of the HRT and CRT patients developed BCF, respectively. Death from any cause, or OM, was reported in 10.6% versus 11.7% of HRT versus CRT patients, respectively. PCaSM was documented in 1.9% and 2.5% of patients in the HRT and CRT groups, respectively. The RD, OR, and RR of all these outcome measures showed no significant differences between the HRT and CRT groups, and no heterogeneity was observed for any of these endpoints (Fig. 2a-d; Figs. E1a-d and E2a-d; available online at www.redjournal.org).

The acute GI toxicities were reported to be significantly greater with HRT (HRT, 29.1% vs CRT, 19.8%) across all 3 effect measures (RD 0.091; OR 1.687, RR 1.470; *P*<.001 for all), with significant heterogeneity for RD (*P*<.001). Wherever stated, the maximum grade of GI and GU toxicities were considered. The incidence of late GI toxicity was similar in both groups (RD 0.006; OR 1.013; RR 1.004; *P*=NS for all). However, significant heterogeneity was observed for the 3 effect measures for late GI toxicity (RD, I^2 = 74.51; OR, I^2 = 74.10; RR, I^2 = 73.78; *P*<.001 for all). Neither the acute nor late GU toxicities exhibited

Table 2 Comparison of patient population and treatment characteristics of hypofractionated and conventional fractionated radiation therapy arms included in meta-analysis

Demographic Variable	Treatment arm		*P* value‡
	CRT*	HRT†	
Patient characteristic			
Tumor stage			
T1-T2	418.00 ± 353.49 (74-979)	418.80 ± 354.69 (72-983)	.636
T3-T4	40.30 ± 67.51 (0-206)	43.60 ± 71.31 (0-214)	.093
Gleason score			
≤6	192.20 ± 184.30 (9-542)	194.10 ± 187.79 (7-550)	.395
≥7	266.30 ± 275.37 (0-694)	268.50 ± 278.56 (0-713)	.429
PSA (ng/mL)			
<10	300.22 ± 209.62 (54-542)	304.33 ± 212.86 (47-550)	.412
≥10	196.67 ± 216.05 (0-544)	198.33 ± 213.29 (0-551)	.671
Risk category			
Low	105.60 ± 165.62 (0-542)	106.60 ± 168.99 (0-550)	.527
Intermediate	276.10 ± 318.69 (0-779)	276.10 ± 322.09 (0-784)	1.000
High	76.80 ± 90.59 (0-290)	79.90 ± 93.01 (0-303)	.144
Treatment parameter			
Patients receiving ADT (%)	43.33 ± 43.80 (0-100)	43.41 ± 43.45 (0-100)	.838
Total dose (Gy)	73.94 ± 5.15 (64-80)	62.33 ± 6.74 (52.5-72)	<.001
Dose/fraction (Gy)	1.96 ± 0.08 (1.8-2.0)	2.85 ± 0.30 (2.4-3.4)	<.001
Fractions (n)	37.80 ± 3.22 (32-42)	22.20 ± 4.13 (19-30)	<.001
Overall treatment time (d)	51.80 ± 4.49 (44-58)	31.90 ± 6.92 (25-43)	<.001
BED (prostate) (α/β = 1.5 Gy) ($Gy_{1.5}$)	170.53 ± 12.41 (149.33-186.67)	180.26 ± 19.38 (144.20-211.03)	.041
BED (acute GI) (α/β = 10 Gy) (Gy_{10})§	52.95 ± 4.34 (47.48-58.78)	60.29 ± 4.46 (51.21-66.19)	.001

Abbreviations: ADT = androgen deprivation therapy; BED = biologically effective dose; CRT = conventional radiation therapy; GI = gastrointestinal; HRT = hypofractionated radiation therapy; PSA = prostate-specific antigen.

Data presented as mean ± standard deviation (range).

* All CRT values, except for PSA, were from 9 studies, because the CRT arm was common for 2 of the HRT arms from Dearnaley et al (4).

† All HRT values, except for PSA, were from 10 studies; PSA was not included in the CRT and HRT arms, because Arcangeli et al (2) classified the PSA level as ≤20 or >20 ng/mL.

‡ *P* values computed using the paired-sample *t* test.

§ With time factor correction.

neither any significant differences between the HRT and CRT arms nor any heterogeneity for all 3 effect measures (Fig. 2e-h; Figs. E1e-h and E2e-h; available online at www.redjournal.org).

No significant publication bias was evident for the endpoints (Fig. E3a-h). The assessment of risk bias is shown in Fig. E4 (available online at www.redjournal.org) (18). Owing to the nature of the study, blinding of the participants, personnel, and outcomes assessments was not feasible. This was also explicitly stated by some of the investigators (2, 4, 5).

Subgroup analysis

The treatment portals, posterior margins of the planning target volumes (PTVs), rectal dose−volume constraints, and the use of ADT varied in these studies (Table 3). Because acute GI toxicity was the only outcome parameter significantly different between the CRT and HRT arms, the treatment offered was closely evaluated in terms of the inclusion of the seminal vesicles (SVs) in the clinical target volume (CTV), posterior margins of the PTV, rectal dose−volume constraints, BED for acute GI toxicity, and use of ADT (Table 3). A subgroup analysis was also undertaken to explore the extent to which certain treatment variables could influence the development of acute GI toxicity. The subgroups included: (*1*) percentage of patients receiving ADT (≤66.8% vs >66.8%); (*2*) percentage of patients with the full volume of the SVs in the CTV (<76% vs ≥76%); and (*3*) BED in HRT for acute GI effects (<62.95 vs ≥62.95 Gy_{10}; Fig. 3a-c). The median values of these variables in the 7 studies evaluated for acute GI toxicity were chosen as the cutoff limits for each of the subgroup classifications.

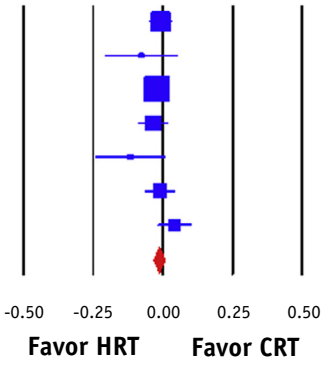
The RD between the CRT and HRT arms for ≤66.8% receiving ADT was 0.052 (P=.009), and for >66.8% receiving ADT, it was 0.136 (P<.001), indicating 8.4% less acute GI toxicity for CRT in favor of the >66.8% ADT subgroup (P=.008). For the subgroup with ≥76% of patients in whom the entire SVs were in the CTV, the RD was 0.130 (P<.001) compared with an RD of 0.034 (P=.028) for the group with <76% of patients with full volume SVs in the CTV. Thus, including the full volume of the SVs in the CTV resulted in an increase in the RD by 9.6% (P<.001) favoring the use of CRT. The BED in HRT for acute GI effects varied from 58.05 to 66.19 Gy_{10} (median

a

Risk difference: Biochemical failure (HRT vs. CRT)

Trial Group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Biochem. fail / Total HRT	Biochem. fail / Total CRT	Relative weight
PROFIT (1)	-0.008	0.021	-0.049	0.034	-0.361	.718	97/608	100/598	22.56
IRE, Roma (2)	-0.077	0.067	-0.209	0.054	-1.153	.249	18/83	25/85	2.28
RTOG 0415 (3)	-0.021	0.017	-0.054	0.011	-1.289	.198	39/550	50/542	37.29
HYPRO (5)	-0.035	0.028	-0.089	0.020	-1.251	.211	70/407	82/397	13.41
RAH, Australia (7)	-0.116	0.066	-0.245	0.013	-1.766	.077	36/108	49/109	2.36
MDACC, USA (8)	-0.010	0.029	-0.066	0.047	-0.341	.733	4/102	5/102	12.38
Lukka et al (9)	0.042	0.032	-0.021	0.106	1.302	.193	217/466	199/470	9.71
Overall	-0.016	0.010	-0.036	0.004	-1.577	.115	481/2324	510/2303	

Test for Heterogenity : I^2 = 15.88, *P* : ns



b

Risk difference: Biochemical and / or clinical failure (HRT vs. CRT)

Trial group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	BCF / Total HRT	BCF / Total CRT	Relative weight
PROFIT (1)	-0.016	0.022	-0.060	0.028	-0.729	.466	109/608	117/598	11.23
CHHiP (HRT : 60Gy) (4)	-0.022	0.013	-0.047	0.002	-1.775	.076	88/1074	111/1065	35.97
CHHiP (HRT : 57Gy) (4)	0.018	0.014	-0.009	0.045	1.339	.181	132/1077	111/1065	30.25
HYPRO (5)	-0.028	0.029	-0.084	0.029	-0.961	.337	80/407	89/397	6.87
FCCC, USA (6)	0.041	0.040	-0.039	0.120	1.003	.316	25/151	19/152	3.47
MDACC, USA (8)	-0.010	0.029	-0.066	0.047	-0.341	.733	4/102	5/102	6.86
Lukka et al (9)	0.062	0.033	-0.002	0.126	1.912	.056	263/466	236/470	5.35
Overall	-0.002	0.008	-0.017	0.013	-0.284	.777	701/3885	688/3849	

Test for heterogenity : I^2 = 45.93, *P* : ns

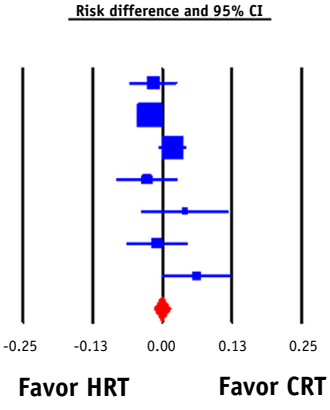


Fig. 2. Risk difference between hypofractionated (HRT) and conventional radiation therapy (CRT) for (a) biochemical failure, (b) biochemical and/or clinical failure, (c) overall mortality, (d) prostate cancer-specific mortality, (e) acute (Ac) gastrointestinal (GI) toxicity, (f) late (Lt) GI toxicity, (g) acute genitourinary (GU) toxicity, and (h) late GU toxicity. All toxicities were grade ≥2. *Abbreviations:* CHHiP = Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; CI = confidence interval; FCCC = Fox Chase Cancer Center; HYPRO = Hypofractionated Irradiation for Prostate Cancer; IRE = Regina Elena National Cancer Institute trial; MDACC = MD Anderson Cancer Center; PROFIT = Prostate Fractionated Irradiation Trial; RAH = Royal Adelaide Hospital; RTOG = Radiation Therapy Oncology Group.

62.95) for the 7 studies included in the evaluation of acute GI toxicity. The RD for the <62.95 Gy_{10} group was 0.124 (*P*=.001) compared with an RD of 0.069 for the ≥62.95 Gy_{10} group (*P*=.016). However, the difference in RD of 5.5% in favor of CRT between these 2 subgroups was not significant (Fig. 3a-c).

Discussion

HRT schedules have been explored ever since the α/β for prostate cancer was estimated to be approximately 1.5 Gy in 1999 by Brenner and Hall (11). Thus, the various randomized trials for HRT versus CRT for LLPCa have been designed with varying time, dose, and fractionation schedules. These studies have now had a minimum follow-up period of 5 years, which allowed for a comprehensive evaluation and synthesis of their outcomes.

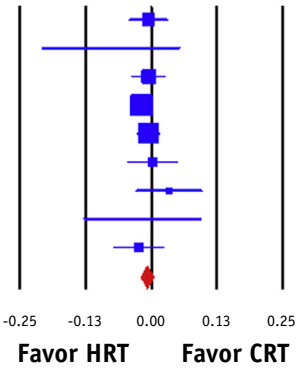
A meta-analysis of randomized controlled trials with escalated RT doses reported significantly reduced BF compared with CRT but no differences in OM or PCaSM (34). However, a significantly greater incidence of late GI toxicity was encountered with higher doses. Botrel et al (35), in their meta-analysis of 9 trials (n=2702), indicated that

c

Risk difference: Overall mortality (HRT vs. CRT)

Trial group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Deaths / Total HRT	Deaths / Total CRT	Realtive weight
PROFIT (1)	-0.005	0.019	-0.043	0.032	-0.283	.777	76/608	78/598	10.77
IRE, Roma (2)	-0.077	0.068	-0.210	0.056	-1.132	.258	19/83	26/85	0.86
RTOG 0415 (3)	-0.005	0.017	-0.039	0.029	-0.287	.774	49/550	51/542	13.05
CHHiP (HRT : 60 Gy) (4)	-0.018	0.012	-0.041	0.004	-1.596	.110	73/1074	92/1065	29.90
CHHiP (HRT : 57 Gy) (4)	-0.006	0.012	-0.029	0.018	-0.469	.639	87/1077	92/1065	27.82
HYPRO (5)	0.001	0.025	-0.048	0.051	0.050	.980	61/407	59/397	6.30
FCCC, USA (6)	0.034	0.033	-0.030	0.098	1.027	.304	16/151	11/152	3.72
RAH, Australia (7)	-0.016	0.058	-0.130	0.097	-0.280	.779	25/108	27/109	1.19
Lukka et al (9)	-0.024	0.025	-0.073	0.025	-0.987	.334	77/466	89/470	6.39
Overall	-0.009	0.006	-0.022	0.003	-1.485	.137	483/4524	525/4483	

Test for Heterogenity : $I^2 = 0.00$, *P* : ns



d

Risk difference: Prostate cancer specific mortality (HRT vs. CRT)

Trial group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Pr. Ca death / Total HRT	Pr. Ca death / Total CRT	Relative weight
PROFIT (1)	-0.004	0.008	-0.019	0.011	-0.469	.639	10/608	12/598	11.51
IRE, Roma (2)	-0.070	0.039	-0.146	0.007	-1.781	.075	3/83	9/85	0.45
RTOG 0415 (3)	-0.002	0.003	-0.008	0.004	-0.589	.556	1/550	2/542	67.94
HYPRO (5)	0.002	0.014	-0.025	0.028	0.113	.910	16/407	15/397	3.72
FCCC, USA (6)	0.013	0.016	-0.018	0.045	0.833	.405	4/151	2/152	2.67
RAH, Australia (7)	-0.018	0.022	-0.062	0.025	-0.819	.413	2/108	4/109	1.39
MDACC, USA (8)	0.000	0.010	-0.019	0.019	0.000	1.000	0/102	0/102	7.30
Lukka et al (9)	-0.010	0.012	-0.033	0.013	-0.890	.373	13/466	18/470	5.02
Overall	-0.002	0.003	-0.007	0.003	-0.902	.367	49/2475	62/2455	

Test for Heterogenity : $I^2 = 0.00$, *P* : ns

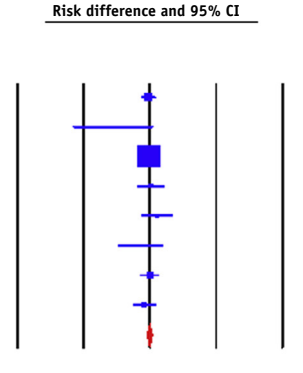


Fig. 2. *(Continued).*

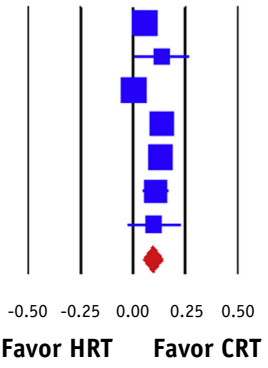
HRT was not superior to CRT and was associated with a greater incidence of acute GI toxicity. Two of their studies were limited to toxicity reporting and another had included a follow-up period of 2.5 years. Moreover, the outcomes of only 457 of the 3216 patients in the CHHiP trial were included. Sun et al (36), from 12 studies (n = 4572), reported that HRT significantly reduced BF but had no effect on PCaSM or OM. No toxicity was evaluated. Of the 12 studies, only 6 were randomized and 3 each were cohort studies or retrospective studies. Another meta-analysis of 9 studies (n = 5969) concluded that BCF survival and disease-free survival were significantly better with HRT than with CRT (37). For other parameters, including toxicity, a nonsignificant difference was observed. However, a closer perusal of their forest plots revealed that the MDACC study had not been included (8). Moreover, a number of discrepancies were found in the data entered to compute the effect measures of the various endpoints; hence, the estimates and conclusions might be ambiguous. Subsequent to that report (37), the PROFIT (1) and the final outcomes from the IRE studies (2, 19, 20) were reported. Thus, it was meaningful and timely to synthesize the outcomes of all reported phase III randomized trials to date.

One of the eligibility criteria for trial inclusion was a minimum follow-up period of 5 years. All studies included in the present meta-analysis had a minimum follow-up period of 5 years. In 7 of the 9 studies, constituting 95.3% of the patients, the follow-up period was 5 years; for the remaining 2 studies, the clinical follow-up period was 7.5 and 10 years. All endpoints, except for late toxicity, were thus scored at the minimum follow-up period of 5 years. Late toxicity in 2 studies was reported at 3 and 9 years (2, 5) (Table 1). In none of these studies were the late GI and GU toxicities significantly different between the HRT and CRT arms. However, both efficacy and the incidence of late toxicities reported at 5 years should be interpreted with caution, because some

e **Risk difference: Acute gastrointestinal toxicity (HRT vs. CRT)**

Trial group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Ac GI toxicity / Total HRT	Ac GI toxicity / Total CRT	Realtive weight
PROFIT (1)	0.059	0.019	0.021	0.097	3.036	.002	99/608	62/598	17.89
IRE, Roma (2)	0.138	0.069	0.003	0.272	2.007	.045	29/83	18/85	7.79
RTOG 0415 (3)	0.003	0.019	-0.033	0.040	0.184	.854	58/545	55/534	18.07
CHHiP (HRT : 60Gy) (4)	0.139	0.024	0.091	0.186	5.713	.000	277/720	176/715	16.84
CHHiP (HRT : 57Gy) (4)	0.133	0.024	0.085	0.180	5.458	.000	270/713	176/715	16.83
HYPRO (5)	0.108	0.034	0.042	0.175	3.189	.001	169/402	122/391	14.51
FCCC, USA (6)	0.100	0.067	-0.030	0.230	1.503	.133	9/50	4/50	8.08
Overall	0.091	0.024	0.044	0.139	3.743	.000	911/3121	613/3088	

Test for Heterogenity : I^2 = 79.88, *P*<.001



f **Risk difference: Late gastrointestinal toxicity (HRT vs. CRT)**

Trial group / Author	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Lt GI toxicity / Total HRT	Lt GI toxicity / Total CRT	Realtive weight
PROFIT (1)	-0.050	0.018	-0.086	-0.014	-2.739	.006	54/608	83/598	15.67
IRE, Roma (2)	-0.020	0.054	-0.126	0.085	-0.378	.705	11/83	13/85	6.24
RTOG 0415 (3)	0.082	0.023	-0.036	0.127	3.500	.000	121/545	75/534	13.95
CHHiP (HRT : 60Gy) (4)	-0.007	0.013	-0.033	0.019	-0.498	.618	105/1049	111/1040	17.24
CHHiP (HRT : 57Gy) (4)	-0.017	0.013	-0.042	0.009	-1.296	.195	95/1057	111/1040	17.34
HYPRO (5)	0.045	0.028	-0.011	0.100	1.566	.117	87/395	68/387	12.25
FCCC, USA (6)	-0.045	0.046	-0.135	0.045	-0.976	.329	27/151	34/152	7.66
MDACC, USA (8)	-0.059	0.037	-0.015	0.132	1.572	.116	11/102	5/102	9.64
Overall	0.006	0.016	-0.026	0.038	0.361	.718	511/3990	500/3938	

Test for Heterogenity : I^2 = 74.51, *P*<.001

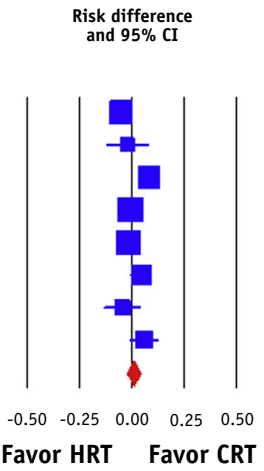


Fig. 2. *(Continued).*

long-term events might have remained uncaptured and require evaluation after longer follow-up periods.

Key outcomes from present meta-analysis

The studies included in the present meta-analysis were performed and reported during a 22-year period, with RT techniques varying from 2D- or 3D-CRT and IMRT or image-guided RT. The earliest trial, initiated in 1995 by Lukka et al (9), had treated all 936 patients with 2D- or 3D-CRT using a 3- or 4-field box technique. In the RAH study (27), which began in 1996, 156 of 217 patients (71.9%) had undergone 2D-CRT and 61 had undergone 3D-CRT. However, the patients undergoing 2D-CRT constituted 1.9% of all included patients in the present meta-analysis. Because the radiation doses and techniques used in these studies did not conform to the present standard of care, we tried to explore whether excluding these studies would have affected the effect measures.

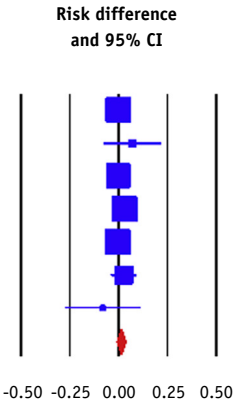
After excluding the studies by Lukka et al (9) and the RAH study (7, 25-27) from the BF, BCF, OM, and PCaSM estimations, the RD for BF changed from −0.016 to −0.020, for BCF from −0.002 to −0.006, for OM from −0.009 to −0.008. However, PCaSM remained unchanged at −0.002 (original RDs shown in Fig. 2a-e). The differences in these computed RDs were nonsignificant. The 2 trials were not included in the acute or late morbidity scoring for either GI or GU for reasons listed in Table 1. Thus, although these trials had been performed with techniques or doses not conforming to the present standard of care, including their data in the present meta-analysis did not alter the outcomes or inferences from the meta-analysis for the endpoints evaluated.

The results of the present meta-analysis showed that HRT provides similar outcomes for BF, BCF, OM, and PCaSM. The GU morbidities, both acute and late, consistently showed no significant differences nor was any heterogeneity observed among the studies. The lack of

g **Risk difference: Acute genitourinary toxicity (HRT vs. CRT)**

Trial group/Author	Statistics for each study						Ac GU toxicity/Total		Relative weight
	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	HRT	CRT	
PROFIT (1)	-0.002	0.027	-0.054	0.050	-0.066	.948	185/608	183/598	21.04
IRE, Roma (2)	0.070	0.076	-0.080	0.219	0.916	.360	39/83	34/85	2.54
RTOG 0415 (3)	-0.002	0.027	-0.055	0.051	-0.067	.947	147/545	145/534	20.22
CHHiP (HRT : 60Gy) (4)	0.032	0.026	-0.020	0.083	1.195	.232	356/720	331/715	21.29
CHHiP (HRT : 57Gy) (4)	-0.004	0.026	-0.056	0.047	-0.163	.870	327/713	331/715	21.26
HYPRO (5)	0.027	0.035	-0.041	0.096	0.787	.431	244/403	226/391	12.16
FCCC, USA (6)	-0.080	0.100	-0.275	0.115	-0.803	.422	24/50	28/50	1.49
Overall	0.009	0.012	-0.015	0.033	0.738	.460	1322/3122	1278/3088	

Test of Heterogenity : I^2 = 0.00, *P* : ns



h **Risk difference: Late genitourinary toxicity (HRT vs. CRT)**

Trial group/Author	Statistics for each study						Lt GU toxicity/Total		Relative weight
	Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	HRT	CRT	
PROFIT (1)	-0.000	0.024	-0.047	0.047	-0.016	.987	136/608	134/598	7.84
IRE, Roma (2)	-0.056	0.056	-0.166	0.055	-0.987	.323	11/83	16/85	1.42
RTOG 0415 (3)	0.069	0.027	0.017	0.121	2.583	.010	161/545	121/534	6.36
CHHiP (HRT : 60Gy) (4)	0.020	0.011	-0.002	0.043	1.789	.074	88/1049	66/1040	34.66
CHHiP (HRT : 57Gy) (4)	0.010	0.010	-0.030	0.011	-0.929	.353	57/1057	66/1040	42.87
HYPRO (5)	0.022	0.035	-0.046	0.091	0.641	.521	163/395	151/387	3.68
FCCC, USA (6)	-0.030	0.057	-0.142	0.082	-0.523	.601	68/151	73/152	1.38
MDACC, USA (8)	-0.010	0.050	-0.108	0.089	-0.195	.845	15/102	16/102	1.79
Overall	0.007	0.007	-0.006	0.020	1.010	.313	699/3990	643/3938	

Test of Heterogenity : I^2 = 38.65, *P* : ns

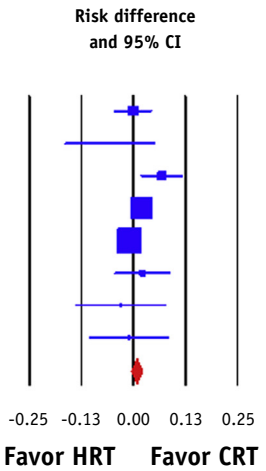


Fig. 2. *(Continued).*

significant differences for either acute or late GU morbidity might have been because the treatment portals in nearly all studies were confined to the prostate with or without the SVs. Only in the FCCC study was pelvic lymph node irradiation used in 31.7% of their patients (24) (Table 3). The incidence of late GI and GU toxicities in the FCCC study was not significantly different (Table 1). However, the significantly increased incidence of acute GI toxicity and the heterogeneity in both acute and late GI effects merits closer examination of the individual studies.

The forest plot of acute GI toxicity showed that, in all the studies except for RTOG 0415 (3) (RD 0.3%), the RD ranged from 5.9% to 13.9%, indicating a significantly greater incidence of acute GI toxicity in HRT patients (Fig. 2e). This contributed to significant heterogeneity (I^2 = 79.88; P<.001). After excluding the RTOG 0415 study, the heterogeneity decreased and the difference became nonsignificant (I^2 = 44.26; P=.11). However, the effect measures maintained significance with greater acute GI toxicity in HRT patients (P<.001). The RTOG 0415 study did not observe any appreciable difference in the incidence of acute GI toxicity between the 2 arms. Plausible reasons for this low RD include: (*1*) that it was the only study with patients exclusively in the low-risk category and smaller irradiated volumes without the SVs in the CTV, consequently minimizing the irradiated rectal volume; (*2*) a moderate BED of 62.95 Gy_{10} for acute GI effects for HRT (range 58.05-66.19 Gy_{10} from all 7 studies); and (*3*) most patients (nearly 80%) underwent IMRT with appropriate rectal dose–volume constraints.

All the effect measures for late GI toxicity also showed significant heterogeneity (Fig. 2f; Figs. E1f and E2f; available online at www.redjournal.org). The 2 extreme RDs of −0.05 and +0.08 were from the PROFIT and RTOG 0415 studies, respectively. After excluding these studies, the heterogeneity decreased to nonsignificant

Table 3 Details of treatment portals and rectal dose–volume constraints for 7 studies included in forest plots for acute GI toxicity evaluation

			Treatment portal		
			SVs in CTV (% of total patients)		
Study	Total ADT patients (%)	RT (% IMRT)	No	Base	Full
PROFIT (1)	5.6 (5.1/6.0)*	3D-CRT or IMRT	91.6	8.4	0 (0/0)*
IRE (2, 19, 20)	100 (100/100)*	3D-CRT	0	0	100 (100/100)*
RTOG 0415 (3)	0 (0/0)*	3D-CRT or IMRT (79.1)	100	0	0 (0/0)*
CHHiP (HRT_{60}) (4)	97.4 (97.3/97.5)*	IMRT	0	23.9†,‡	76.1†,‡ (77.1/75.2)*
CHHiP (HRT_{57}) (4)	97 (97.3/96.8)*	IMRT	0	23.7†,‡	76.3†,‡ (77.1/75.5)*
HYPRO (5, 21, 22)	66.8 (67.2/66.3)*	3D-CRT or IMRT (95)	19.6	0	80.4§ (80.1/80.6)*,§
FCCC (6, 23, 24)	45.9 (46.7/45.0)*	IMRT	0	65.7-71.6‖	28.4†,‖ (28.3/28.5)*,†,‖

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; ADT = androgen deprivation therapy; BED = biologically effective dose (for acute GI effects, computed assuming α/β = 10 Gy with time factor corrections; details in text); CHHiP = Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; CRT = conventional radiation therapy; CTV = clinical target volume; Dx = radiation dose delivered to X% of target; FCCC = Fox Chase Cancer Center; Fx = fraction; GI = gastrointestinal; HRT = hypofractionated radiation therapy; HYPO = Hypofractionated Irradiation for Prostate Cancer; IMRT = intensity modulated radiation therapy; IRE = Regina Elena National Cancer Institute trial; LN = lymph node; PROFIT = Prostate Fractionated Irradiation Trial; PTV = planning target volume; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SVs = seminal vesicles; Vx = volume receiving X (Gy) of prescription dose.

* Percentage of patients receiving CRT/percentage of patients receiving HRT.

† Received a reduced dose.

‡ Data available only from preliminary analysis of the CHHiP trial (Dearnaley et al. Lancet Oncol 2012; 13: 42-54), including only 14.2% of all finally included patients.

§ Included both total and reduced doses to full SVs.

‖ As reported by Shaikh et al (24).

values. The I^2 for RD, OR, and RR decreased from 74.51, 74.10, and 73.78 ($P<.001$) to 34.39, 34.13, and 34.03, respectively (P=NS for all). However, all the effect measures continued to remain nonsignificant, indicating no differences in late GI toxicity. The estimated BED for late GI effects in the CRT group was 130 Gy_3 and 118.08 Gy_3 in the PROFIT and RTOG 0415 study, respectively. Thus, the BED for late GI effects was 10.1% greater in the PROFIT than in RTOG 0415 in the CRT arm. This could have contributed to the greater incidence of late GI effects in the CRT arm of the PROFIT ($P=.006$) compared with the RTOG 0415 study. In contrast, the BED for late GU effects in the HRT arm was 6.9% greater in the RTOG 0415 study than that in the PROFIT (RTOG 0415, 128.33 Gy_3 vs PROFIT, 120 Gy_3). This could have resulted in greater late GU effects in the HRT arm of the RTOG 0415 study ($P=.005$; Table 1; Fig. 2h; Figs. E1h and E2h; available online at www.redjournal.org).

Acute GI toxicity: subgroup analysis

Because acute GI toxicity was the only outcome parameter significantly in favor of CRT, the likely contributory factors merited further investigation. The RD for acute GI toxicity ranged from 0.3% to 13.9%, indicating that the incidence of acute GI toxicity was significantly greater in the HRT arm of all studies, except for RTOG 0415 and FCCC. However, even in the RTOG 0415 and FCCC trials, the RD was in favor of CRT at 0.3% and 10%, respectively, although the difference was not significant (Fig. 2e).

All 7 studies evaluated for acute GI toxicity included patients with various risk categories who had undergone varying RT techniques, a diverse volume of SVs in the CTV, variable posterior margins of the PTV, distinctive rectal dose–volume constraints, dissimilar BEDs for acute GI toxicity for the CRT and HRT arms, and a wide range of ADT usage (Table 3). These could all have influenced the development of acute GI toxicity. Thus, from the data that could be extracted and synthesized from the published reports of these trials, a subgroup analysis was performed for some of the key treatment covariates (Fig. 3a-c).

A greater proportion of patients in whom the entire SVs had been included in the CTV had a significantly greater RD ($P<.001$), favoring CRT (Fig. 3b). Incidentally, the RD was also significantly greater in favor of CRT for those with a greater percentage of patients receiving ADT ($P=.008$; Fig. 3a). A closer examination revealed that the studies in

Table 3 Details of treatment portals and rectal dose–volume constraints for 7 studies included in forest plots for acute GI toxicity evaluation *(continued)*

Treatment portal		BED (Gy_{10}; acute GI)		Rectal dose–volume constraints	
LN (%)	Posterior margin of PTV (mm)	CRT	HRT	CRT	HRT
No	+7	57.17	62.95	D50 ≤53 Gy; D30 ≤71 Gy	D50 ≤37 Gy; D30 ≤46 Gy
No	+6	58.78	60.63	V70 ≤30%; V50 ≤50%	V54 ≤30%; V39 ≤50%
No	+4-10	47.48	62.95	D15 ≤75 Gy; D25 ≤70 Gy; D35 ≤65 Gy; D50 ≤60 Gy	D15 ≤74 Gy; D25 ≤69 Gy; D35 ≤64 Gy; D50 ≤59 Gy
No	Different PTV with posterior margins of 0-10	53.95	62.95	Dose–volume constraints given as dose for 2 Gy/Fx for prescribed dose: range 30-74 Gy	Dose–volume constraints given as dose for 2 Gy/Fx for prescribed dose: range 30-74 Gy
No	Different PTV with posterior margins of 0-10	53.95	59.84	Dose–volume constraints given as dose for 2 Gy/Fx for prescribed dose: range 30-74 Gy	Dose–volume constraints given as dose for 2 Gy/Fx for prescribed dose: range 30-74 Gy
No	3-10 (boost margins, 0)	57.17	58.05	Rectal wall, V65 ≤50%	Rectal wall, V54 ≤50%
Yes (31.7)	5 (CRT); 3 (HRT)	55.56	66.19	V65 ≤17%; V40 ≤35%	V50 ≤17%; V31 ≤35%

which a greater proportion of patients had the entire SVs irradiated also had a greater use of ADT (Pearson correlation $r=0.959$; $P=.001$), as most of these patients were in the high-risk group. Neoadjuvant ADT is known to induce prostate volume shrinkage (38-42). This would be expected to minimize the rectal volume in the CTV and thus contribute to reducing the incidence of acute GI toxicity.

The BED for acute GI effects was significantly greater in the HRT arm than in the CRT arm in the 7 trials evaluated for acute GI toxicity (mean ± standard deviation, CRT 54.86 ± 3.71 Gy_{10} vs 61.93 ± 2.65 Gy_{10}; $P=.01$). This could be expected to contribute to the increased rate of acute toxicity with HRT. However, on subgroups analysis using a median BED cutoff for HRT of 62.95 Gy_{10}, the difference in the RD between the subgroups was not statistically significant. Although the RD significantly favored CRT for each of the individual subgroups of <62.95 Gy_{10} ($P<.001$) and ≥62.95 Gy_{10} ($P=.016$), the differences were not statistically significant when comparing the 2 groups (Fig. 3c). This could have been because of the 4 studies in the ≥62.95 Gy_{10} subgroup, the full SVs were not included in the CTVs for most patients in the RTOG 0415 trial and PROFIT. None of the patients in the RTOG 0415 study had the SVs included in the CTV. In the PROFIT, only the base of the SVs was irradiated in 8.4% and in the remaining 91.6%, the entire SVs had been excluded from the CTV. These would have resulted in appreciably lower rectal volumes in the treatment portals in these 2 studies. Incidentally, both these studies contributed to nearly 60% of the weightage in this subgroup and, hence, had a strong bearing on the computed RD. Furthermore, the BED for HRT for acute GI effects for all studies was computed according to the prescribed radiation dose and the fractionation schedules as stated in the treatment protocols. However, the actual rectal doses received by patients would have been limited by the rectal dose constraints and the posterior margins of the PTV prescribed in the individual treatment protocols. These values were quite variable in these studies and, hence, could have obscured the comparative effects of the computed BED of HRT toward the RD for acute GI toxicity (Table 3).

BED estimates for prostate cancer

One of the other issues requiring careful consideration is computation of the BED for prostate cancer without any time factor to derive the CRT and HRT schedules. It has

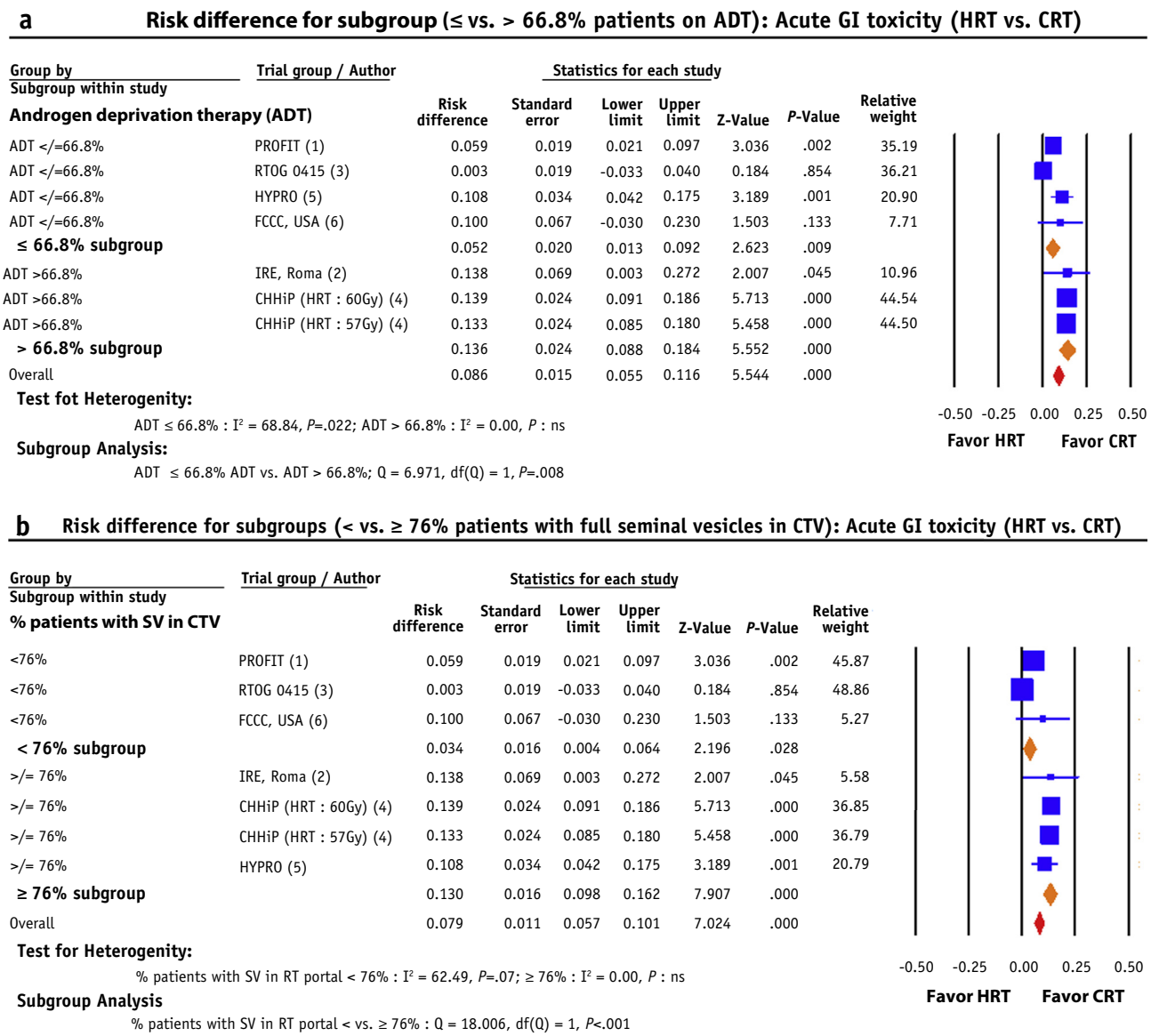
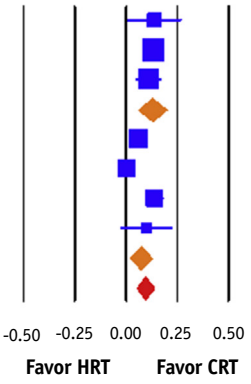


Fig. 3. Forest plots showing the risk difference with subgroup analysis for acute gastrointestinal (GI) toxicity for hypofractionated radiation therapy (HRT) versus conventional radiation therapy (CRT) for (a) percentage of patients receiving androgen deprivation therapy (ADT): ≤66.8% versus >66.8% ($P=.008$); (b) percentage of patients with full seminal vesicles (SV) in irradiated portal, <76% versus ≥76% ($P<.001$); and (c) biologically effective doses (BEDs) of HRT for acute GI effects (<62.95% vs ≥62.95 Gy_{10}; $P=$NS). The cutoff values for the subgroups were chosen as per the respective median values of the variables. The subgroups were analyzed using mixed-effects analysis. *Abbreviations:* CHHiP = Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; CI = confidence interval; CTV = clinical target volume; df = degrees of freedom; FCCC = Fox Chase Cancer Center; HYPRO = Hypofractionated Irradiation for Prostate Cancer; IRE = Regina Elena National Cancer Institute trial; PROFIT = Prostate Fractionated Irradiation Trial; RTOG = Radiation Therapy Oncology Group.

been reasonably accepted that prostate cancer proliferates slowly and, therefore, the OTT and treatment prolongation might not have a significant effect on therapeutic outcomes. Thus, a time factor correction is usually not included in most BED computations for prostate cancer, which was also followed in the present study (11, 13, 14). However, lately, it has been suggested that significant tumor cell repopulation could occur in low- and intermediate-risk prostate cancer. These tumors could show an accelerated repopulation after 4 to 5 weeks with an effective clonogenic time of 12 days (43). D'Ambrosio et al (44) suggested that a longer duration could be adverse for low-risk patients and proposed that the ratio of the nontreatment days as a percentage of the total RT duration of ≥33% should be avoided. Gao et al (45) suggested that the tumor repopulation could start no later than 58 days,

C **Risk difference for subgroups(BED of HRT for acute GI effects < vs. ≥ 62.95 Gy_{10}): Acute GI toxicity (HRT vs. CRT)**

Group by Subgroup within study	Trial group /Author	Statistics for each study						
BED of HRT for acute GI toxicity		Risk difference	Standard error	Lower limit	Upper limit	Z-Value	*P*-Value	Relative weight
< 62.95 Gy	IRE,Roma (2)	0.138	0.069	0.003	0.272	2.007	.045	18.57
< 62.95 Gy	CHHiP (HRT : 57Gy) (4)	0.133	0.024	0.085	0.180	5.458	.000	44.25
< 62.95 Gy	HYPRO (5)	0.108	0.034	0.042	0.175	3.189	.001	37.18
< 62.95 Gy subgroup		0.124	0.036	0.053	0.196	3.432	.001	
>/= 62.95 Gy	PROFIT (1)	0.059	0.019	0.021	0.097	3.036	.002	29.87
>/= 62.95 Gy	RTOG 0415 (3)	0.003	0.019	-0.033	0.040	0.184	.854	30.22
>/= 62.95 Gy	CHHiP (HRT : 60Gy) (4)	0.139	0.024	0.091	0.186	5.713	.000	27.78
>/= 62.95 Gy	FCCC, USA (6)	0.100	0.067	-0.030	0.230	1.503	.133	12.13
≥ 62.95 Gy subgroup		0.069	0.029	0.013	0.126	2.413	.016	
Overall		0.091	0.023	0.046	0.135	4.022	.000	



Test for Heterogenity:

BED < 62.95 Gy : I^2 =0.00, *P*: ns; ≥ 62.95 Gy : I^2 = 85.00, *P*<.001

Subgroup Analysis:

BED for acute GI toxicity: < vs. ≥ 62.95 Gy; Q = 1.422, df(Q) = 1, *P* : ns

Fig. 3. *(Continued).*

with a tumor doubling times of 9 to 34 days. However, both these estimates were computed using data from retrospective studies.

Recently, Gulliford et al (46) derived the α/β values and T_k from the outcomes of the CHHiP, HYPRO, PROFIT, and RTOG 0415 studies. They estimated that with the assumption of an OTT, the α/β and T_k values for each trial could vary from 3.8 to 31.5 Gy and 17 to 44 days, respectively. However, without assuming a time factor, the α/β could range from 1.3 to 6.9 Gy in these trials. The study by Gulliford et al (46) is currently available only in abstract form. Furthermore, following the reporting of the iso-effective phase III randomized trials between CRT and HRT, the generic use of a low α/β for prostate cancer in all risk categories, with or without the use of ADT, has been questioned (47).

It therefore appears that questions are emerging regarding the assumption of a constant α/β value for the various risk categories of prostate cancer and also the time factors for the BED calculations. These might need to be considered in the near future when computing the dose equivalence between CRT and HRT schedules.

Limitations of present meta-analysis

The number of events for the evaluated endpoints was not always explicitly stated for all the studies. In some cases, these had to be determined directly from the Kaplan-Meier plots. The scoring of the toxicity profiles was also quite heterogeneous, because the studies were conducted and reported during a 22-year period. However, every study had adhered to the same reporting guidelines for both treatment arms during their follow-up period. Moreover, in the relevant studies, details of the ADT prescription were not always available nor were the outcomes given in terms of ADT usage.

The issue of acute GI toxicity is certainly of clinical importance; however, it was beyond the scope of the present study to consider additional contributing factors or the concomitant interplay of ADT, prostate volume shrinkage, extent of SVs in the CTV, and sequential changes in the rectal dose–volume histograms that could influence the BED of acute GI toxicity. These could have potential repercussions in the incidence of acute GI toxicity.

Future considerations

The outcomes of the subgroups analyses should be treated as observational. Also, owing to the limited number of studies, a meta-regression using some of these covariates could not be undertaken (48). Thus, the implications from the subgroup analyses warrant careful evaluation in future prospective studies to assess their individual or collective effects. Furthermore, effective and practical measures could be explored to minimize this morbidity without adversely affecting the other outcome parameters. Reducing the SV volume in the CTV for low- and intermediate-risk patients and using ADT for high-risk patients to induce prostate shrinkage could minimize the irradiated rectal volumes and thereby mitigate the incidence and severity of acute GI toxicity. Furthermore, the hydrogel spacers introduced in the prostate–rectal interspace have been reported to reduce the rectal dose and toxicity by increasing the prostate–rectal separation (49, 50). This could be one of measures that could be explored for HRT patients, especially those for whom the entire SVs will be included in the CTVs.

In addition to the endpoints evaluated in the present meta-analysis, patient-reported outcomes measures are emerging as important additional tools to assist in understanding the patients' perspective of a particular therapeutic approach (24, 51, 52). Once validated and uniformly

applied across centers, the use of patient-reported outcomes measures could facilitate decision making with regard to the therapeutic options.

Conclusions

The results of the present meta-analysis have reaffirmed HRT as a viable alternative for patients with LLPaC, because the therapeutic outcomes closely aligned with those of CRT. Furthermore, HRT could shorten the treatment duration, require fewer hospital visits, and reduce the costs for health care providers (16, 53). However, the incidence of acute GI toxicity might be greater than that with CRT and requires careful evaluation in future studies.

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