

Moderate hypofractionated radiotherapy vs conventional fractionated radiotherapy in localized prostate cancer: a systemic review and meta-analysis from Phase III randomized trials

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Purpose: To determine the efficacy and late toxicities of moderate (2.5–4 Gy) hypofractionated radiotherapy (H-RT) in localized prostate cancer, a meta-analysis of published randomized clinical trials comparing moderate H-RT with conventional fractionated RT (C-RT) was performed.

Materials and methods: Systematic search on published randomized clinical trials in English according to Cochrane review guidelines in databases of Pubmed, Embase, Cochrane, web of science, and Wiley Online Library was carried out. Outcomes of interests were biochemical and clinical disease failure (BCDF), biochemical failure (BF), overall survival (OS), and late toxicities.

Results: Seven of the 365 studies fulfilled inclusion criteria with 8,156 participants. Compared with C-RT, moderate H-RT showed a lower BF rate (risk ratio [RR] = 0.80, 95% CI: 0.68–0.95, $P=0.009$), while did not improve OS (RR = 0.68, 95% CI: 0.78–1.02, $P=0.10$). There was no significant difference in BCDF rates between H-RT and C-RT (RR = 0.92, 95% CI: 0.82–1.02, $P=0.12$). The H-RT was deeply grouped into dose-escalated H-RT (with a higher biologically effective dose [BED_{1.5}] than C-RT) and no dose-escalated H-RT; dose-escalated H-RT significantly decreased BCDF rate compared with C-RT (RR = 0.84, 95% CI: 0.73–0.96, $P=0.01$). Regarding late toxicities, there is no significant difference in late gastrointestinal (GI; RR = 0.97, 95% CI: 0.71–1.33, $P=0.85$) and genitourinary (GU) toxicities (RR = 1.04, 95% CI: 0.87–1.24, $P=0.69$). When subgrouped into dose-escalated H-RT (with a higher BED₃ compared with C-RT) and no dose-escalated H-RT, dose-escalated H-RT increased GI toxicity (RR = 1.62, 95% CI: 1.26–2.09, $P=0.0002$) and GU toxicity (RR = 1.28, 95% CI: 1.05–1.55, $P=0.01$), while no dose-escalated H-RT significantly lowered GI toxicity (RR = 0.81, 95% CI: 0.70–0.94, $P=0.005$) and placed no influence on GU toxicity (RR = 1.02, 95% CI: 0.88–1.20, $P=0.77$).

Conclusion: This meta-analysis provides reliable evidence that moderate H-RT decreases BF rate, while does not improve OS. Compared with C-RT, H-RT with an increase in BED_{1.5} improved BCDF rates significantly, and accordingly, an increase in BED₃ will result in elevated late GI and GU toxicities.

Keywords: prostate neoplasm, hypofractionation, radiotherapy, randomized trial

Introduction

Prostate cancer is one of the predominant malignancies in men throughout the world. External beam radiotherapy is one of the most important treatment options. Previous randomized trials have shown that dose-escalation conventional fractionated

RT (C-RT) with a dose >75.6 Gy decreased biochemical recurrence, albeit with increasing incidence rates of gastrointestinal (GI) and genitourinary (GU) toxicities, and is the current standard care for patients with prostate cancer.^{1–3} With the development of radiotherapy technologies, intensity-modulated radiotherapy, with improved conformity of high dose focused on target volume while sparing normal organs, is considered as the standard treatment technique rather than conventional radiotherapy.

The vast majority of the evidence supports the hypothesis that α/β ratio is really low for prostate cancer radiation biology, at ~ 1.5 Gy.^{4,5} And theoretically, hypofractionation would offer therapeutic benefit with improved tumor control by increasing biologically effective dose (BED).⁶ Hypofractionated radiotherapy (H-RT) delivered fewer fractions each with a higher dose, which significantly increased resource use and improved patient convenience, and thus had been a promising treatment in the past decades.⁷ Therefore, radiation oncologists showed great interests in applying hypofractionation and exploring different fraction sizes, including moderate hypofractionation (2.4–4 Gy) and extreme hypofractionation (>4 Gy).⁸ Moderate H-RTs were used more widely, and several large-scale Phase III randomized trials, including noninferiority trials and superiority trials, have published their results recently.^{9–11} However, large, Phase III trials on extreme hypofractionation, also known as Stereotactic Body Radiation Therapy, which is a more recent development, are lacking. Only retrospective trials and small sample prospective trials are available, and no standard fractionation size recommendation is made. Thus, extreme H-RT is restricted to clinical trials.^{12,13}

In order to investigate the current status of moderate H-RT in the treatment of prostate cancer, including efficacy and toxicity, in this meta-analysis, only Phase III randomized trials comparing moderate H-RT with C-RT in nonsurgery prostate cancer were included.

Materials and methods

Search strategy and selection criteria

This meta-analysis is reported in accordance with the Preferred Reporting Items for systematic Reviews and Meta-analyses Statement and was registered at International Prospective Register of Systematic Reviews (number CRD42016049464).

Published randomized controlled trials comparing H-RT and C-RT for localized prostate cancer were included. We searched Pubmed, Embase, Science Direct, Wiley online library, the Cochrane Library, and CENTRAL

from the date of their inception until August 22, 2018, for relevant articles. We also searched abstracts from the most important international meetings: ASTRO, ESTRO, ASCO. We searched for “prostate cancer” AND “hypofractionation” AND “radiotherapy”. All relevant keyword variations were used for these three terms. We restricted our searches to reports published in English. Two independent reviewers screened the title and abstract of retrieved articles. Studies that seemed to meet the inclusion criteria were selected for full-text review. Disagreements between the two reviewers were resolved by discussion.

Study selection and data extraction

We regarded studies as eligible for inclusion if they are randomized Phase III clinical trials comparing H-RT with C-RT in patients with localized prostate cancer without surgery. Exclusion criteria were as follows: observational and retrospective studies. Two reviewers independently reviewed abstracts and full-text articles. We resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer. Standardized data abstraction forms were used by trained reviewers to extract data from each study. To assess the risk of bias of randomized clinical trials, we used predefined criteria based on the Cochrane Risk of Bias tool (ratings: low, unclear, high risk of bias). We synthesized the data on the majority of outcomes qualitatively. To retrieve data not reported in publications, we contacted authors of the respective papers.

Outcomes

The primary end point of interest was biochemical and clinical disease failure (BCDF) rate, and other main end points of interests were biochemical failure (BF) rate, overall survival (OS), and late GI and GU toxicities.

Statistical analyses

All rates assessed were carried out for statistical efficacy analysis using the risk ratio. We used the Cochran Q test to assess heterogeneity between studies. We also did I^2 testing to assess the magnitude of the heterogeneity between studies, with values $<25\%$ as minimal, from 25% to 50% as moderate, and $>50\%$ as substantial heterogeneity. The fixed-effect model was used for meta-analysis in cases of nonsubstantial heterogeneity. If there was a significant heterogeneity, the random-effect model was used. Subgroup analysis was used if heterogeneity is moderate to severe. In this meta-analysis, P -value <0.05 was considered statistically significant.

Results

Our initial search identified 365 studies; only nine studies were Phase III randomized trials that fulfilled the inclusion criteria,^{9–11,14–24} of which seven studies (with data for 8,156 participants) were included in this analysis (Figure 1).^{9–11,17,18,20} Two studies published in early time were excluded, for the reason that these two studies were delivered with low radiation dose (64–66 Gy), which is much lower than the concurrent standard of care. Thus, only seven studies were included in this meta-analysis. It is to be noted that there were two pairs of comparisons in the CHHiP trial, which was counted twice. The characteristics of all these trials are presented in Table 1. All the studies were with follow-up time >5 years.

Efficacy

Six studies reported on BCDF rates. There was no significant difference in 5-year BCDF rates between H-RT and C-RT (relative risk [RR]=0.92, 95% CI: 0.82–1.02, $P=0.12$), with a moderate heterogeneity ($\chi^2=9.67$; $df=6$ [$P=0.14$]; $I^2=38\%$) as shown in Figure 2A. Since the prostate cancer has a low α/β ratio at approximately 1.5 Gy, $BED_{1.5}$ was recalculated and all

the trials were grouped into dose-escalated H-RT (with higher $BED_{1.5}$ compared with C-RT) and no dose-escalated H-RT (without increasing $BED_{1.5}$ compared with C-RT; Table S1). As displayed in Figure 2B, one pair of comparisons in CHHiP trial (H-RT: 57 Gy/3.0 Gy [$BED_{1.5}=171$ Gy] vs C-RT: 74 Gy/2.0 Gy [$BED_{1.5}=173$ Gy]) and the study from Catton et al²³ (H-RT: 60 Gy/3.0 Gy [$BED_{1.5}=180$ Gy] vs C-RT: 78 Gy/2.0 Gy [$BED_{1.5}=182$ Gy]) were categorized into no dose-escalation H-RT group (RR=1.04, 95% CI: 0.88–1.23, $P=0.63$). Other studies were grouped into dose-escalated H-RT with a $BED_{1.5} > 180$ Gy, equally to $EOD_2 > 76$ Gy, which significantly reduced BCDF rates compared with C-RT (RR=0.84, 95% CI: 0.73–0.96, $P=0.01$), with a small heterogeneity ($\chi^2=4.11$; $df=4$ [$P=0.39$]; $I^2=3\%$).

Four studies reported on BF rates. Patients who received H-RT showed a lower BF rate compared with C-RT (RR=0.80, 95% CI: 0.68–0.95, $P=0.009$), without heterogeneity ($\chi^2=0.99$; $df=3$ [$P=0.80$]; $I^2=0\%$), as shown in Figure 3A. And six studies reported on OS rates. There was no significant difference in OS (RR=0.89, 95% CI: 0.78–1.02, $P=0.10$) between H-RT and C-RT; also no heterogeneity was noted ($\chi^2=3.94$; $df=6$ [$P=0.68$]; $I^2=0\%$), as shown in Figure 3B.

Toxicity

There is no significant difference in late GI (RR=0.97, 95% CI: 0.71–1.33, $P=0.85$; Figure 4A) and GU toxicities (RR=1.04, 95% CI: 0.87–1.24, $P=0.69$; Figure 5A) at 5 years. Since severe heterogeneities existed, subgroups were deeply analyzed. Several studies have supported that α/β ratio is 4–6 Gy for GI and GU late toxicities. Therefore, BED_5 was calculated for late toxicities.^{9,17} Studies were also divided into dose-escalated (BED_5 in H-RT higher than that in C-RT) and no dose-escalated H-RT groups (BED_5 in H-RT was lower than that in C-RT; Table S1). Dose-escalated H-RT was associated with higher late toxicity of GI (RR=1.62, 95% CI: 1.26–2.09, $P=0.0002$; Figure 4B) and GU (RR=1.28, 95% CI: 1.05–1.55, $P=0.01$) at 5 years (Figure 5B), without heterogeneities. Whereas, no dose-escalated H-RT significantly decreased GI toxicity (RR=0.81, 95% CI: 0.72–1.33, $P=0.005$, Figure 4B) and did not increase GU toxicity (RR=1.02, 95% CI: 0.94–1.28, $P=0.77$, Figure 5B).

Publication bias

Publication bias regarding outcomes was not assessed because there are fewer than 10 studies required to detect funnel plot asymmetry.

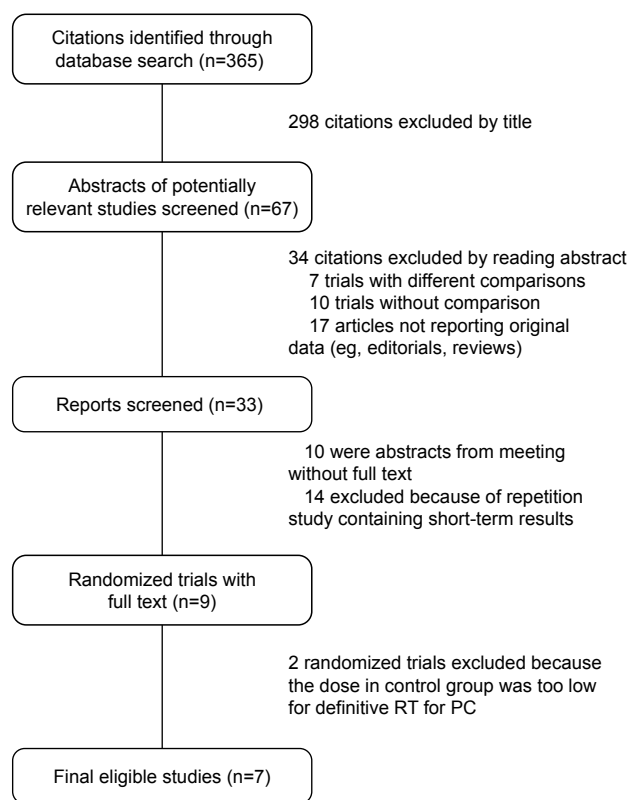


Figure 1 Study selection.

Abbreviations: PC, prostate cancer; RT, radiotherapy.

Table 1 Characteristics of randomized studies comparing H-RT with C-RT for localized prostate cancer

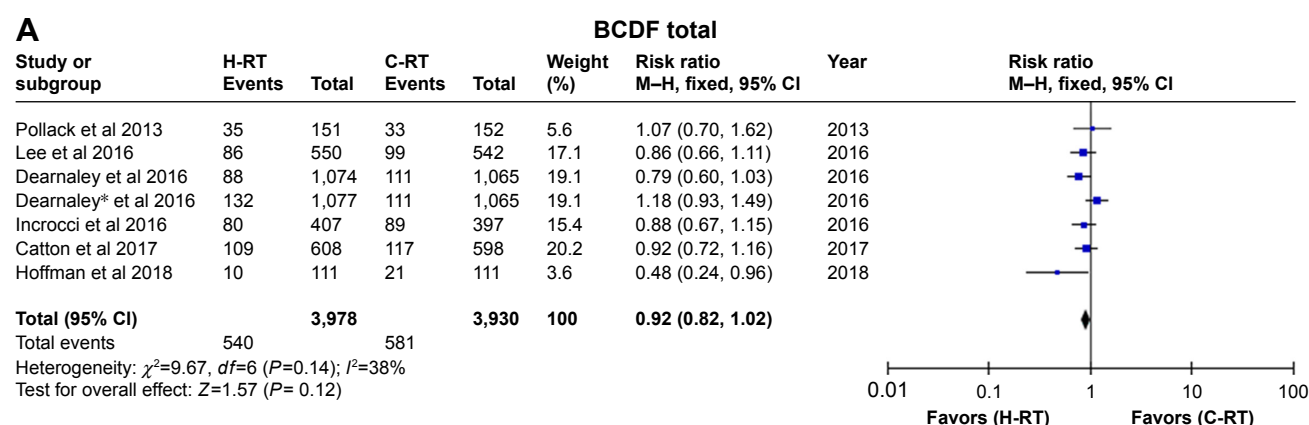
Study	Patients	Comparison	N	BCDF	BF	OS	GI	GU	Primary end point	Follow-up (months)
Hoffman et al ²⁴ / <i>J Clin Oncol</i> 2018	Low–high risk T1b–2 N0	H-RT: 72/2.4 Gy C-RT: 75.6/1.8 Gy	111 111	10 21	– –	19 24	11 5	15 15	Toxicity	102
Catton et al ²³ / <i>J Clin Oncol</i> 2017	Intermediate risk (T1–2c N0)	H-RT: 60/3.0 Gy C-RT: 78 Gy/2.0 Gy	1,206	109 117	97 100	76 78	54 82	135 133	BCDF	72
Lee et al ¹¹ / <i>J Clin Oncol</i> 2016	Low risk (T1–2 N0)	H-RT: 70/2.5 Gy C-RT: 73.8/1.8 Gy	1,092	86 99	39 50	49 51	121 75	161 121	BCDF	69.6
Dearnaley et al ¹⁰ / <i>Lancet Oncol</i> 2016	Low–high risk (T1–T3a N0)	H-RT1: 60/3.0 Gy H-RT2: 57/3.0 Gy C-RT: 74/2.0 Gy	3,216	88 132 111	– – –	87 73 92	105 95 111	88 57 66	BCDF	62
Incrocci et al ⁹ / <i>Lancet Oncol</i> 2016	Intermediate– high risk (T1b–4Nx–0)	H-RT: 64.6/3.4 Gy C-RT: 78/2.0 Gy	804	80 89	– –	61 59	– –	– –	BCDF (relapse-free survival)	60
Pollack et al ¹⁷ / <i>J Clin Oncol</i> 2013	Intermediate– high risk (T1–3 N0)	H-RT: 70.2/2.6 Gy C-RT: 76/2.0 Gy	303	35 33	– –	– –	16 22	13 14	BCDF	68.4
Arcangeli et al ¹⁶ / <i>Int J Radiat Oncol Biol Phys</i> 2012	Predominately high risk (T1–3 N0)	H-RT: 62/3.1 Gy C-RT: 80/2.0 Gy	168	– –	13 22	7 15	– –	– –	FFBF	70

Abbreviations: BCDF, biochemical and clinical disease failure; BF, biochemical failure; C-RT, conventional fractionated radiotherapy; FFBF, freedom from biochemical failure; H-RT, hypofractionated radiotherapy; GI, gastrointestinal; GU, genitourinary; OS, overall survival.

Discussion

Several previously randomized Phase III clinical trials compared traditional radiation dose (64–70 Gy) to dose-escalated RT (74–80 Gy), and all consistently demonstrated improved disease-free survival with escalated dose.^{1,25} Thus, dose escalation has become the current standard for care, although with increased acute and late GI and GU toxicities. Because of the lower α/β ratio in prostate tumor compared with surrounding normal tissue, hypofractionation, theoretically, may bring about an additional increase in biological equivalent dose, which means, compared with C-RT, higher dose per

fraction may achieve better tumor killing and bring treatment benefit. Our findings in this meta-analysis supported this hypothesis; moderate H-RT significantly decreased biological failure rate, though without improving OS. Because of the low progression and long natural history of prostate cancer, it is difficult to increase OS significantly. One comparison of trial from Dearnaley et al¹⁰ (57 Gy/3 Gy vs 76 Gy/2 Gy) and a study from Catton et al²³ (60 Gy/3 Gy vs 78 Gy/2 Gy) are no dose escalation, which showed no improvement in BCDF rates compared with C-RT. Other comparisons with dose-escalated H-RT presented a significantly decreased risk

**Figure 2** (Continued)

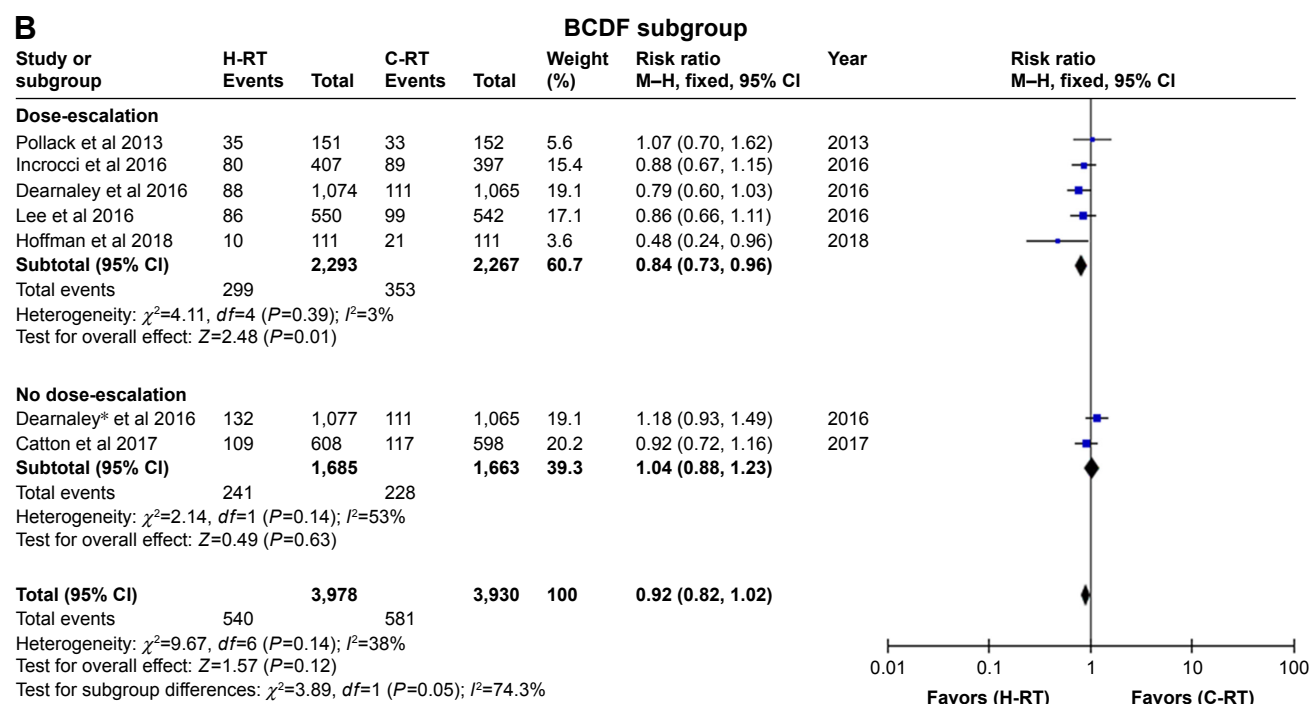


Figure 2 Forest plots for biochemical and clinical disease failure survival with hazard ratios. (A) Overall BCDF. (B) BCDF sub-grouped into dose escalation and no escalation groups.

Note: *Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison.

Abbreviations: BCDF, biochemical and clinical disease failure; C-RT, conventional fractionated radiotherapy; H-RT, hypofractionated radiotherapy.

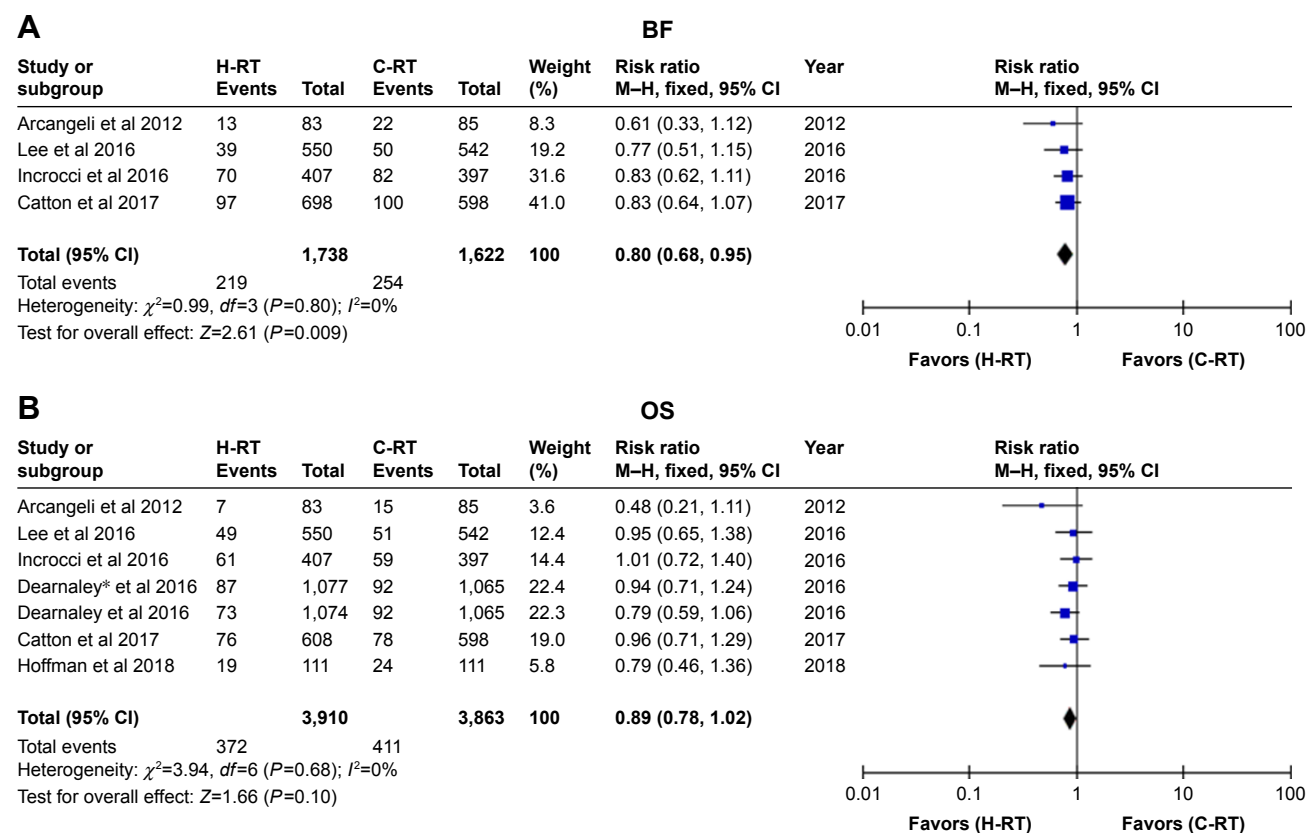


Figure 3 Forest plots for survival with hazard ratios. (A) Biochemical failure. (B) Overall survival.

Note: *Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison.

Abbreviations: C-RT, conventional fractionated radiotherapy; H-RT, hypofractionated radiotherapy; OS, overall survival.

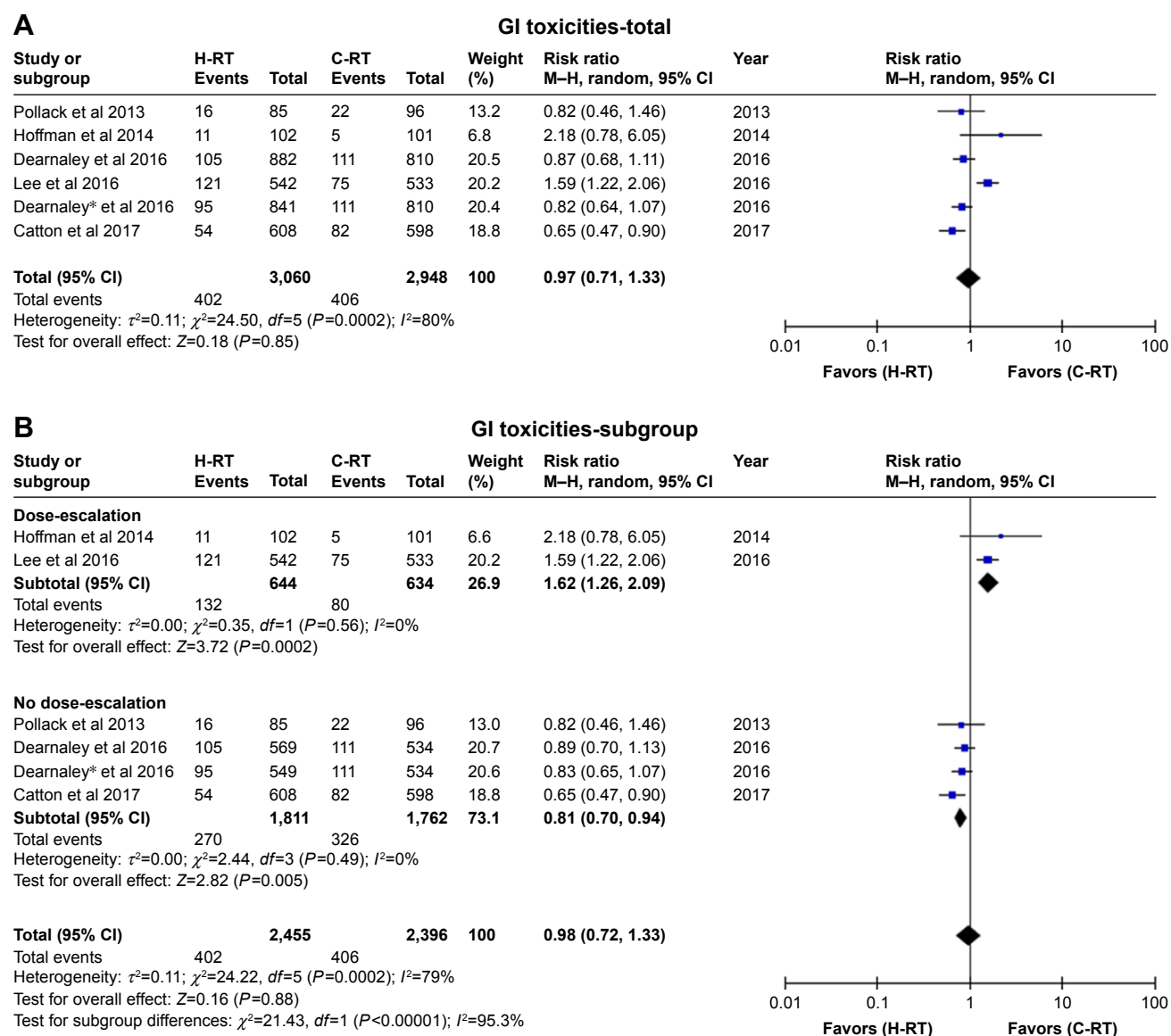


Figure 4 Forest plots for GI toxicity with hazard ratios. **(A)** Overall GI toxicity. **(B)** GI toxicity sub-grouped into dose escalation and no escalation groups.

Note: *Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison.

Abbreviations: C-RT, conventional fractionated radiotherapy; H-RT, hypofractionated radiotherapy; GI, gastrointestinal.

of BCDF (RR =0.84, 95% CI: 0.73–0.96, $P=0.01$, $I^2=3\%$), which means that moderate H-RT with a dose escalation helps decreasing BCDF.

Radiation-induced toxicity is an extremely important limitation and can cause great concerns when H-RT is delivered with dose escalation. It is difficult for radiotherapy oncologists to balance between efficacy and toxicity. Previous randomized trials using C-RT had demonstrated that dose escalation increased GI and GU toxicities. What matters is that whether moderate H-RT, especially those with an increase in BED, brings about increase in late toxicities. The results showed that there are no significant differences in GI (RR =0.97, 95% CI: 0.71–1.33) and GU (RR =1.04, 95% CI: 0.87–1.24) toxicities in patients available for analysis,

but with severe heterogeneity. BED₅ were recalculated and used as a predictor for late GI and GU toxicities. For those with an increase in BED₅ in H-RT, the results showed a significant increase in late GI toxicity with an RR of 1.62 (95% CI: 1.26–2.09, $P=0.0002$) and in late GU toxicity with an RR of 1.28 (95% CI: 1.05–1.55, $P=0.01$), while for those without an increase in BED₅, the results favored to H-RT with an RR of 0.81 (95% CI: 0.70–0.94, $P=0.005$) in GI toxicity and showed no difference in GU toxicity with an RR of 1.02 (95% CI: 0.88–1.20, $P=0.78$). There is no doubt that an increasing in BED₅ is intimate connected with an increasing in late toxicity.

From the results in this meta-analysis, radiation dose is directly associated with treatment outcomes and toxicities.

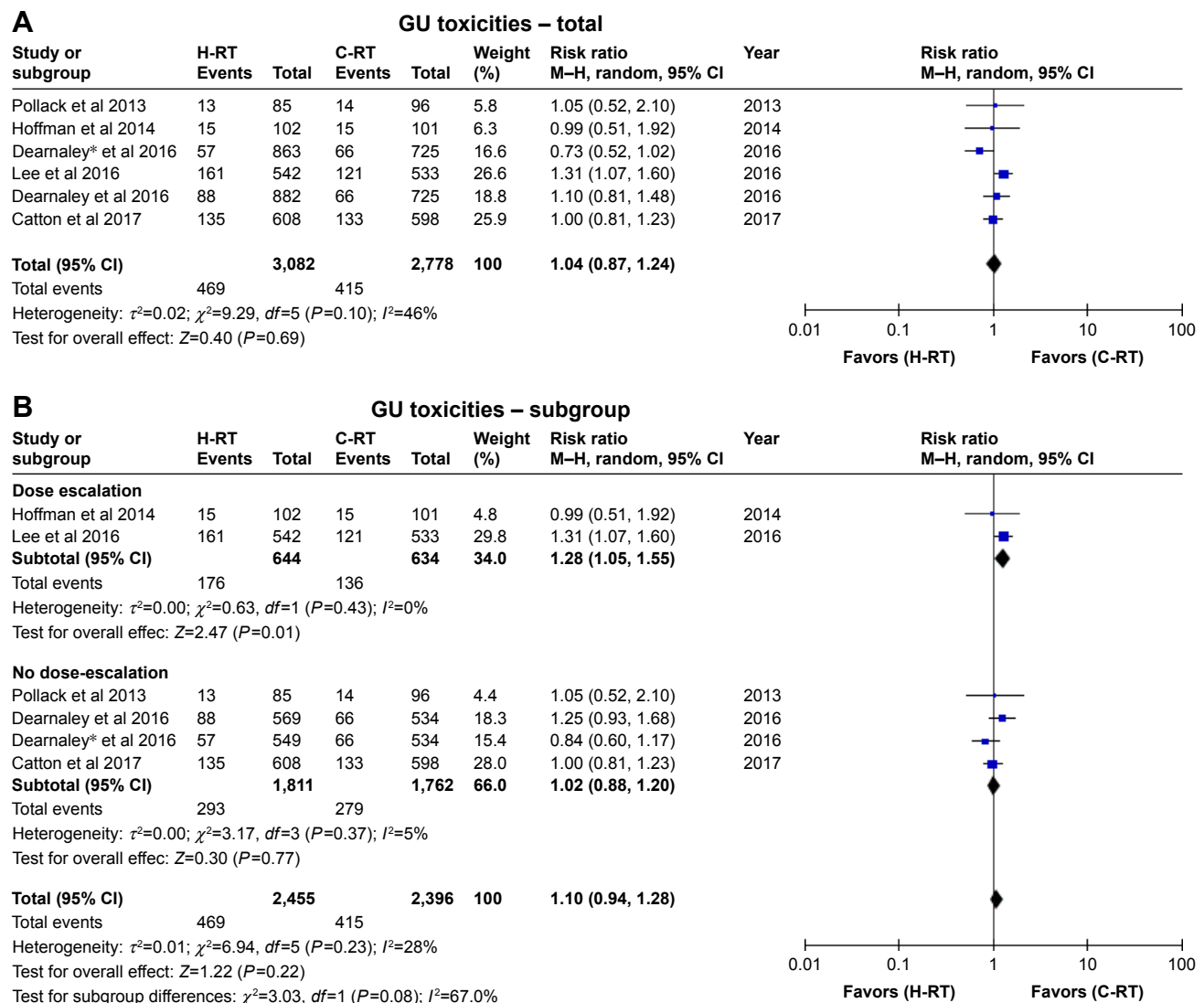


Figure 5 Forest plots for GU toxicity with hazard ratios. **(A)** Overall GU toxicity. **(B)** GU toxicity sub-grouped into dose escalation and no escalation groups.

Note: *Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison.

Abbreviations: C-RT, conventional fractionated radiotherapy; H-RT, hypofractionated radiotherapy; GU, genitourinary.

Compared with C-RT, H-RT delivered a higher $BED_{1.5}$ to treatment target, significantly decreased BCD rates, and the outcomes are favorable. Also, H-RT with a higher BED_5 than C-RT would undoubtedly increase the late GI and GU toxicities. As is well known, clinical trials comparing moderate H-RT with C-RT were usually designed for two purposes: one is to increase $BED_{1.5}$ to target volume without increasing BED_5 to normal tissue in order to improve outcomes and with a purpose of not increasing late toxicities; another is with a similar tumor dose but decreased normal tissue dose to minimize toxicity. Therefore, it is quite important to balance the treatment benefits and toxicities when designing fraction size and total dose for radiotherapy, which is also the most difficult part when designing a protocol, according to the results from Brenner and Hall.²⁶ Brenner et al²⁶ suggested that BEDs for moderate H-RT should not exceed

approximately a $BED_{1.5}$ of 183 Gy or a BED_5 of 102 Gy; under this guideline, several fraction patterns may be adopted. However, different fraction patterns may result in events including both disease failure and complication; there is still no consensus about the standard fraction and total dose of moderate hypofractionation.²⁷

Several elements of this meta-analysis may be criticized. First, two early randomized trials comparing H-RT with C-RT, conducted by Yeon et al²¹ and Lukka 2005,²² were excluded from this meta-analysis, because the dose used in C-RT was 64–66 Gy, which is much lower than the current standard treatment of care, resulting in much higher failure rates (40%–50%) in these two trials compared with 15%–20% reported under the current standard treatment. Second is that the participants in these seven trials had low-to-high risk prostate cancer, and the prescription doses

in the control group, namely in C-RT, are various, ranging from 74 to 80 Gy. Therefore, it is difficult to ascertain which group would benefit most from hypofractionation. Third, the follow-up duration is moderate, ranging from 58 to 102 months in these trials. This length of follow-up is sufficient to predict toxicities related to therapy because most chronic toxicities develop within the first 5 years. However, such a follow-up is still immature in terms of cancer outcomes due to the long natural history of prostate cancer. Lastly, to our knowledge, a meta-analysis is already available in the literature from Cao et al.²⁸ However, several special aspects in this analysis are different from the study of Cao et al, including the differentiation of dose concepts with a fixed α/β ratio of 1.5 for prostate cancer and 5 for late toxicities, and thus a definition of dose escalation and no dose escalation. Moreover, exclusion of older studies with lower doses in the standard arm and the addition of newly published trials make the conclusion more dependable.

Although with the limitations mentioned above, this meta-analysis is a pooled analysis of seven large-scale Phase III randomized trials with reliable data. The findings suggested moderate H-RT with increase in BED_{1.5} improved the treatment outcomes, while toxicity may also be increased when delivered with a higher dose in BED₅. In order to achieve excellent tumor control and low complication, BED_{1.5} for prostate cancer and BED₅ for late normal tissue toxicity should both be taken into consideration when designing a protocol.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 The biological effective dose recalculated with α/β ratio as 1.5 Gy for prostate tumor and 5 Gy for GI and GU toxicities

Study	N	Patients	Comparison	BED _{1.5}	BED ₅
Lee et al ¹ / <i>J Clin Oncol</i> 2016	1,092	Low risk (T1-2 N0)	H-RT: 70/2.5 Gy C-RT: 73.8/1.8 Gy	H-RT: 187 Gy C-RT: 162 Gy	H-RT: 105 Gy C-RT: 100 Gy
Dearnaley et al ² / <i>Lancet Oncol</i> 2016	3,216	Low-high risk (T1-T3a N0)	H-RT1: 60/3.0 Gy H-RT2: 57/3.0 Gy C-RT: 74/2.0 Gy	H-RT1: 180 Gy H-RT2: 171 Gy C-RT: 173 Gy	H-RT1: 96 Gy H-RT2: 91 Gy C-RT: 104 Gy
Incrocci et al ³ / <i>Lancet Oncol</i> 2016	804	Intermediate-high risk (T1b-4Nx-0)	H-RT: 64.6/3.4 Gy C-RT: 78/2.0 Gy	H-RT: 211 Gy C-RT: 182 Gy	H-RT: 109 Gy C-RT: 109 Gy
Hoffman et al ⁴ / <i>Int J Radiat Oncol Biol Phys</i> 2014	203	Low-high risk T1b-2N0	H-RT: 72/2.4 Gy C-RT: 75.6/1.8 Gy	H-RT: 187 Gy C-RT: 166 Gy	H-RT: 107 Gy C-RT: 103 Gy
Pollack et al ⁵ / <i>J Clin Oncol</i> 2013	303	Intermediate-high risk (T1-3 N0)	H-RT: 70.2/2.6 Gy C-RT: 76/2.0 Gy	H-RT: 192 Gy C-RT: 177 Gy	H-RT: 106 Gy C-RT: 106 Gy
Arcangeli et al ⁶ / <i>Int J Radiat Oncol Biol Phys</i> 2012	168	High risk (T1-3 N0)	H-RT: 62/3.1 Gy C-RT: 80/2.0 Gy	H-RT: 190 Gy C-RT: 187 Gy	H-RT: 100 Gy C-RT: 112 Gy

Abbreviations: BED, biologically effective dose; C-RT, conventional fractionated radiotherapy; GI, gastrointestinal; GU, genitourinary; H-RT, hypofractionated radiotherapy.

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