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Comparison of the safety and efficacy of moderately hypofractionated and conventionally fractionated radiotherapy for localized prostate cancer: evidence from 9074 men in 13 randomized clinical trials

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Abstract

Objectives While moderately hypofractionated radiotherapy (HFRT) has been recommended as the standard regimen in localized prostate cancer (LPCa) based on non-inferiority trials compared to conventionally fractionated radiotherapy(CFRT), the conclusions on its efficacy and toxicity have not been consistent among all trials. This study aims to systematically compare the efficacy and safety of HFRT with CFRT for LPCa based on the present randomized controlled trials. The longest follow-up data from all the trials were adopted.

Methods and materials This research followed the steps outlined in the PRISMA statement for meta-analyses and systematic reviews. This study presents a meta-analysis of phase III trials comparing CFRT with HFRT for LPCa. The included trials reported relapse-free survival over five years and the incidence of acute or at least 3 years of late gastrointestinal (GI) and genitourinary (GU) toxicity.

Results We were able to include 18 papers in our final analysis. There was no statistically significant difference in relapse-free survival after five years of treatment between the HFRT and CFRT groups. In subgroup analyses, with an α/β of 1.5, a higher equivalent dose of HFRT compared to CFRT is associated with improved relapse-free survival over five years. Acute GI toxicity of Grade 2 or worse was more common in the HFRT group compared to the CFRT group ($p < 0.00001$). The incidence of acute GI toxicity of Grade 2 or worse rose by 8.78% when moderate HFRT was administered (95% CI = 4.69%-12.87%, $p < 0.0001$). Subgroup analyses suggested that a single dose of 2.4–3.0 Gy in HFRT may not contribute to an increase in acute GI complications. Moreover, in other outcomes, including acute GI toxicity Grade 3 or worse, acute GU toxicity, and late GI/GU toxicity, no significant differences were observed between the CFRT and HFRT groups.

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Conclusion The clinical outcomes of HFRT and CFRT were comparable, with similar five-year relapse-free survival, and without different risks of acute or late, severe GI or GU toxicity. HFRT treatment may increase the risk of Grade 2 or worse acute GI toxicity. Thus, proper monitoring and management are required. Less than 3.0 Gy of a single dose or a lower α/β value may be worth considering in the HFRT scheme. Further comprehensive examination of the findings in subgroup analyses is required, such as appropriate dose ranges and management of acute toxicity.

Keywords Moderately hypofractionated radiotherapy, Conventionally fractionated radiotherapy, Relapse-free survival over five years, Gastrointestinal toxicity, Genitourinary toxicity, Localized prostate cancer

Introduction

The Global Burden of Cancer Study (GLOBCAN 2020) ranks prostate cancer as the fifth most prevalent malignancy and the second most common disease overall in males [1]. Among males in Western Europe and the US, it ranks second in terms of cancer mortality rates and is the most prevalent solid tumor [2]. Radical treatment with radiation therapy (RT) has been on the rise for many years, particularly in males aged 65 and above [3]. Despite the drawbacks of long-term treatment, dose-escalating CFRT, with or without androgen deprivation therapy (ADT), was previously considered the standard for radiation treatment for LPCa patients. This approach has excellent cure rates [4–6].

However, HFRT may be a better way to treat prostate cancer because it uses the principle that high-dose segmentation targets malignant tissue more effectively than surrounding normal tissue (i.e., compared to normal tissue, the tumor exhibits a decreased α/β ratio). This concept is made more plausible by recent advancements in external beam radiation therapy (EBRT) methods that enable the safe administration of larger radiation doses. The development of radiotherapy technology from two-dimensional radiotherapy to three-dimensional conformal radiation therapy (3D-CRT) [7, 8] and intensity-modulated radiotherapy (IMRT) [9] has made possible the application of HFRT, with higher doses to the target area and better protection of the surrounding organs. In regard to treating LPCa, the effectiveness of moderate HFRT against CFRT has since been assessed in various phase III randomized trials.

Alternatively, previous randomized controlled trials (RCTs) have demonstrated that moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) are noninferior to CFRT [10–16], while research by Hoffman KE et al. demonstrated that moderate HFRT with dosage escalation achieves better cancer control with less treatment time required [17]. In addition, toxicity was comparable between conventional and moderately hypofractionated regimens in several RCTs [10, 13, 14, 16, 17]; however, this was not the case in all trials [15, 18]. Dissimilar fractionation schedules are likely responsible for these inconsistencies in safety and effectiveness [19]. The high survival rate of prostate cancer patients highlights the need to analyse the most current and longest follow-up data. Therefore, we hope to determine whether it is possible to shorten treatment times and lower treatment costs while increasing local tumor control rates. Thus, to compare the long-term effectiveness and side effects of HFRT to those of CFRT, a meta-analysis is required.

The trials utilized different radiation techniques, included different risk groups, and used androgen deprivation therapy or not. However, the large enrollment of randomized trials and extended posttreatment follow-up allowed us to thoroughly examine the predictive value of covariates to assess the potential effects and analyse the therapeutic efficacy of HFRT for LPCa treatment.

This study is a meta-analysis that contains the most recent phase III clinical trials comparing the efficacy of HFRT and CFRT in LPCa and the longest follow-up data (10 years), it will also compare the acute phase and late toxicity effects of these two treatment options and provide an upfront basis and rationale for future analyses to establish the most effective treatment plan for moderate HFRT for LPCa.

Materials and methods

Search strategy and protocol

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards [20], we conducted a thorough and methodical assessment of all published trials that compared CFRT with HFRT for LPCa. We searched the PubMed, Medline, Embase, and Cochrane Library databases; the most recent search was performed on 2 March 2024. The complete search technique is presented in Supplement 1. A record with PROSPERO (CRD42024520002) indicates that the protocol was approved.

Inclusion criteria

The PICOS inclusion criteria were utilized in the literature search to determine the articles that were included in this analysis [21]. The following is the synopsis:

(1) Population: Males who were diagnosed with low, intermediate, or high-risk prostate cancer based on pathology findings.
(2) Interventions: To conduct the research, patients had to undergo therapeutic EBRT with a moderate HFRT.

The American Urological Association, American Society of Clinical Oncology, and American Society of Radiation Oncology all endorse these regimens as safe and effective for patients with low, intermediate, or high-risk diseases [22]. Moderate HFRT is defined in this work as a single dosage of 2.4–3.4 Gy, and severe HFRT (ultra-HFRT) is defined as a fraction size of 5 Gy.

(3) Control group: Patients receiving CFRT with a single 1.8–2.0 Gy dose.

(4) Outcome: Both effectiveness and safety were evaluated in the study. The effectiveness of the treatment was assessed by the number of patients who were able to avoid recurrence, defined as relapse-free survival, as long as they did not experience biochemical failure, clinical relapse, local or distant recurrence, the need for hormonal therapy, or death. Biochemical failure was defined in Phoenix as a prostate-specific antigen (PSA) increase of more than 2 ng/mL after radiation treatment. Adverse events involving the GU system and the GI tract were reported in every included trial according to the toxicity reporting protocols, such as the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC) [23], Common Terminology Criteria for Adverse Effect (CTCAE) all versions [24], the standardized National Cancer Institute of Canada toxicity scale [25] or modified Late effects Normal Tissue Task Force–Subjective, Objective, Analytics (LENT-SOMA) scales [26] to ensure patient safety.

(5) Study type: The studies that were considered were prospective phase III randomized controlled trials that excluded individuals with metastatic disease or who were undergoing radical prostatectomy. Studies that used stereotactic body radiotherapy (SBRT) were also excluded.

Literature selection process

The literature search produced 550 records, of which 146 were excluded due to duplication or inaccessible full text. Of the remaining 404 articles, 327 were excluded for not being randomized trials or for having different treatment patterns. The remaining 77 articles were read in full, of which 24 were excluded for having outdated results in ongoing updates, and 35 were excluded for not reporting the outcome of interest. In total, 18 articles from 13 studies [10, 12–18, 25, 27–35] reported outcomes that met the criteria and were included in the analysis, with a total of 9,074 patients. The process flow diagram for selecting literature is displayed in Fig. 1.

Data extraction

18 articles and 13 studies were included. The author, publication year, sample size (endpoint), radiotherapy technique, total radiation dosage, single dose, an equivalent dose at 2 Gy/fraction (EQD_2), planning target volume (PTV) condition, daily image-guided radiotherapy (IGRT), and ADT use are summarized in Table 1. In addition, data on relapse-free survival over five years, and the incidence of GI and GU toxicities in acute and late Grade 2/3 or worse reported in each of the toxicity reporting systems were collected.

Radiobiology model

The formula that was used to calculate the biologically effective dosage (BED) is as follows:

$$BED = \mathrm{D}[1 + \frac{\mathrm{d}}{\left(\frac{\alpha}{\beta}\right)}] \tag{1}$$

D stands for the overall dose, d for dose/fraction, and α/β for the segmentation's radiosensitivity.

The following formula was used to determine the equivalent dose at 2 Gy/fraction (EQD_2):

$$EQD_2 = \frac{\mathrm{BED}}{1 + 2/\left(\frac{\alpha}{\beta}\right)} \tag{2}$$

Equations (1) and (2) did not account for incomplete repairs since they only resulted in a small percentage change to the BED/EQD_2. The targeted volume at the high level of planning (PTV) (prostate with and without seminal vesicle) was converted using Eqs. (1) and (2), and then the dosage was used. Detailed dose-volume histograms (DVH) data of the rectum and bladder in these studies were not available. The EQD_2 α/β values were 1.5 and 3 Gy, respectively, for relapse-free survival and toxicity in each study.

Data analysis

The hazard ratios (HR) and related data for relapse-free survival over five years were retrieved directly from the studies. The risk ratio (RR) and 95% confidence interval (CI) between HFRT and CFRT were computed for the following outcomes: acute GI/GU toxicity of Grade 2/3 or worse, and late GI/GU toxicity of Grade 2/3 or worse. The findings of each analysis were displayed using a forest plot. If the Q test for heterogeneity did not show any statistical significance and the I^2 was less than 40%, then a fixed-effects model was used. On the other hand, a random-effects model was used if the P value for

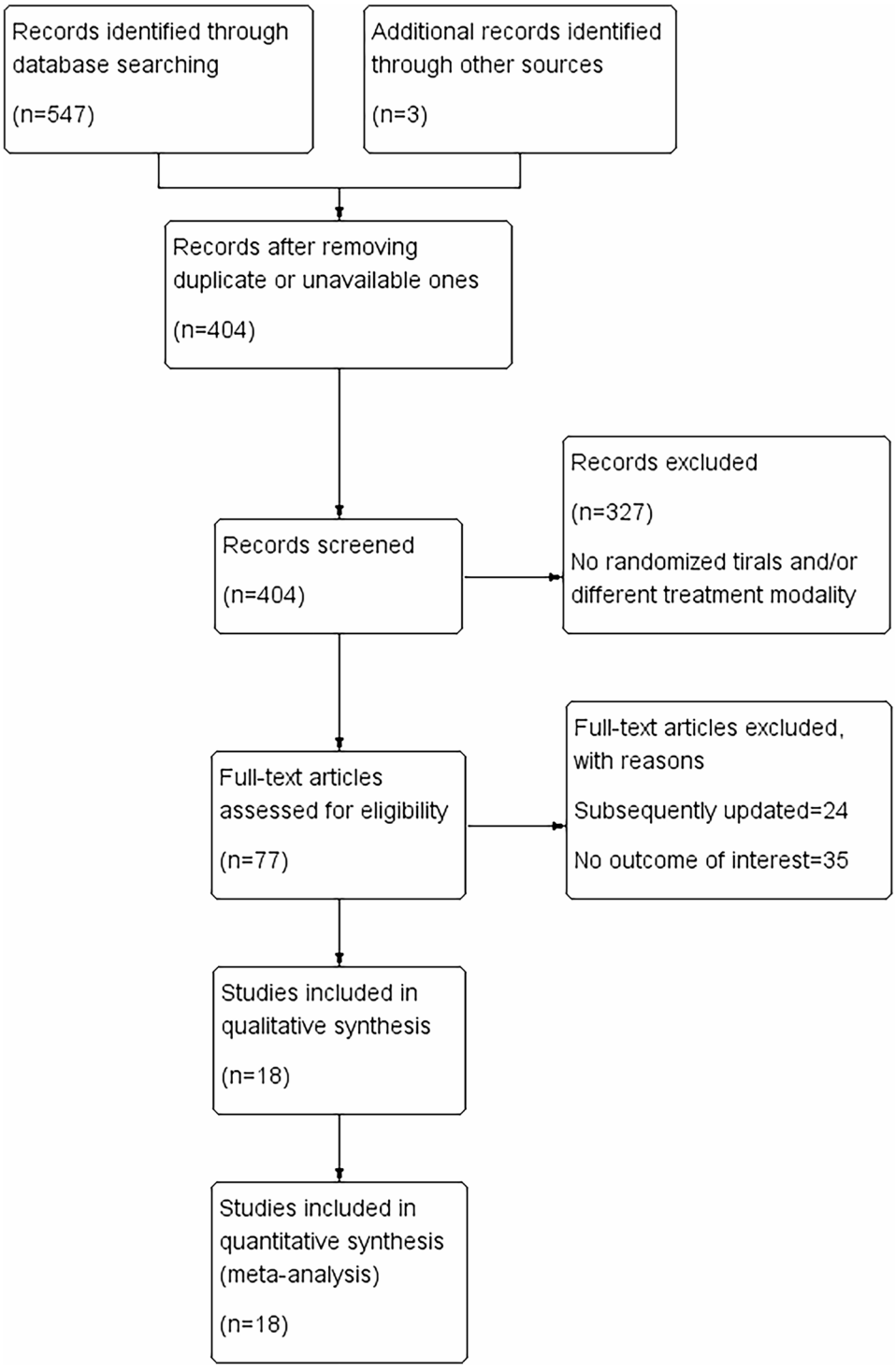

Fig. 1 PRISMA flow diagram depicting the process of literature selection

heterogeneity was greater than 0.10 and the I^2 was greater than 50%. Possible causes of variation were examined using sensitivity analysis. We used funnel plots and Egger's test to quantitatively and qualitatively examine the impact of the small sample size. The meta package in R (version 4.3.3) was used to conduct the statistical analysis.

Risk of bias and confounding assessment

The quality of the included studies was evaluated using the standard Cochrane Collaboration Risk of Bias (RoB) tool, which evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment,

Table 1 Baseline data for the included studies

Baseline Characteristics								
18 manuscripts from 13 randomized trials								
Study	**Sample**	**Dosimeteric information (mean)**				**Technique**	**PTV(exclude rectum or not)[2]**	**ADT[3]**
		Total dose(Gy)	**Dose/fraction(Gy)**	**EQD2/1.5(Gy)[1]**	**EQD2/3(Gy)**			
Aluwini S 2015,2016; Incrocci L 2019								
HFRT	407	64.6	3.4	90.4	82.7	IMRT[4]	Yes	0.66
CFRT	397	78	2	78	78	IMRT[4]	Yes	0.67
Arcangeli G 2011,2017								
HFRT	83	62	3.1	81.5	75.6	3DCRT[5]	No	1
CFRT	85	80	2	80	80	3DCRT[5]	No	1
Catton CN 2017								
HFRT	608	60	3	77.1	72	IMRT[4]	No	Unclear
CFRT	598	78	2	78	78	IMRT[4]	No	Unclear
Dearnaley D 2016，2020，Syndikus I 2023								
CHHiP57	1077	57	3	73.3	68.4	IMRT[4]	Yes	0.97
CHHiP60	1074	60	3	77.1	72	IMRT[4]	Yes	0.97
CFRT	1065	74	2	74	74	IMRT[4]	Yes	0.97
Hoffman KE 2018								
HFRT	104	72	2.4	80.2	77.8	IMRT[4]	No	0.26
CFRT	102	75.6	1.8	71.3	72.6	IMRT[4]	No	0.23
Karklelyte A 2018								
HFRT	115	63	3.15	83.7	77.5	IG-IMRT	No	1
CFRT	106	76	2	76	76	IG-IMRT	No	1
Lee WR 2016								
HFRT	550	70	2.5	80	77	IMRT: 434; 3DCRT: 111	No	Unclear
CFRT	542	73.8	1.8	69.6	70.8	IMRT: 420; 3DCRT: 114	No	Unclear
Lukka H 2005								
HFRT	466	52.5	2.62	61.9	59.1	Four-field box technique	No	Unclear
CFRT	470	66	2	66	66	Four-field box technique	No	Unclear
Niazi T 2023								
HFRT	159	68	2.72	82	77.8	IMRT:95; 3DCRT: 61	Unclear	1
CFRT	161	76	2	76	76	IMRT:101; 3DCRT: 57	Unclear	1
Pollack A 2013								
HFRT	151	70.2	2.7	84.2	80	IMRT[4]	No	0.45
CFRT	152	76	2	76	76	IMRT[4]	No	0.47
Soni A 2022								
HFRT	84	67.5	2.7	81	77	VMAT	No	1
CFRT	84	78	2	78	78	VMAT	No	1
Viani GA 2013								
HFRT	112	69	3	88.7	82.8	CRT	No	0.625
CFRT	105	78	2	78	78	CRT	No	0.8

Table 1 (continued)

Baseline Characteristics								
18 manuscripts from 13 randomized trials								
Study	**Sample**	**Dosimeteric information (mean)**				**Technique**	**PTV(exclude rectum or not)[2]**	**ADT[3]**
		Total dose(Gy)	**Dose/fraction(Gy)**	**EQD2/1.5(Gy)[1]**	**EQD2/3(Gy)**			
Yeoh EE 2010								
HFRT	108	55	2.75	66.8	63.2	3DCRT: 32; 2DCRT:76	Unclear	Unclear
CFRT	109	64	2	64	64	3DCRT: 29; 2DCRT:80	Unclear	Unclear

[1]Equivalent Dose at 2 Gy/fraction

[2]Planning Target Volume

[3]Androgen Deprivation Therapy

[4]Intensity Modulated Radiotherapy

[5]3D Conformal Radiotherapy

inadequate outcome data, selective reporting, and additional sources of bias [36]. To check if the authors balanced or adjusted for any potential prognostic confounding factors and if the groups were properly included in the study, we analysed each one individually. A significant risk of confounding bias was indicated by the color red if any confounding factors were either not reported or were provided in a way that did not ensure balance between the treatment groups. Furthermore, a confounding variable was deemed to have a low risk of bias if it was either disclosed and balanced in the therapy or imbalanced but controlled for in the statistical analysis (green). The potential for confounding bias is deemed unclear (yellow) in all other instances. The results are presented in Fig. 2 using R (version 4.3.3).

Results

General characteristics and study quality

All trials included and pooled patients with LPCa who were treated between the ages of 44 and 88 years, with a median age of approximately 70 years. The exclusion criteria included a history of pelvic irradiation, radical prostatectomy, distant metastases, World Health Organization (WHO) performance status more than 2, or Zubrod performance status more than or equal to 2. Table 1 displays the specific baseline features of each trial.

The results of 9074 patients who were eligible for inclusion in the trials were reported in 18 publications from 13 randomized trials. The same CFRT arm (74 Gy/37 fractions) was used to evaluate two distinct HFRT schedules (60 Gy/20 fractions and 57 Gy/19 fractions) in the CHHiP study [13, 29, 30]. We compared the CFRT arm to both the HFRT and CFRT-plus arms in this meta-analysis. To compare HFRT and CFRT, a total of twenty-one randomized study arms were included. Figures 2 and 3 display the results of the assessment of RoB and confounders for each arm.

Comparison of the efficacy of HFRT versus CFRT

In the meta-analysis of the relevant cohort, none of the remaining studies showed a significant difference. Overall, over five years, there was no discernible variation in the rate of relapse-free survival (as shown in Fig. 4, $p = 0.49$), $I^2 = 59\%$, $Chi^2 = 12.16$, $df = 5$, $p = 0.03$, using the random effect model. The variation in results may be attributed to the varying sample sizes across studies, potential publication bias, and differences in outcome descriptions. The results from sensitivity analyses were robust, and neither funnel plots nor Egger's test indicated any publication bias.

Subgroup analyses were conducted for the radiotherapy technique, single dose, $EQD_2(1.5)$, and $EQD_2(3)$, respectively (refer to Supplement 2). The findings indicate that when taking into account an α/β of 1.5, HFRT may be more beneficial for survival with a higher EQD_2 than CFRT. However, it should be noted that the studies included in the analysis were modest, and we eagerly await the inclusion of additional data and further thorough investigations in future studies (as shown in Fig. 5). There were no significant differences in the other subgroups analysed.

Comparison of the early safety of HFRT versus CFRT

HFRT increases the incidence of grade 2 or worse acute GI toxicity compared to CFRT

In the relevant cohort, the results of four studies showed that the HFRT group had significantly higher acute GI toxicity than the CFRT group [13, 16, 18, 32]. The remaining studies did not show significant differences. $I^2 = 0\%$, $Chi^2 = 7.03$, $df = 8$, $p = 0.53$. Therefore, the fixed-effect model was selected. Overall, compared to the CFRT group, the HFRT group had a higher incidence of acute GI toxicity, Grade 2 or worse (as shown in Fig. 6, $p < 0.00001$).

Meta-analysis of the cohort of interest was performed, and the pooled results indicated that moderate HFRT

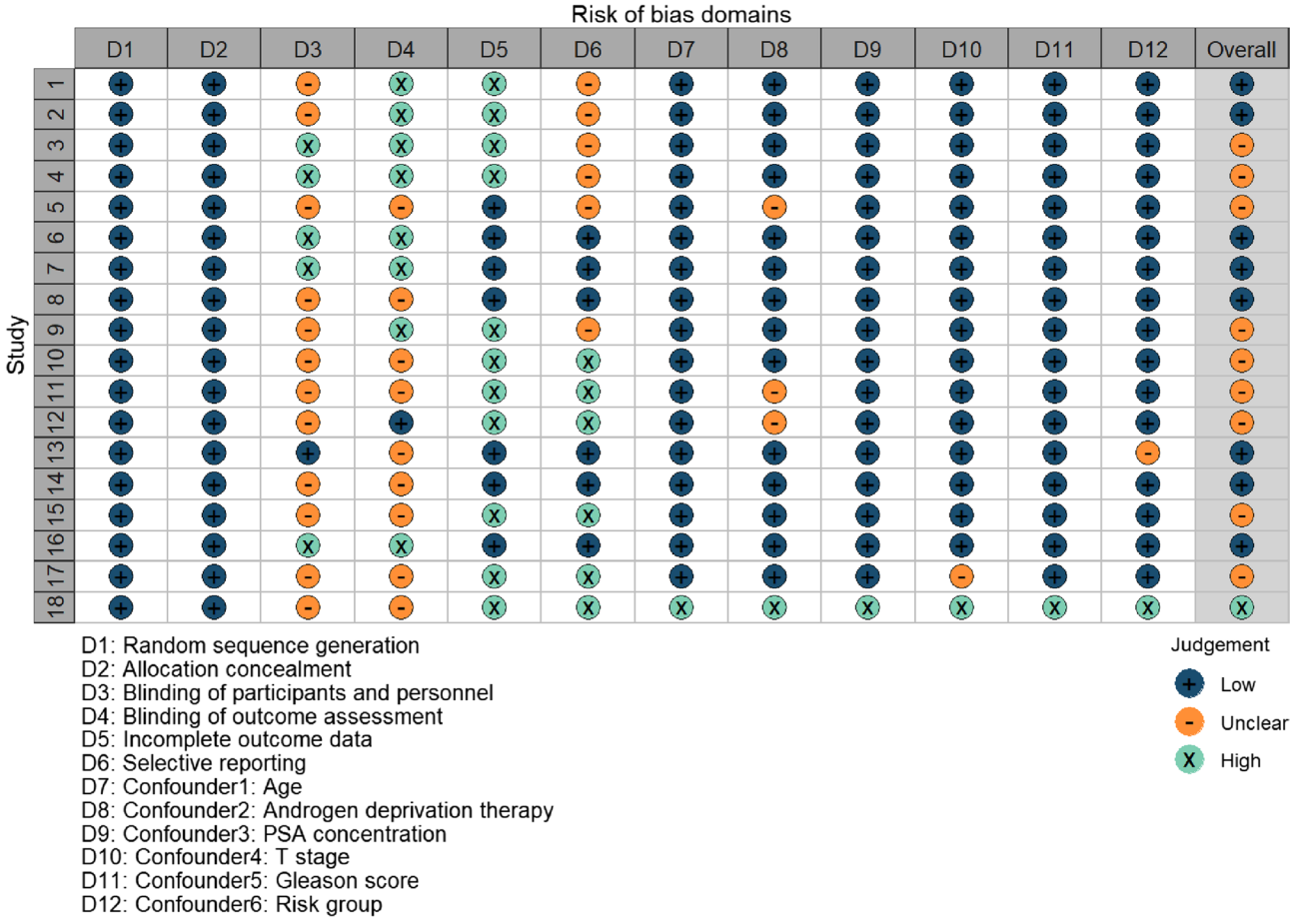

Fig. 2 Risk of bias assessment for each study using the Cochrane Collaboration Risk of Bias tool. green = high risk of bias; orange = unclear risk of bias; blue = low risk of bias

increased the risk of grade 2 or worse acute GI toxicity by 8.78% (95% CI = 4.69%–12.87%, $p < 0.0001$) (as shown in Fig. 7). $I^2 = 74\%$, $Chi^2 = 31.01$, df = 8, $p < 0.01$. A model with random effects was chosen.

Subgroup analysis for grade 2 or worse acute GI toxicity

The subgroup analysis of this study revealed that patients in the HFRT group who received IMRT had a higher risk of Grade 2 or worse acute GI toxicity compared to those in the CFRT group. The results of the IMRT subgroup analysis were consistent with the overall results. Regarding the conformal radiotherapy (CRT) group, there was no discernible variation in side effects between the two groups (refer to Fig. 8).

Regarding the single dose aspect, subgroup analyses indicated that a single dose of ≥ 3 Gy was associated with an increase in Grade 2 or worse acute GI toxicity reactions after HFRT treatment (refer to Fig. 9). While a single dose of 2.4–3.0 Gy may not contribute to an increase in that.

In addition, we calculated and analysed the EQD_2 using α/β values of 1.5 and 3 Gy. Our analysis showed that the HFRT group had a greater incidence of Grade 2 or worse acute GI toxicity reactions compared to the CFRT group, regardless of whether the EQD_2 of the HFRT group was higher or lower than that of the CFRT group or whether the rectum was part of the PTV (see Supplement 2).

Neither HFRT nor CFRT substantially differed in terms of acute GI toxicity grade 3 or worse

Research comparing HFRT with CFRT for this outcome revealed no statistically significant difference in the occurrence of acute GI toxicity Grade 3 or worse. (as shown in Fig. 10, $p = 0.11$). $I^2 = 0\%$, $Chi^2 = 2.64$, df = 6, $p = 0.85$, and the fixed-effect model was chosen.

Neither HFRT nor CFRT substantially differed in terms of acute GU toxicity grade 2 or worse

Meta-analysis of the relevant cohorts did not reveal significant differences among the included studies. Overall, the occurrence of Grade 2 or worse acute GU toxicity did not vary significantly between the HFRT and CFRT groups (as shown in Fig. 11, $p = 0.21$). $I^2 = 0\%$, $Chi^2 = 2.60$, df = 8, $p = 0.96$, and the fixed-effect model was chosen.

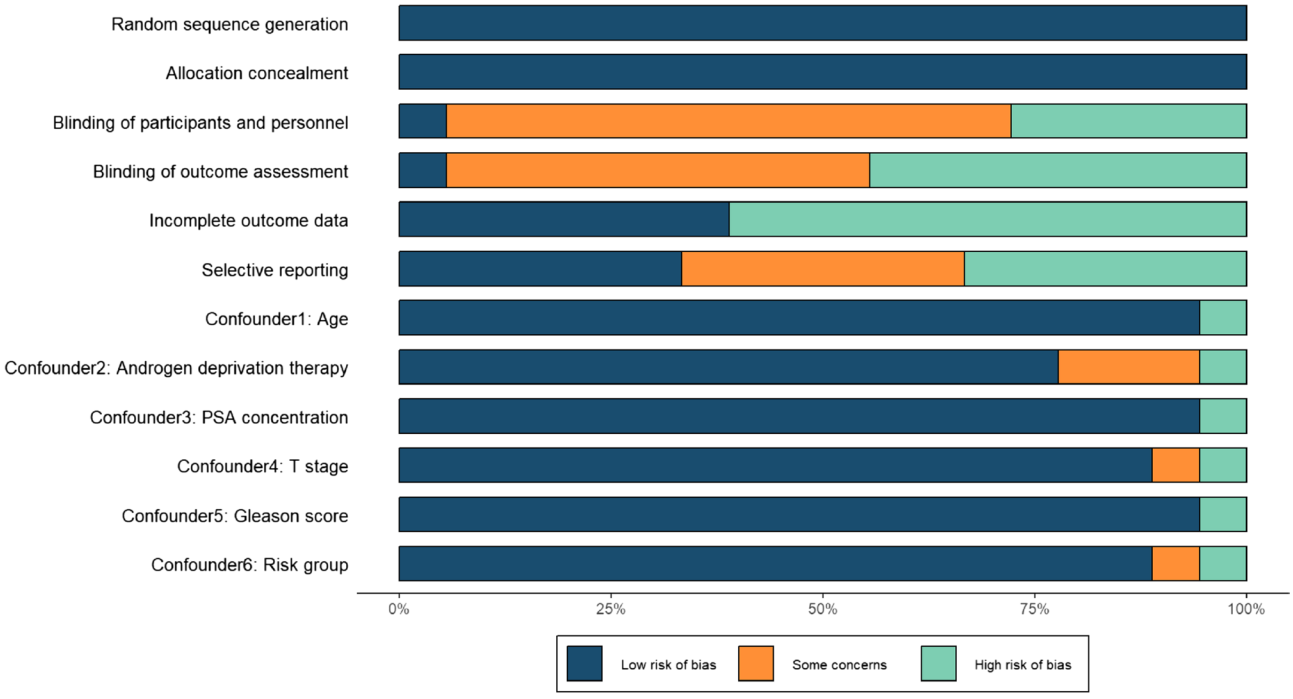

Fig. 3 Summary of the risk of bias assessment. green = high risk of bias; orange = unclear risk of bias; blue = low risk of bias

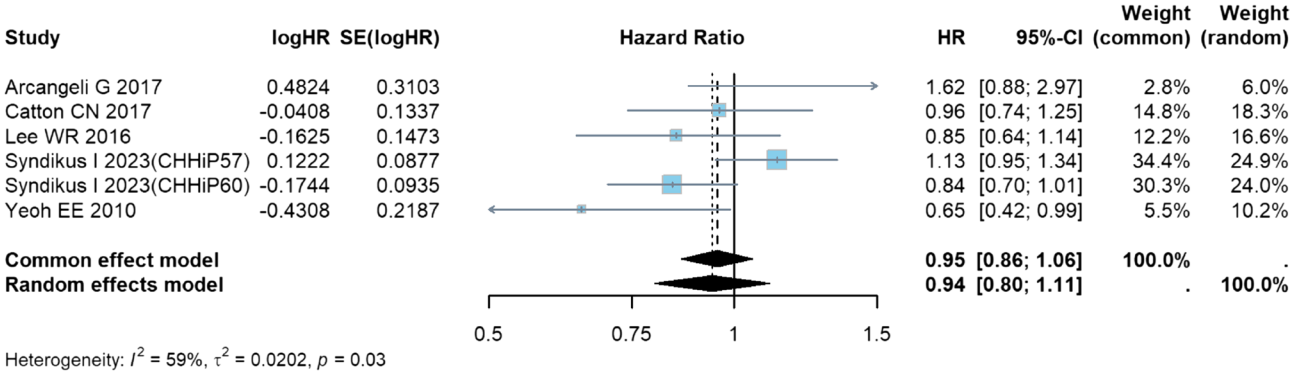

Fig. 4 Forest plot of the hazard ratio between HFRT and CFRT for relapse-free survival over five years

Neither HFRT nor CFRT substantially differed in terms of acute GU toxicity grade 3 or worse

The meta-analysis of the relevant cohort revealed that only Lukka H et al. [25] reported a significantly higher incidence of Grade 3 or more acute GU toxicity in the HFRT group (40/466, 8.6%) compared to the CFRT group (23/470, 4.9%) (RR = 1.75, 95% CI = 1.07–2.88). The remaining studies did not show any significant differences. Overall, there was no significant difference in Grade 3 or worse acute GU toxicity between the HFRT and CFRT groups (as shown in Fig. 12, $p = 0.05$). $I^2 = 0\%$, $Chi^2 = 3.74$, df = 7, $p = 0.81$, and the fixed-effect model was selected.

Comparison of the late safety of HFRT versus CFRT

Neither HFRT nor CFRT substantially differed in terms of late GI toxicity grade 2 or worse

By meta-analysis of the relevant cohort, there was no significant difference in late GI toxicity between the HFRT and CFRT groups (as shown in Fig. 13, $p = 0.37$). Catton CN et al. [16] and Lee WR et al. [15] demonstrated opposite conclusions. None of the remaining studies reported showing significant differences between the two groups. $I^2 = 63\%$, $Chi^2 = 24.06$, df = 9, $p < 0.01$, select the random effect model. The funnel plot shows that the publication bias of the included studies was not obvious, possibly because of heterogeneity due to the significant sample size difference between the studies.

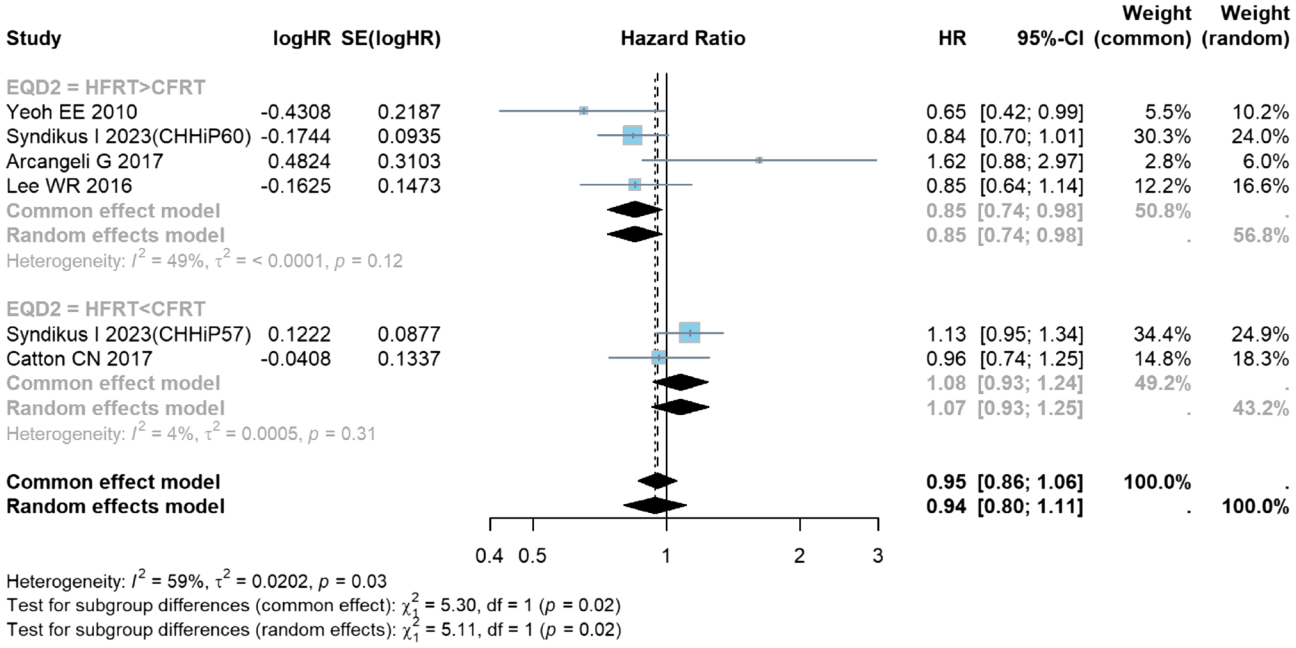

Fig. 5 Forest plot of subgroup analysis of relapse-free survival over five years against EQD_2(1.5)

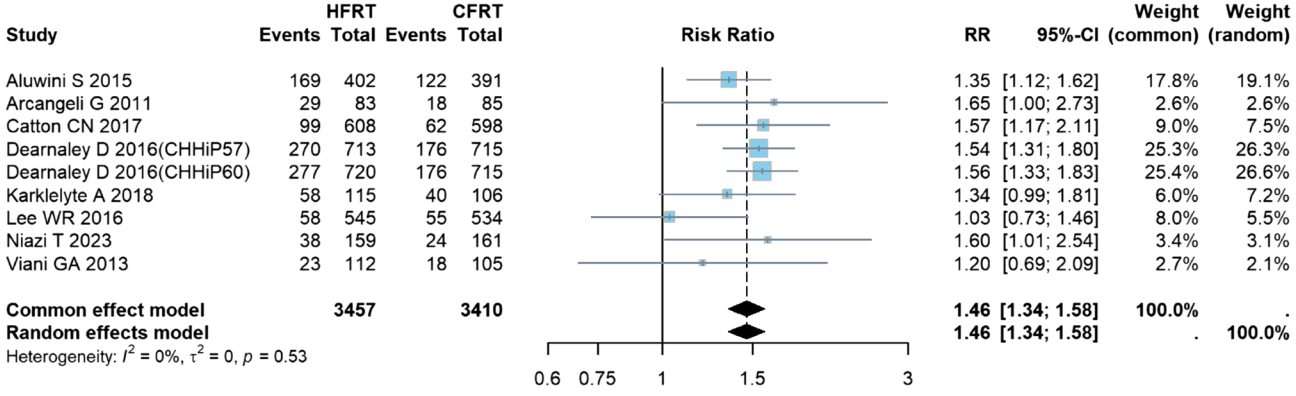

Fig. 6 Forest plot of the risk ratio between HFRT and CFRT for Grade 2 or worse acute GI toxicity

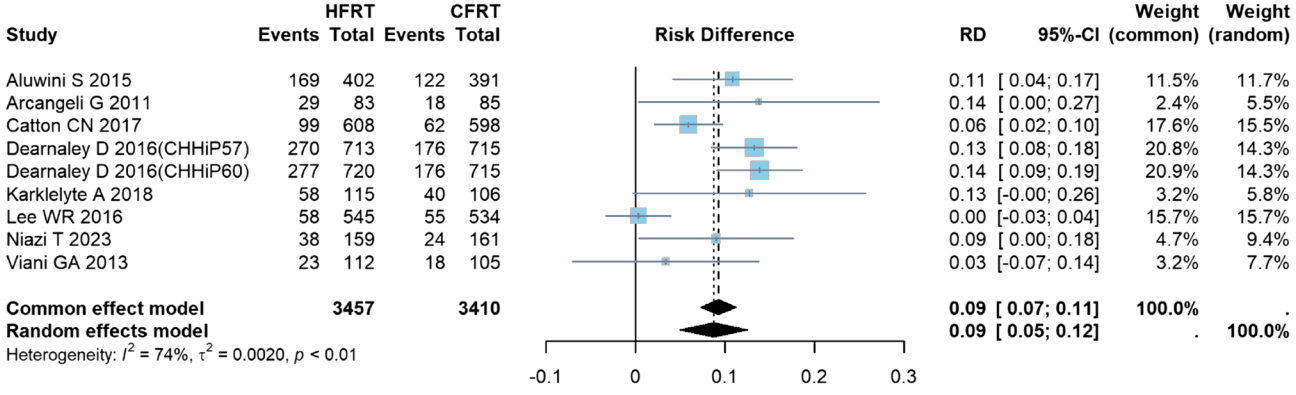

Fig. 7 Forest plot of risk difference between HFRT and CFRT for Grade 2 or worse acute GI toxicity

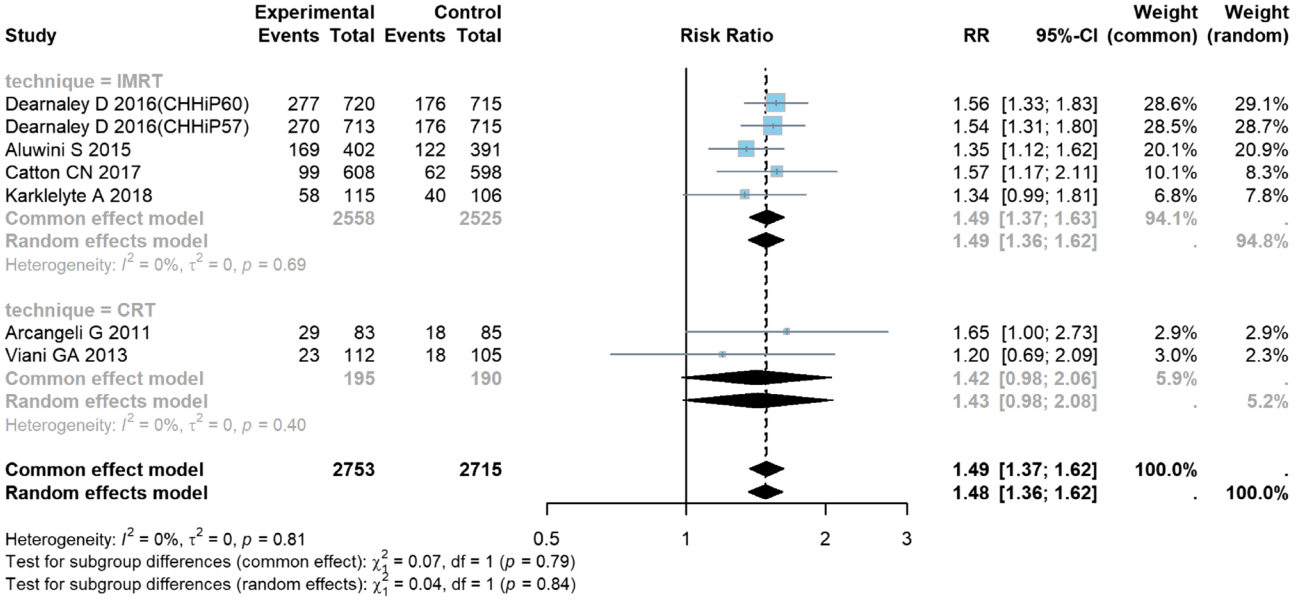

Fig. 8 Forest plot of subgroup analysis of Grade 2 or worse acute GI toxicity against radiotherapy technique

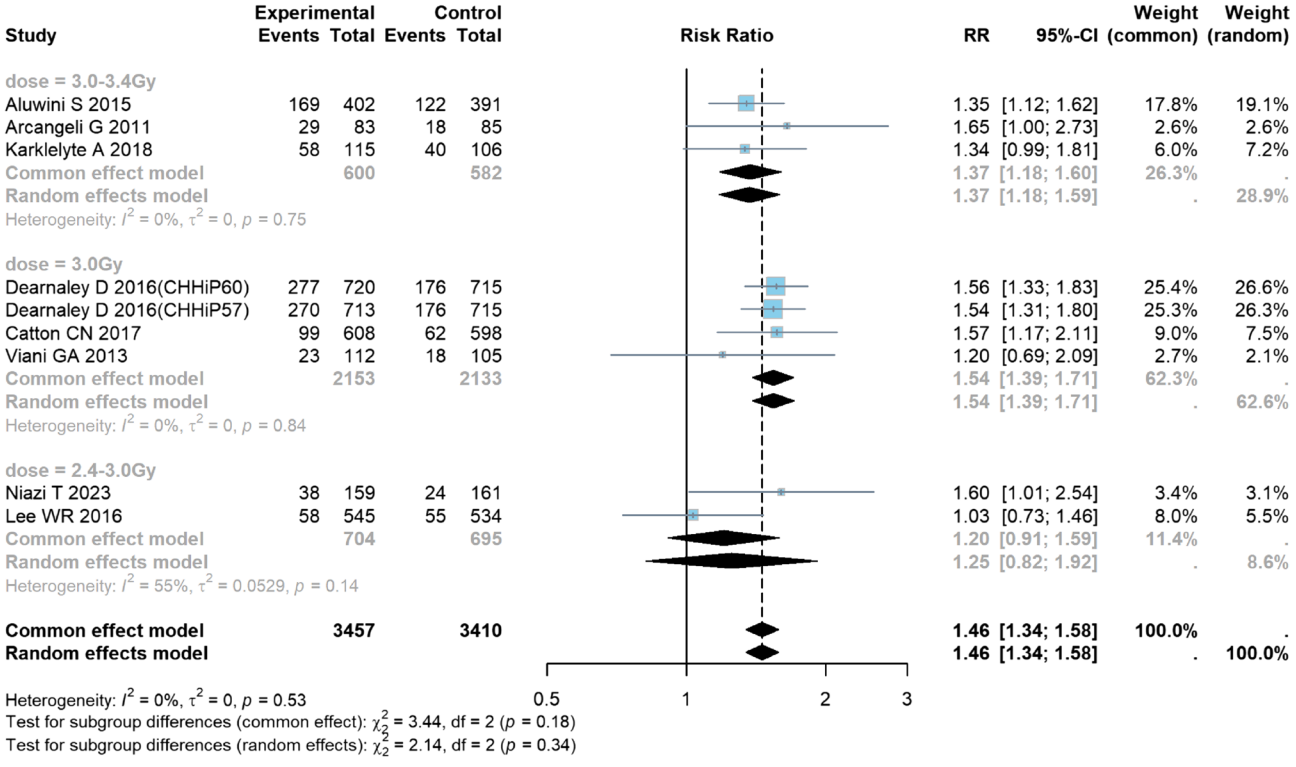

Fig. 9 Forest plot of subgroup analysis of Grade 2 or worse acute GI toxicity against single dose

Neither HFRT nor CFRT substantially differed in terms of late GI toxicity grade 3 or worse

When looking at the studies that reported this result, a meta-analysis revealed that neither HFRT nor CFRT had significantly different rates of Grade 3 or worse late GI toxicity (as shown in Fig. 14, $p = 0.55$). $I^2 = 0\%$, $Chi^2 = 6.62$, $df = 7$, $p = 0.47$, and the fixed-effect model was chosen.

Neither HFRT nor CFRT substantially differed in terms of late GU toxicity grade 2 or worse

For the relevant cohort, results from Lee WR et al. [15] and Niazi T et al. [32] were incongruous. The remaining studies did not demonstrate any significant differences. Overall, comparing HFRT and CFRT, we found no statistically significant variation in the occurrence of Grade

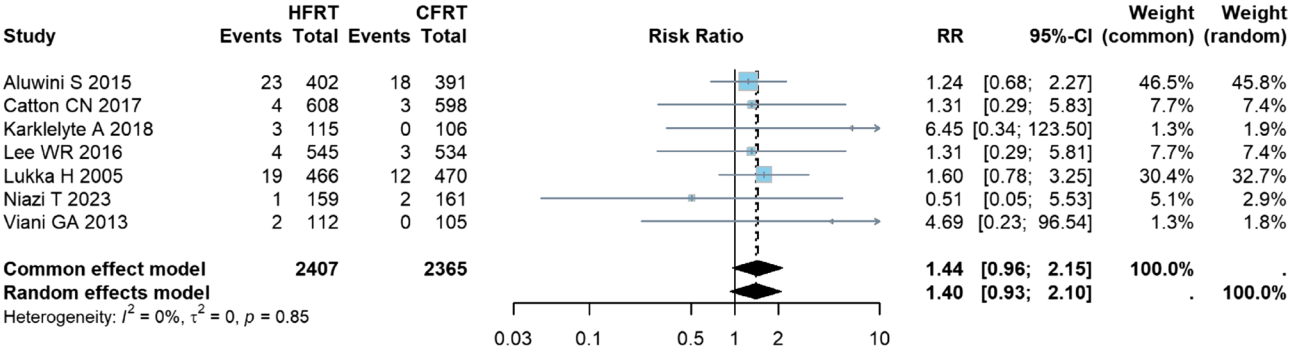

Fig. 10 Forest plot of the risk ratio between HFRT and CFRT for Grade 3 or worse acute GI toxicity

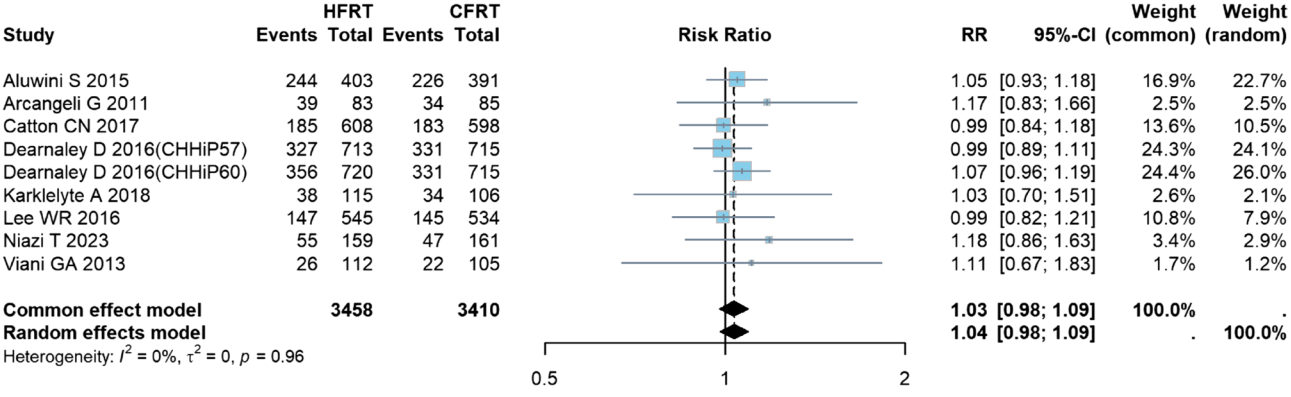

Fig. 11 Forest plot of the risk ratio between HFRT and CFRT for Grade 2 or worse acute GU toxicity

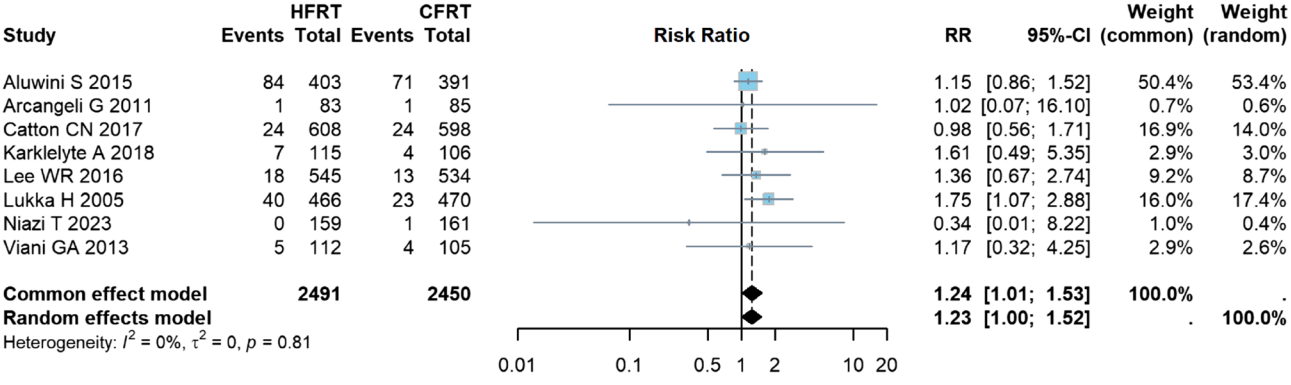

Fig. 12 Forest plot of the risk ratio between HFRT and CFRT for Grade 3 or worse acute GU toxicity

2 or worse late GU toxicity (as illustrated in Fig. 15, $p = 0.51$). $I^2 = 40\%$, $Chi^2 = 15.07$, df = 9, $p = 0.09$, and the random effect model was selected.

Neither HFRT nor CFRT substantially differed in terms of late GU toxicity grade 3 or worse

Grade 3 or worse late GU toxicity was found to be more common in the HFRT group (75/395, 19.0%) in only one meta-analysis of the relevant cohort compared to the CFRT group (50/387, 12.9%) (RR = 1.47, 95%CI = 1.06–2.04), conducted by Aluwini S et al. [27]. The remaining studies did not show any significant differences. Overall, both the HFRT and CFRT groups experienced Grade 3 or worse late GU toxicity at similar rates (as shown in Fig. 16, $p = 0.10$). $I^2 = 19\%$, $Chi^2 = 7.38$, df = 6, $p = 0.29$, and the fixed-effect model was selected.

Discussion

Patients who opt for external irradiation for LPCa are strongly advised to use a moderately hypofractionated radiotherapy regimen, with a single dose of 2.4–3.4 Gy, according to evidence-based guidelines published by the American Society for Radiation Oncology, the American Society of Clinical Oncology, and the American

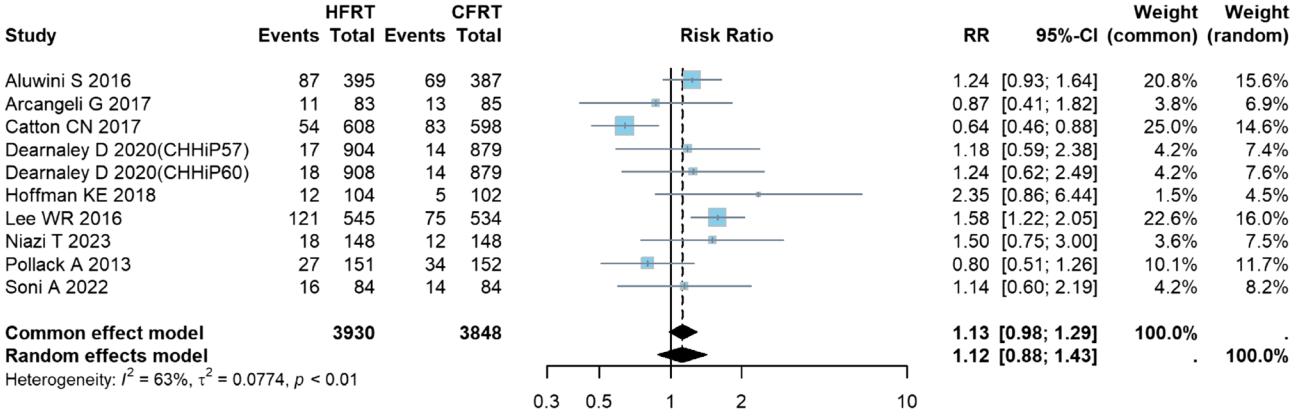

Fig. 13 Forest plot of the risk ratio between HFRT and CFRT for Grade 2 or worse late GI toxicity

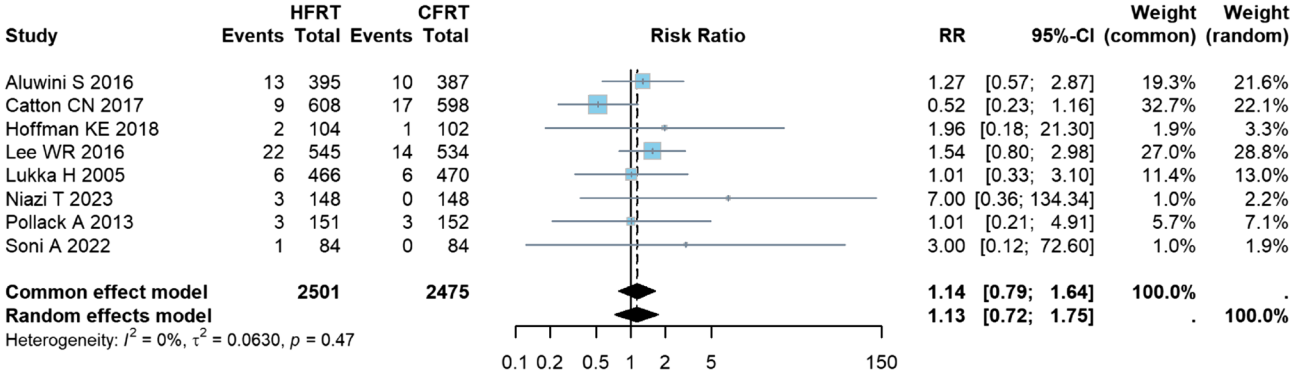

Fig. 14 Forest plot of the risk ratio between HFRT and CFRT for Grade 3 or worse late GI toxicity

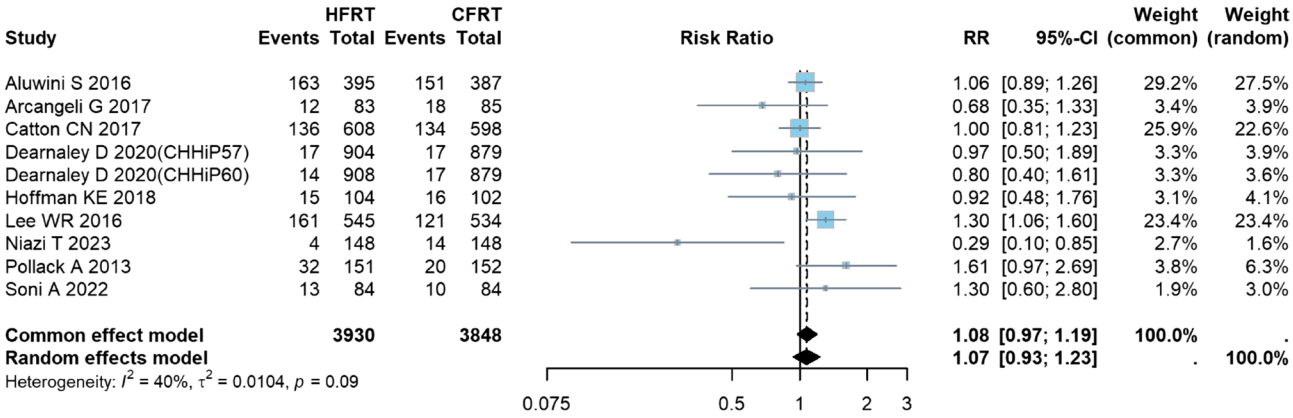

Fig. 15 Forest plot of the risk ratio between HFRT and CFRT for Grade 2 or worse late GU toxicity

Urological Association. Our results suggested that there is no significant difference in efficacy (relapse-free survival over five years) between HFRT and CFRT. However, subgroup analysis indicated that a higher equivalent dose of HFRT, compared to CFRT, led to a higher 5-year relapse-free survival over five years when taking α/β as 1.5. We are excitedly looking forward to future research that incorporates more data and conducts more comprehensive investigations. Furthermore, patients undergoing moderate HFRT or CFRT did not significantly vary in terms of late GI or GU, according to the study. On the other hand, men who undergo moderate HFRT should be warned about the slightly higher risk of acute GI toxicity [22].

This study evaluated the incidence of adverse reactions based on Grade 2 or worse toxicity reactions. Eight investigations reported radiation-related acute rectal and bladder problems in HFRT patients as opposed to CFRT patients. Acute GI toxicity of Grade 2 or worse was 8.78% more likely to occur with HFRT regimens than with

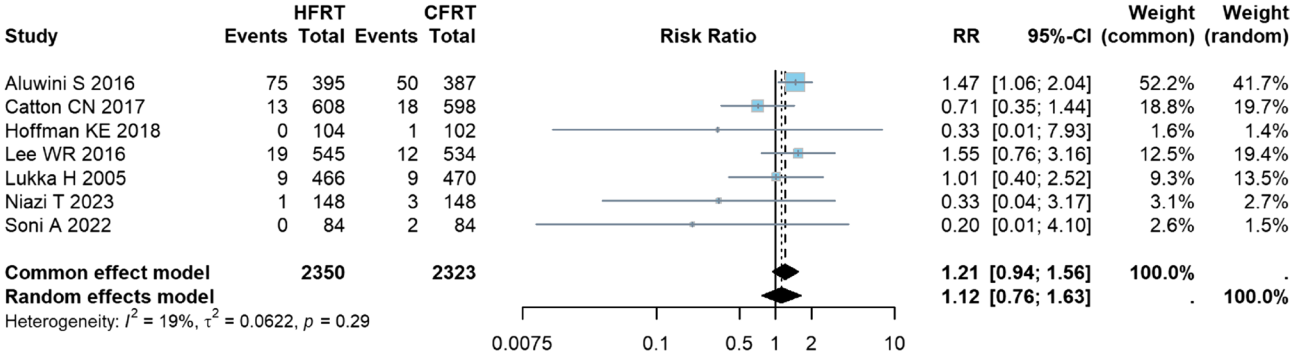

Fig. 16 Forest plot of the risk ratio between HFRT and CFRT for Grade 3 or worse late GU toxicity

CFRT regimens, according to the combined data. On the other hand, the likelihood of acute GU toxicity of Grade 2 or worse did not change significantly. The findings were considered more reliable due to the low heterogeneity between these studies. These results agree with those of Sinzabakira F et al. [37] and Francolini G et al. [38]. A single dose of 2.4–3.4 Gy was associated with a 6.3% pooled risk difference (HFRT vs. CFRT) for acute GI toxicity (95% CI = 2.0%–10.6%), as proven in the study conducted by Sinzabakira F et al. [37]. For a single dose of 3.0–4.5 Gy, Francolini G et al. discovered that acute GI toxicity was 9.8% (95% CI = 4.8%–14.7%) more likely to occur than in CFRT-treated patients, while patients with acute GU toxicity did not show any such statistically significant risk difference [38].

To determine the best way to lessen the likelihood of severe acute Grade 2 or worse GI toxicity, we performed subgroup analysis for radiotherapy technique, single dose, and EQD_2. The finding of a higher incidence of acute Grade 2 or worse GI with HFRT compared to CFRT in the present study is consistent with previous studies. IMRT was used in most patients included in this meta-analysis. The results of the IMRT subgroup analysis were consistent with the overall results. We conjecture that perhaps the rectum is more sensitive to a higher single dose, but more experimental exploration is needed. The most relevant factor to the incidence of rectal side effects is the dose of the rectum, such as V60, V70, etc., but detailed DVH data of the rectum in these studies were not available. In addition, most of the RCTs did not explain whether different dose assessment parameters of OARs were used for HFRT and CFRT, so it is hard to identify the reason for the current results. It is hoped that more relevant dosimetric data will be released. This is the first meta-analysis to set radiation technology (IMRT or 3DCRT) as a subgroup factor in comparing HFRT and CFRT. Further, the fact that no significant difference was found for CRT may be related to the small sample size or the same poor protection of the rectum in both the HFRT and CFRT groups that received CRT. Hence, given future data, in the era of intensity-modulated radiotherapy, including IMRT and VMAT, the relationship between the HFRT and the risk of acute GI injury may be further illuminated [39–41]. We will continue our research and explore potential factors leading to the different findings in subgroup analysis. Acute GI toxicity of Grade 2 or worse was more common in patients who received a single dose of 3 Gy or more of HFRT, according to the subgroup analysis. Nevertheless, we eagerly await additional data and future investigations because of the limited number of included studies and some heterogeneity among studies in the less than 3.0 Gy grouping. Additionally, regardless of whether the EQD_2 of HFRT was higher than CFRT, at an α/β of 1.5 and 3 Gy, there was an increased occurrence of Grade 2 or worse acute GI toxicity in the HFRT group. This suggests that the adverse effects may not be related to an increase or decrease in the equivalent dose compared to CFRT.

Most acute side effects of radiation treatment disappear after about three months of treatment [18]. However, there was some evidence in the literature suggesting that patients with acute issues were more likely to acquire late difficulties. A systematic review by Peach et al. [42] showed that acute damage from prostate cancer radiation indirectly produced late toxicity. In contrast, neither the HYPRO [27] nor the CHHiP [13] trials discovered a correlation between higher levels of acute GI toxicity and higher levels of late GI toxicity.

By pooling data from nine trials with similar results, we were able to determine that HFRT and CFRT did not differ significantly in the occurrence of late Grade 2 or worse GI/GU toxicity. This is consistent with previous meta-analyses and reviewed studies [37, 43, 44]. Late GI toxicity rates were not significantly different between HFRT and CFRT in a meta-analysis of nine trials including 7317 patients (12.9% HFRT vs. 16.2% CFRT; RD=−0.01; 95% CI=−0.04–0.02; $p = 0.41$; $I^2 = 58\%$). Furthermore, the two regimens did not differ significantly in terms of late GU toxicity (28.7% HFRT vs. 28.0% CFRT; RD=−0.01; 95%CI=−0.04–0.03; $p = 0.67$; $I^2 = 52\%$) [43]. In another meta-analysis of seven studies involving 8156 patients, HFRT and CFRT did not differ significantly

concerning late GI toxicity (RR = 0.97; 95%CI = 0.71–1.33; $P = 0.85$) and GU toxicity (RR = 1.04; 95%CI = 0.87–1.24; $P = 0.69$) issues [44].

Additionally, ultra-hypofractionated radiation, moderate HFRT, or CFRT did not differ significantly in terms of late toxicity. Baccaglini W et al. [45] collected data from 2,929 LPCa patients across eight research studies and analysed it. The analysis revealed no significant differences in terms of late GI and GU adverse events between CFRT or moderate HFRT (which can be collectively referred to as standard fractionated radiotherapy, SF) and ultra-hypofractionated radiotherapy (HF) (GI, 2.1% HF vs. 3.5% SF, RD=−0.01; 95% CI=−0.03–0.00; $p = 0.05$; $I^2 = 22\%$ and GU, 3.9% HF vs. 4.7% SF, RD=−0.01; 95% CI=−0.03–0.00; $p = 0.16$; $I^2 = 19\%$).

The study assessed the incidence of serious adverse events by Grade 3 or worse toxic reactions. No statistically significant difference was found between moderate HFRT and CFRT in the GI and GU systems during either the acute or late phases of the disease. In conclusion, there is no evidence that moderate HFRT increases the risk of acute or late severe GI or GU toxicity.

The results confirmed the safety of moderate HFRT and were in line with earlier review studies; however, they did show a slight increase in acute GI issues. Since there is a global shortage of radiation resources, low-income countries may benefit from moderate HFRT by being able to treat more patients in less time, by shortening the treatment cycle. Radiation techniques, dosage levels, tumor stages, and the availability of modern imaging tools for localization are only a few of the other factors that must be considered when assessing the toxicity potential.

We added to the guideline recommendations for continued long-term follow-up after using moderate HFRT in patients with LPCa by conducting a meta-analysis of all available phase III clinical trials, including the most recent ones with the longest follow-up data (10 years). Additionally, we investigated potential factors that affect acute GI and provided a subgroup analysis of these issues to encourage more thorough research on these topics.

Nevertheless, there are still certain limitations to this study. One of these is the lack of individual-level data, such as DVHs, which makes it difficult for this study to conduct a more refined hazard stratification and identify groups that would benefit more from moderate HFRT. This highlights the need for further in-depth exploration and provides ideas for future research. Furthermore, additional research is needed to clarify the role of moderate HFRT in the acute-phase clinical management of LPCa, especially in nations that have developed with advanced intensity-modulation and imaging technology [37]. Although our subgroup analysis suggests that a dose of 2.4–3.0 Gy is feasible without loss of efficacy or increased acute GI toxicity, more data are required to support these findings and to explore associations between radiation technique, single dose, and acute GI adverse events. And a key subsequent issue is to determine whether an optimal moderate HFRT regimen may exist that effectively minimizes the risk of acute GI and even GU toxicities, and still achieves the desired oncological outcome.

Conclusion

Our meta-analysis, which included the latest phase III clinical studies and the longest follow-up data (10 years), showed no significant difference in relapse-free survival over five years between patients treated with HFRT and those treated with CFRT. The subgroup analysis suggested that a higher equivalent dose of HFRT, compared to CFRT, results in higher relapse-free survival over five years when taking the α/β as 1.5. Since men with prostate cancer tend to live longer than those with other types of cancer, longer-term follow-up results are anticipated. Regarding safety, we evaluated the overall incidence of adverse reactions based on Grade 2 or worse toxic reactions. An estimated risk difference of + 8.78% suggested that HFRT treatment may increase the likelihood of Grade 2 or worse acute GI toxicity. This highlights the importance of proper oversight and administration. Subgroup analyses indicated that a single dose of less than 3 Gy may not increase acute GI complications, which requires more research. What's more, moderate HFRT did not increase the overall risk of GU toxicity, late GI toxicity, or GU toxicity compared to CFRT. The incidence of serious adverse reactions, as assessed by Grade 3 or more toxicity reactions, showed no statistically significant variation in the GI and GU systems between moderate HFRT and CFRT during either the acute or late stages. In conclusion, moderate HFRT may increase non-severe acute GI toxicity, but it does not increase the risk of acute phase or late severe GI or GU toxicity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15018-7.

Additional file 1: Table S1. Initial literature search strategy.

Additional file 2:Figure S1. Funnel plot. Figure S2-3. Sensitivity analyses. Figure S4. Subgroup analyses of relapse-free survival over five years. Figure S5. Subgroup analyses of Grade 2 or worse acute GI toxicity.

Acknowledgements

Color should be used for all figures in print.

Authors' contributions

The study's original concept was created by HC and JC. HC and JC collaborated on the scope and methodology planning. With help from JC and XG, HC carried out the meta-analysis, drafted the protocol for the study, and registered the study with PROSPERO. The update to the meta-analysis was organized by JC. Jointly, HC and JC created the search parameters, ran the search, exported the results, and eliminated duplicate entries. The

systematic review was conducted by HC and JC, who were responsible for screening abstracts and texts, extracting pertinent data from the publications, and assessing their quality. HC and JC prepared the data for additional examination. HC conducted the meta-analysis and wrote the computer code. All authors helped with significant revisions after HC and JC authored the initial draft. In this research, XG is considered the corresponding author. The final manuscript was read and approved by all writers.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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