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Association of Perirectal Hydrogel Spacer Placement with Clinical Outcomes in Patients with Prostate Cancer Undergoing Radiotherapy: A Systematic Review and Meta-Analysis

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Purpose: To assess the relationship between perirectal hydrogel spacer placement and the clinical outcomes in men undergoing radiotherapy (RT) for prostate cancer.

Materials and Methods: An extensive literature review was conducted using the PubMed/Medline, Embase, Cochrane Library, and Web of Science databases, encompassing studies published through June 2024. Group comparisons were performed using the weighted mean difference for continuous variables and the risk ratio for dichotomous measures. The primary endpoint was to compare rectal radiation doses with or without a perirectal spacer. Secondary outcomes included gastrointestinal (GI) and genitourinary (GU) toxicities (acute/late and any/grade ≥2, with subgroup analyses for hypofractionated RT.

Results: We reviewed 35 studies comprising 4,664 males. Rectal spacers effectively reduced the mean and maximum rectal radiation exposure, with reductions of 51.8% in V50 (mL) and 56.8% in V70 (mL). Furthermore, the percentage-based analysis showed reductions of 54.5% in V50 (%) and 62.2% in V70 (%). Acute GU toxicities (any grade and grade ≥2) showed no significant difference between the spacer and no-spacer groups, with no subgroup differences by fractionation. Late GU toxicities (any grade) were lower in the spacer group, while grade ≥2 toxicities showed no difference. Acute GI toxicities (any grade) were significantly reduced with spacers, particularly in hypofractionated RT, while grade ≥2 toxicities showed no difference. Late GI toxicities (any grade) were lower in the spacer group, with a stronger protective effect in hypofractionated RT. No significant difference was observed in grade ≥2 late GI toxicities.

Conclusions: Hydrogel spacers significantly reduced rectal radiation exposure and overall GI toxicity. However, their limited impact on severe toxicity highlights the need for further research on high-risk treatments and advanced RT techniques.

Keywords: Hydrogels; Meta-analysis; Prostatic neoplasms; Radiometry; Radiotherapy

INTRODUCTION

Radiotherapy (RT) is the primary treatment approach for patients diagnosed with localized or locally advanced prostate cancer [1,2]. Advances in radiation modalities, including intensity-modulated RT, image-

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guided RT, and proton beam therapy, have enabled dose escalation and improved tumor control outcomes in prostate cancer management [3,4]. Dose-escalated external beam RT is a potent curative method because delivering higher radiation doses to the prostate enhances biochemical control [5]. However, the improved biochemical and clinical outcomes achieved through dose escalation are often accompanied by an increase in late grade 2 or higher gastrointestinal (GI) and genitourinary (GU) toxicities [6,7]. This concern is particularly relevant in the context of hypofractionated RT using stereotactic body radiotherapy (SBRT), which has been gaining attention in recent years [8-13].

The anterior rectal wall is particularly susceptible to radiation-induced damage owing to its close anatomical location to the prostate, with the two organs typically separated by only 2 to 3 mm [14]. Mitigating rectal toxicity involves increasing the distance between the prostate and rectum. Consequently, a biodegradable gel has been implemented to create greater separation between these structures in patients undergoing prostate RT, aiming to minimize radiation-related adverse effects [15]. Despite several drawbacks, including the risk of infection and bleeding during insertion, pain caused by spacer migration, localized discomfort due to tissue compression, and the possibility of insufficient protection in high-dose radiation areas, hydrogel spacers have been widely studied as a potential strategy to mitigate concerns regarding long-term radiation-related complications. A phase III clinical trial has assessed the placement of a perirectal hydrogel spacer, demonstrating improvements in dosimetric and clinical outcomes, such as reduced toxicity and better bowel quality of life [16]. Furthermore, various studies have indicated that hydrogel spacers may lower the incidence of GU toxicity, particularly concerning lower urinary tract symptoms, by reducing the radiation dose delivered to the bladder in patients receiving prostate cancer RT [17,18].

Several systematic reviews and meta-analyses have offered qualitative and quantitative assessments of various perirectal spacer materials used before prostate RT [19-21]. However, previous meta-analysis included only a small number of studies using conventional RT protocols and may have been based on lower levels of evidence [19]. Since the previous meta-analysis, several follow-up studies have been conducted, particularly recent studies on hypofractionated RT, highlighting the effects of spacer placement before RT on clinical outcomes and treatment-related toxicities. To bridge these gaps and supplement the findings of previous meta-analysis, we gathered the latest evidence and conducted a systematic review and meta-analysis to investigate the association between perirectal hydrogel spacer placement and the clinical outcomes in patients with prostate cancer undergoing prostate RT.

MATERIALS AND METHODS

This systematic review was registered in PROSPERO (CRD420246132663).

1. Literature search

We extensively reviewed the literature using the PubMed/Medline, Embase, Cochrane Library, and Web of Science databases, covering studies published up to June 2024. This analysis focused on English-language publications without study design limitations. Abstracts from meetings and conferences were excluded. The search strategy employed a combination of medical subject headings (MeSH), EmTree terms, and relevant keywords related to anatomy (prostate), diseases (cancer and carcinoma), treatments (radiation therapy), and devices (hydrogel, perirectal spacer, polyethylene glycol, rectal spacer, and SpaceOAR). The search terms are specified in the supplement. Two authors, JKK and DKK, independently screened the titles and abstracts of the retrieved articles using predefined inclusion and exclusion criteria. Any disagreements were resolved through consultation with a third reviewer (JJ), who facilitated a consensus on the study selection (Supplement Materials 1).

2. Trial inclusion criteria and exclusion criteria

This study assessed the impact of placing a perirectal spacer prior to RT (intervention) on rectal dosimetry and the associated toxicities (any grade and grade ≥2; acute and late) (outcomes) in prostate cancer patients undergoing RT (population), compared to patients with prostate cancer who did not receive a perirectal spacer (comparators).

The analysis excluded the following: 1) reviews, correspondences, editorials, conference abstracts, and case reports; 2) studies where outcome data extraction was not possible; 3) studies focusing on other factors influencing outcomes; 4) studies that did not report relevant

outcomes; and 5) studies without a control group.

The primary endpoint was the difference in the radiation dose delivered to the rectum between patients with prostate cancer who underwent RT with and without perirectal spacer placement. Secondary outcomes included differences in the incidence of GI and GU toxicities (acute/late and any/≥2 grade) between the two groups.

3. Data extraction

Two authors (JKK and DKK) independently extracted the data of the included studies using predesigned templates. These templates included the following details: authorship, publication year, study location, study design type, number of participants, participant age, prostate volume (mL), risk classification of the disease, number of patients who underwent androgen deprivation therapy, outcome data (*e.g.*, rectal dosimetry values [mean and standard deviation] and toxicity data [number of events and total cases]), and declarations of potential conflicts of interest. Data were presented in various formats. When the mean and standard deviation (SD) were not reported or not clearly specified, the median was used as an estimate of the mean using previously described methods [22,23]. GI and GU toxicities were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0/5.0. Acute toxicities were defined as adverse events occurring during RT or within 3 months post-treatment, while late toxicities were defined as events occurring beyond 3 months after RT completion.

4. Study quality assessments and quality of evidence

To evaluate the quality of the included studies, we used the ROBINS-I tool for non-randomized studies and the Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCTs) [24,25].

The certainty of evidence was assessed using the Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) framework [26]. This evaluation considered the methodology, result precision, inconsistency, indirectness, and publication bias. According to the GRADE approach, evidence certainty is classified into four levels: high, moderate, low, and very low. GRADEpro software (available at https://gradepro.org) was used to create the "Summary of Findings" table.

5. Statistical analyses

The authors collected the means and SDs of the rectal dosimetry values and the number of toxicity events to evaluate the outcomes. Continuous outcomes of rectal dosimetry values are reported as a combination of the weighted mean difference (MD) with a 95% confidence interval (CI) and p-value using pooled data. Dichotomous outcomes for toxicity events are reported as risk ratios (RRs) and 95% CIs in stratified 2×2 contingency tables. If the mean and SD included zero events, a small value (*e.g.*, 0.01) was added to enable analysis using the inverse variance method. This adjustment is unlikely to affect the overall results but may cause minor variations. Studies with zero events in either arm were excluded from the meta-analysis because of statistical limitations. We evaluated the heterogeneity among the studies using the Cochrane Q test and the I^2 statistic significant heterogeneity was identified when the Cochrane Q test yielded a p-value of <0.05 or the I^2 statistic exceeded 50% [27]. To address heterogeneity, sensitivity analyses were performed by sequentially excluding individual studies and by restricting the analysis to high-quality studies with low risk of bias (Supplement Fig. 1, 2). Additionally, subgroup analyses were conducted based on radiation fractionation regimens (conventional *vs.* hypofractionated RT) to assess the stability of findings. We applied a random-effects model based on the Der Simonian and Laird approach to address the heterogeneity [28]. A random-effects model was chosen due to the inherent clinical and methodological heterogeneity among studies, including differences in study design, radiation techniques, and spacer types. This model accounts for between-study variability and provides more generalizable estimates, in contrast to a fixed-effects model that assumes a single true effect size. Publication bias was assessed using funnel plots; symmetry indicated the absence of publication bias. Statistical analyses were performed using Review Manager version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008). Two-tailed p-values were calculated, and statistical significance was defined as $p < 0.05$.

RESULTS

1. Systematic review process

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram out-

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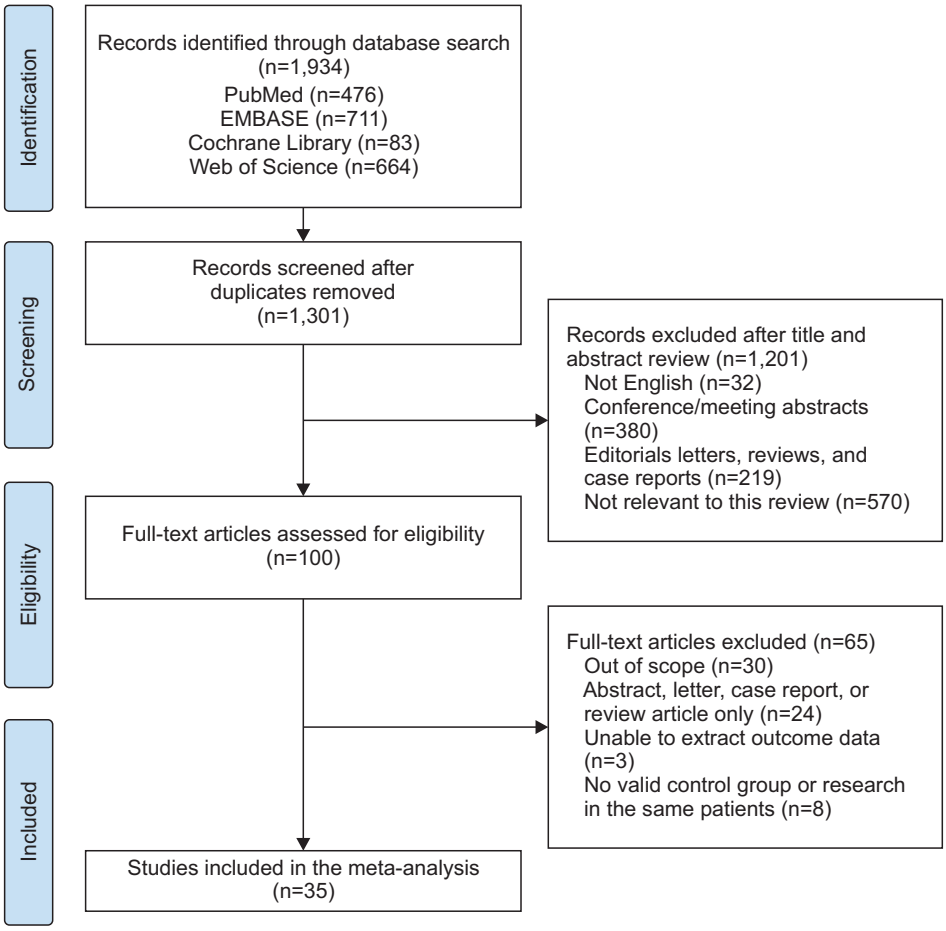

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart.

lines this study's systematic review process (Fig. 1). In total, 35 studies were included in the final analysis, of which eight were RCTs and the rest employed either retrospective or prospective designs. All included studies evaluated the effect of placing a perirectal spacer before RT on clinical outcomes in patients with prostate cancer receiving RT. Table 1 provides a detailed summary of study characteristics (Supplement Materials 2).

2. Rectal dosimetry (D)

1) Rectal Dmax and Dmean

Three and two studies analyzed the rectal Dmax and Dmean, respectively. The rectal Dmax (MD=-20.46; 95% CI: -37.80 to -3.12; p=0.02) and Dmean (MD=-8.33; 95% CI: -13.47 to -3.18; p=0.002) were significantly lower in the spacer group than in the no-spacer group. Significant heterogeneity was detected for Dmax (p<0.00001, I^2=98%), whereas moderate heterogeneity was observed for Dmean (p=0.09, I^2=65%) (Fig. 2).

2) Rectal V-matrix (rectal volume received radiation, Gy, mL, or %)

The rectal V50 (mL) and V70 (mL) were significantly lower in the spacer group than in the no-spacer group. The pooled MD was -9.34 (95% CI: -17.90 to -0.77; p=0.03) for rectal V50 (mL) and -6.56 (95% CI: -10.72 to -2.40; p=0.002) for rectal V70 (mL), favoring the spacer group. For the remaining endpoints, including V60, V75, V100, and the additional % V-matrix, the spacer group consistently showed a trend toward reduced rectal dose exposure compared with the no-spacer group (Fig. 2).

3. GI and GU toxicities

1) Acute GU toxicity

Acute GU toxicities (any grade and grade ≥2) did not significantly differ between the spacer and no-spacer groups (Fig. 3).

For any grade acute GU toxicity, the RR was 0.99 (95% CI: 0.92–1.07, p=0.88), with no detected heterogeneity (I^2=0%, p=0.44). When stratified by fractionation

Table 1. Characteristics of the studies included in the meta-analysis

Study year	Country	Design of study	Total number of participants		Age (y)		Prostate volume (mL)		Class of risk		Androgen deprivation therapy (n)		Types of radiation therapy/ dose/fractionation	Conflicts of interest
			Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer		
Alongi et al (2021)	Italy	Prospective	10	10	70 (54–78)	66 (56–75)	62.5 (49.8–79)	55.5 (29.7–79)	(Low/favorable intermediate/ unfavorable intermediate) 3/4/3	(Low/favorable intermediate/ unfavorable intermediate) 2/6/2	3	2	Intensity-modulated radiation therapy/35 Gy/5	Elekta and Boston Scientific
Butler et al (2021)	United States	Retrospective	174	174	64.8 (7.4)	64.8 (6.7)	23.1 (6.0)	23.4 (6.1)	(Low/intermediate/ high/very high) 0/113/57/4	(Low/intermediate/ high/very high) 3/119/52/0	NA	NA	External beam radiation therapy/20–125 Gy	None
Cousins et al (2022)	United States	Retrospective	30	30	NA	NA	NA	NA	NA	NA	NA	NA	Combination-brachytherapy/45, 90 Gy/25	None
Farjam et al (2021)	United States	Retrospective	10	10	75 (67–81)	65.5 (63–80)	NA	NA	NA	NA	NA	NA	MR-guided radiotherapy/26.26 Gy/5	None
Fukumitsu et al (2022)	Japan	Prospective	130	30	46–82	54–86	NA	NA	(Low/favorable intermediate/ unfavorable intermediate) 2/23/5	(Low/favorable intermediate/ unfavorable intermediate) 9/71/50	NA	NA	Proton beam radiation therapy/63 Gy/21	None
Hamstra et al (2017)	United States	RCT	149	73	66.4	67.7	47	50	NA	NA	NA	NA	Intensity-modulated radiation therapy/79.2 Gy/44	Augmenix
Hamstra et al (2018)	United States	RCT	94	46	66.4	67.7	NA	NA	NA	NA	NA	NA	Intensity-modulated radiation therapy/79.2 Gy/44	Augmenix
Kahn et al (2020)	United States	Retrospective	40	40	63.0 (7.3)	64.0 (6.4)	NA	NA	(Low/intermediate/ high) 2/23/15	(Low/intermediate/ high) 6/32/2	17	6	Low-dose-rate brachytherapy/45, 110, 145 Gy	NA
Ahmad Khalil et al (2022)	Germany	Prospective	15	8	66.65 (7.36)	60.67 (21.18)	NA	NA	NA	NA	10		Intensity-modulated proton beam therapy/60, 72 Gy/30	None
Kobayashi et al (2021)	Japan	Retrospective	53	17	69 (55–83)	69 (54–77)	39.3 (16.0–91.8)	40.1 (10.4–81.2)	(Low/intermediate) 16/37	(Low/intermediate) 2/15	NA	NA	Stereotactic body radiation therapy/36.25 Gy/5	NA
Kundu et al (2022)	United States	Retrospective	51	41	72 (52–85)	71 (46–85)	45.7 (16.5–86.8)	52.2 (27.3–112.3)	(Low/favorable intermediate/ unfavorable intermediate/high) 5/10/28/8	(low/favorable intermediate/unfavorable intermediate/ high) 2/13/14/12	18	16	Stereotactic body radiation therapy/40 Gy/5	None
Lee et al (2023)	United States	Prospective	20	21	73 (67–76)	70 (67–77)	28.1 (6.4)	27.0 (12.4)	NA	NA	NA	NA	High-dose-rate brachytherapy/24 Gy	None

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Table 1. Continued 1

Study year	Country	Design of study	Total number of participants		Age (y)		Prostate volume (mL)		Class of risk		Androgen deprivation therapy (n)		Types of radiation therapy/dose/fractionation	Conflicts of interest
			Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer		
Lin et al (2021)	Australia	Retrospective	28	42	64.9 (6.3)	66.9 (7.0)	NA	NA	(Low/favorable intermediate/unfavorable intermediate) 11/15/2	(Low/favorable intermediate/unfavorable intermediate) 13/28/1	3	6	Low-dose-rate brachytherapy/145 Gy	None
Mariados et al (2015)	United States	RCT	149	73	66.4	67.7	47.3	49.6	NA	NA	NA	NA	Image guided intensity-modulated radiation therapy/79.2 Gy/44	Augmenix
Mariados et al (2023)	United States	RCT	136	65	68.6 (7.2)	68.4 (7.3)	NA	NA	NA	NA	43	20	Hypofractionated radiation therapy/60 Gy/20	None
Morita et al (2020)	Japan	Retrospective	100	200	70 (49–84)	72 (61–79)	21.3 (8.9–66.9)	23.7 (9.0–61.0)	(Very low/low/favorable intermediate/unfavorable intermediate/high/very high) 9/18/19/17/26/11	(Very low/low/favorable intermediate/unfavorable intermediate/high/very high) 10/34/41/32/68/15	44	91	1. Low-dose-rate brachytherapy/183.8 Gy 2. Low-dose-rate brachytherapy+External beam radiation therapy/134.2+45 Gy/25	NA
Morita et al (2024)	Japan	Retrospective	394	337	70 (47–86)	72 (48–88)	NA	NA	(Very low+low/intermediate/high+very high) 109/157/128	(Very low+low/intermediate/high+very high) 81/127/129	246	224	1. Low-dose-rate brachytherapy/160 Gy 2. Low-dose-rate brachytherapy + External beam radiation therapy/110 Gy/25	NA
Nakai et al (2024)	Japan	Retrospective	186	186	70 (66–75)	71 (66–75)	21.4 (16.3–26.8)	21.0 (15.8–26.6)	NA	NA	NA	NA	1. Low-dose-rate brachytherapy/160 Gy 2. Low-dose-rate brachytherapy+External beam radiation therapy/155 Gy/25	NA
	Japan	Retrospective	70	70	69 (64–75)	71 (66–76)	14.7 (12.8–20.2)	15.7 (12.7–19.1)	NA	NA	5	6	1. Low-dose-rate brachytherapy/160 Gy 2. Low-dose-rate brachytherapy+External beam radiation therapy Proton beam radiation/155 Gy/25	NA
Navaratnam et al (2020)	United States	Retrospective	51	21	73.9 (70.0–78.0)	74.9 (73.0–78.05)	NA	NA	NA	NA	26	19	Proton beam radiation therapy/67.5–79 Gy/25–44	None

Table 1. Continued 2

Study year	Country	Design of study	Total number of participants		Age (y)		Prostate volume (mL)		Class of risk		Androgen deprivation therapy (n)		Types of radiation therapy/ dose/fractionation	Conflicts of interest
			Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer		
Nehlsen et al (2021)	United States	Retrospective	22	146	70 (63–75)	66 (59–73)	43.1 (10.52)	41.8 (15.41)	(Low/intermediate/ high) 27/57/62	(Low/intermediate/ high) 3/13/6	0	0	External beam radiation therapy+low-dose-rate brachytherapy /45+25 Gy/25, 5	None
Pinkawa et al (2017)	Germany	Retrospective	101	66	72 (49–82)	73 (53–85)	NA	NA	(Low/intermediate/ high) 19/22/13	(Low/intermediate/ high) 19/28/13	NA	NA	Intensity-modulated radiation therapy, Volumetric modulated arc therapy/76–78 Gy/38–39	None
Pinkawa et al (2017)	Germany	Retrospective	54	60	73 (56–82)	73 (53–84)	NA	NA	(Low/intermediate/ high) 33/37/30	(Low/intermediate/ high) 22/28/17	NA	NA	Intensity-modulated radiation therapy/76–80 Gy/38–40	None
Prada et al (2009)	Spain	RCT	36	33	68 (55–78)	69 (57–76)	35 (14–66)	35 (14–55)	(Low/intermediate) 25/11	(Low/intermediate) 17/16	16	15	Low-dose-rate brachytherapy with I-125 seeds/145 Gy	None
Quinn et al (2020)	United States	RCT	149	73	NA	NA	NA	NA	NA	NA	0	0	Intensity-modulated radiation therapy/79.2 Gy/44	Augmenix
Anton Sagayanathan et al (2024)	Australia	Retrospective	80	82	72.2 (60–83)	70.1 (54–82)	34 (10–120)	43 (8.7–137)	NA	NA	61	59	Volumetric modulated arc therapy/78 Gy/39	NA
Seymour et al (2020)	United States	RCT	146	69	65.9 (7.8)	67.3 (6.6)	50.9 (26.6–100.1)	59.1 (25.9–111.5)	NA	NA	0	0	Intensity-modulated radiation therapy, Volumetric modulated arc therapy/79.2 Gy/44	Augmenix
	Germany	Prospective	99	66	70.6 (6.5)	71.8 (7.0)	75.5 (40.25)	66.25 (28.25)	NA	NA	0	0	Intensity-modulated radiation therapy, Volumetric modulated arc therapy/79.2 Gy/44	
Seymour et al (2023)	United States + Germany	RCT+ Prospective	83	45	64.2 (7.4)	65.9 (6.7)	51.3 (43.0–62.4)	57.5 (49.0–69.5)	NA	NA	0	0	Intensity-modulated radiation therapy/79.2 Gy/44	Augmenix Boston Scientific
Taggar et al (2018)	United States + Thailand	Retrospective	74	136	68.9	69.1	29.34 (12.35)	34.55 (12.11)	NA	NA	NA	NA	1. Low-dose-rate brachytherapy/100 Gy 2. Low-dose-rate brachytherapy+external beam radiation therapy/45 Gy/25	None
Te Velde et al (2017)	Australia	Retrospective	65	60	71.5	72.3	39	32.7	(Low/intermediate/ high) 1/20/44	(Low/intermediate/ high) 0/21/49	63	57	Intensity-modulated radiation therapy/81 Gy/45	None

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Table 1. Continued 3

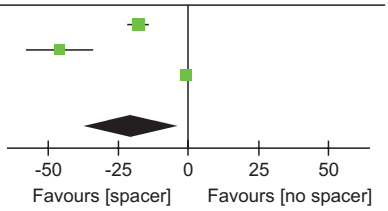
Study year	Country	Design of study	Total number of participants		Age (y)		Prostate volume (mL)		Class of risk		Androgen deprivation therapy (n)		Types of radiation therapy/ dose/fractionation	Conflicts of interest
			Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer	Spacer	No spacer		
Te Velde et al (2019)	Australia	Retrospective	65	56	71.5 (56.9–86.6)	72.3 (54.2–86.0)	39 (15.4–142.2)	32.7 (14.7–81.6)	(Low/intermediate/ high) 1/20/44	(Low/intermediate/ high) 2/23/15	65	54	Intensity-modulated radiation therapy/81 Gy/45	None
Teyateeti et al (2022)	United States + Thailand	Retrospective	224	139	65 (43–84)	67 (48–80)	32.4 (11.0–79.4)	30.0 (12.7–78.9)	(Low/favorable intermediate/ unfavorable intermediate/high) 14/76/98/36	(Low/favorable intermediate/ unfavorable intermediate/high) 4/44/47/44	55	56	1. Low-dose-rate brachytherapy/100 Gy 2. Low-dose-rate brachytherapy+intensity-modulated radiation therapy / Stereotactic body radiation therapy/45, 25 Gy/25, 5	Boston Scientific
Whalley et al (2016)	Australia	Prospective	30	110	72 (59–84)	NA	NA	NA	(Intermediate/high) 14/16	(intermediate/high) 49/61	15	61	Intensity-modulated radiation therapy/80 Gy/40	None
Wolf et al (2015)	Australia	Prospective	30	19	NA	NA	NA	NA	NA	NA	NA	NA	Intensity-modulated radiation therapy/75.85 Gy/41	None
Wu et al (2018)	United States	Retrospective	18	36	66.2 (7.8)	64.8 (6)	34.5 (17)	33 (14)	NA	NA	NA	NA	High-dose-rate brachytherapy/19–21	None
Yang et al (2020)	United States	Retrospective	16	35	NA	NA	NA	NA	NA	NA	NA	21	Volumetric modulated arc therapy/79.2/44	Augmenix/ Boston Scientific

References are provided in the Supplementary Materials 2.
NA: not available, RCT: randomized controlled trial.

1.1 Rectal Dmax

Study or subgroup	Spacer Mean	Spacer SD	Spacer Total	No spacer Mean	No spacer SD	No spacer Total	Weight	Mean difference IV, random, 95% CI
Butler et al. 2021	33.9	12.5	174	51.8	23	174	34.7%	-17.90 [-21.79, -14.01]
Kahn et al. 2020	60.9	18.3	40	107.1	34.5	40	30.1%	-46.20 [-58.30, -34.10]
Khalil et al. 2022	73.15	0.89	15	74.15	0.87	8	35.2%	-1.00 [-1.75, -0.25]
Total (95% CI)			**229**			**222**	**100.0%**	**-20.46 [-37.80, -3.12]**

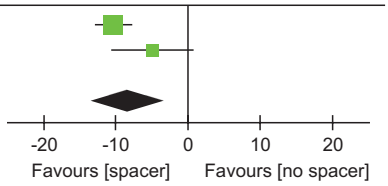
Heterogeneity: Tau^2=221.98; Chi^2=121.86, df=2 (p<0.00001); I^2=98%
Test for overall effect: Z=2.31 (p=0.02)



1.2 Rectal Dmean

Study or subgroup	Spacer Mean	Spacer SD	Spacer Total	No spacer Mean	No spacer SD	No spacer Total	Weight	Mean difference IV, random, 95% CI
Butler et al. 2021	23.8	8.5	174	34.2	15.4	174	61.6%	-10.40 [-13.01, -7.79]
Khalil et al. 2022	19.1	4.6	15	24.1	7.56	8	38.4%	-5.00 [-10.73, 0.73]
Total (95% CI)			**189**			**182**	**100.0%**	**-8.33 [-13.47, -3.18]**

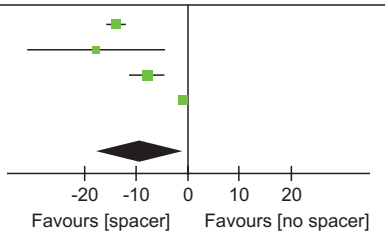
Heterogeneity: Tau^2=9.41; Chi^2=2.82, df=1 (p=0.09); I^2=65%
Test for overall effect: Z=3.17 (p=0.002)



1.3 Rectal V50 (mL)

Study or subgroup	Spacer Mean	Spacer SD	Spacer Total	No spacer Mean	No spacer SD	No spacer Total	Weight	Mean difference IV, random, 95% CI
Cousins et al. 2022	12.92	1.35	30	26.9	5.48	30	27.9%	-13.98 [-16.00, -11.96]
Khalil et al. 2022	28.49	10.13	15	46.34	17.88	8	16.7%	-17.85 [-31.26, -4.44]
Navaratnam et al. 2020	10	5.2	51	18	7.4	21	27.1%	-8.00 [-11.47, -4.53]
Yang et al. 2020	3	1	16	4	1.5	35	28.3%	-1.00 [-1.70, -0.30]
Total (95% CI)			**112**			**94**	**100.0%**	**-9.34 [-17.90, -0.77]**

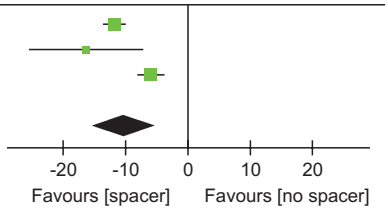
Heterogeneity: Tau^2=67.39; Chi^2=156.42, df=3 (p<0.00001); I^2=98%
Test for overall effect: Z=2.14 (p=0.03)



1.4 Rectal V60 (mL)

Study or subgroup	Spacer Mean	Spacer SD	Spacer Total	No spacer Mean	No spacer SD	No spacer Total	Weight	Mean difference IV, random, 95% CI
Cousins et al. 2022	11.63	2.35	30	23.53	4.62	30	41.3%	-11.90 [-13.75, -10.05]
Khalil et al. 2022	16.39	7.97	15	32.8	11.98	8	18.4%	-16.41 [-25.64, -7.18]
Navaratnam et al. 2020	6	4.4	51	12	4.4	21	40.3%	-6.00 [-8.24, -3.76]
Total (95% CI)			**96**			**59**	**100.0%**	**-10.35 [-15.58, -5.13]**

Heterogeneity: Tau^2=16.32; Chi^2=17.95, df=2 (p=0.0001); I^2=89%
Test for overall effect: Z=3.89 (p=0.0001)



1.5 Rectal V65 (mL)

Study or subgroup	Spacer Mean	Spacer SD	Spacer Total	No spacer Mean	No spacer SD	No spacer Total	Weight	Mean difference IV, random, 95% CI
Khalil et al. 2022	10.8	6.36	15	24.73	8.62	8	42.9%	-13.93 [-20.72, -7.14]
Navaratnam et al. 2020	3	3	51	8	3	21	57.1%	-5.00 [-6.52, -3.48]
Total (95% CI)			**66**			**29**	**100.0%**	**-8.83 [-17.49, -0.17]**

Heterogeneity: Tau^2=33.58; Chi^2=6.33, df=1 (p=0.01); I^2=84%
Test for overall effect: Z=2.00 (p=0.05)

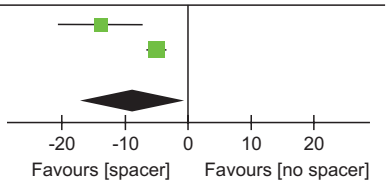


Fig. 2. Forest plots comparing rectal dosimetry between the spacer and no-spacer groups based on V-matrix parameters (mL and %). CI: confidence interval, IV: inverse variance, SD: standard deviation.

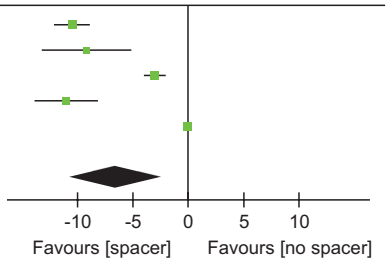
scheme, hypofractionated RT showed an RR of 0.83 (95% CI: 0.50–1.38, p=0.48, I^2=44%), while conventional RT had an RR of 1.00 (95% CI: 0.92–1.08, p=0.98, I^2=0%). No significant subgroup difference was observed (p=0.49).

For grade ≥2 acute GU toxicity, the pooled RR was 0.87 (95% CI: 0.66–1.15, p=0.33), with no detected heterogeneity (I^2= 0%, p=0.92). In subgroup analysis, hypo-

1.6 Rectal V70 (mL)

Study or subgroup	Spacer Mean	SD	Total	No spacer Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Cousins et al. 2022	9.69	2.02	30	20.17	4.14	30	20.6%	-10.48 [-12.13, -8.83]
Khalil et al. 2022	5.32	3.13	15	14.49	5.35	8	17.7%	-9.17 [-13.20, -5.14]
Navaratnam et al. 2020	1	1.1	51	4	2.2	21	21.0%	-3.00 [-3.99, -2.01]
Pinkawa et al. 2017	5	6.5	54	16	9.1	60	19.3%	-11.00 [-13.88, -8.12]
Yang et al. 2020	0.3	0.1	16	0.4	0.15	35	21.3%	-0.10 [-0.17, -0.03]
Total (95% CI)			**166**			**154**	**100.0%**	**-6.56 [-10.72, -2.40]**

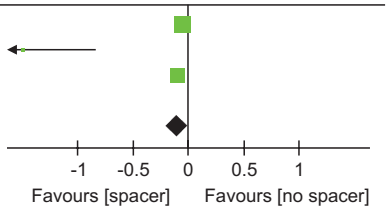
Heterogeneity: Tau^2=21.16; Chi^2=258.40, df=4 (p<0.00001); I^2=98%
Test for overall effect: Z=3.09 (p=0.002)



1.7 Rectal V75 (mL)

Study or subgroup	Spacer Mean	SD	Total	No spacer Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Lee et al. 2023	0.01	0.01	20	0.06	0.04	21	50.4%	-0.05 [-0.07, -0.03]
Navaratnam et al. 2020	0.5	0.6	51	2	1.5	21	2.3%	-1.50 [-2.16, -0.84]
Yang et al. 2020	0.1	0.05	16	0.2	0.1	35	47.3%	-0.10 [-0.14, -0.06]
Total (95% CI)			**87**			**77**	**100.0%**	**-0.11 [-0.21, 0.00]**

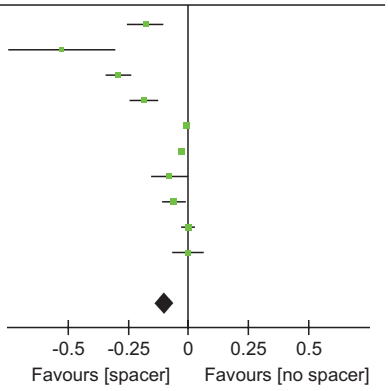
Heterogeneity: Tau^2=0.01; Chi^2=22.98, df=2 (p<0.0001); I^2=91%
Test for overall effect: Z=2.03 (p=0.04)



1.8 Rectal V100 (mL)

Study or subgroup	Spacer Mean	SD	Total	No spacer Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Kahn et al. 2020	0.001	0.001	40	0.18	0.25	40	8.8%	-0.18 [-0.26, -0.10]
Lin et al. 2021	0.001	0.001	28	0.53	0.74	42	2.6%	-0.53 [-0.75, -0.31]
Morita et al. 2020	0.026	0.14	100	0.318	0.34	200	10.6%	-0.29 [-0.35, -0.24]
Morita et al. 2024	0.029	0.37	394	0.215	0.45	337	10.1%	-0.19 [-0.25, -0.13]
Nakai et al. 2024 (LDR-BT)	0.001	0.001	186	0.007	0.015	186	13.2%	-0.01 [-0.01, 0.00]
Nakai et al. 2024 (LDR-BT+EBRT)	0.001	0.001	70	0.031	0.059	70	13.0%	-0.03 [-0.04, -0.02]
Nehlsen et al. 2021	0.09	0.148	22	0.17	0.289	146	8.8%	-0.08 [-0.16, 0.00]
te Velde et al. 2017	0.01	0.05	65	0.07	0.19	60	11.0%	-0.06 [-0.11, -0.01]
Teyateeti et al. 2022	0	0.083	224	0	0.167	139	12.3%	0.00 [-0.03, 0.03]
Whalley et al. 2016	0	0.13	30	0	0.25	110	9.7%	0.00 [-0.07, 0.07]
Total (95% CI)			**1,159**			**1,330**	**100.0%**	**-0.10 [-0.14, -0.06]**

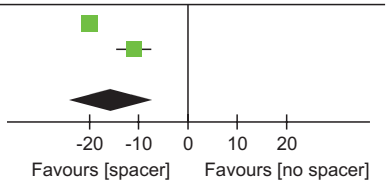
Heterogeneity: Tau^2=0.00; Chi^2=197.83, df=9 (p<0.00001); I^2=95%
Test for overall effect: Z=4.77 (p<0.00001)



1.9 Rectal V50 (%)

Study or subgroup	Spacer Mean	SD	Total	No spacer Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Cousins et al. 2022	20	1.53	30	40	2.55	30	51.8%	-20.00 [-21.06, -18.94]
Hamstra et al. 2018	10	12.21	149	21	12.79	73	48.2%	-11.00 [-14.53, -7.47]
Total (95% CI)			**179**			**103**	**100.0%**	**-15.66 [-24.48, -6.85]**

Heterogeneity: Tau^2=38.73; Chi^2=22.91, df=1 (p<0.00001); I^2=96%
Test for overall effect: Z=3.48 (p=0.0005)



1.10 Rectal V70 (%)

Study or subgroup	Spacer Mean	SD	Total	No spacer Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Cousins et al. 2022	15	1.02	30	30	2.04	30	33.6%	-15.00 [-15.82, -14.18]
Hamstra et al. 2017	2	3.66	149	10	6.83	73	33.2%	-8.00 [-9.67, -6.33]
Sagayanathan et al. 2024	7	5.78	80	10.2	5.7	82	33.1%	-3.20 [-4.97, -1.43]
Total (95% CI)			**259**			**185**	**100.0%**	**-8.76 [-16.13, -1.39]**

Heterogeneity: Tau^2=41.85; Chi^2=168.89, df=2 (p<0.00001); I^2=99%
Test for overall effect: Z=2.33 (p=0.02)

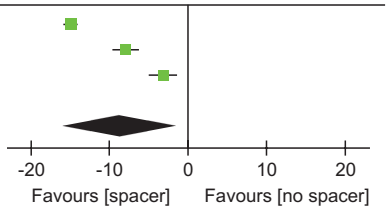
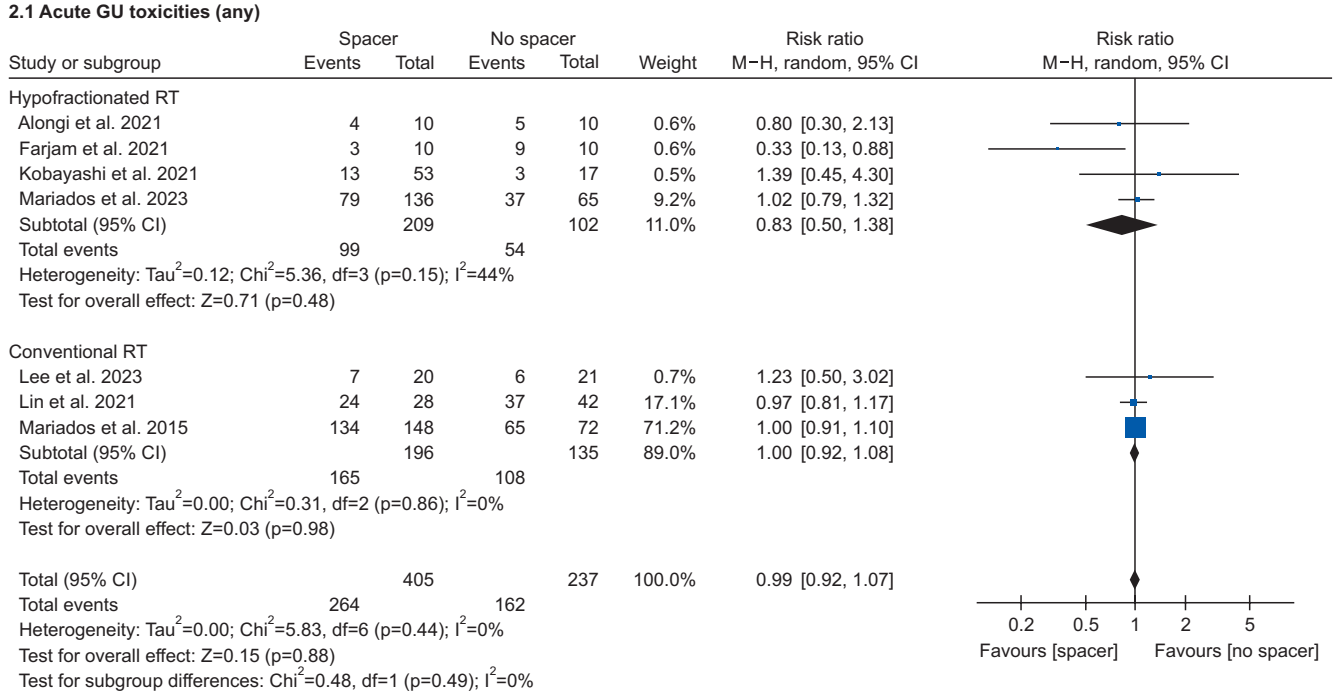


Fig. 2. Continued.



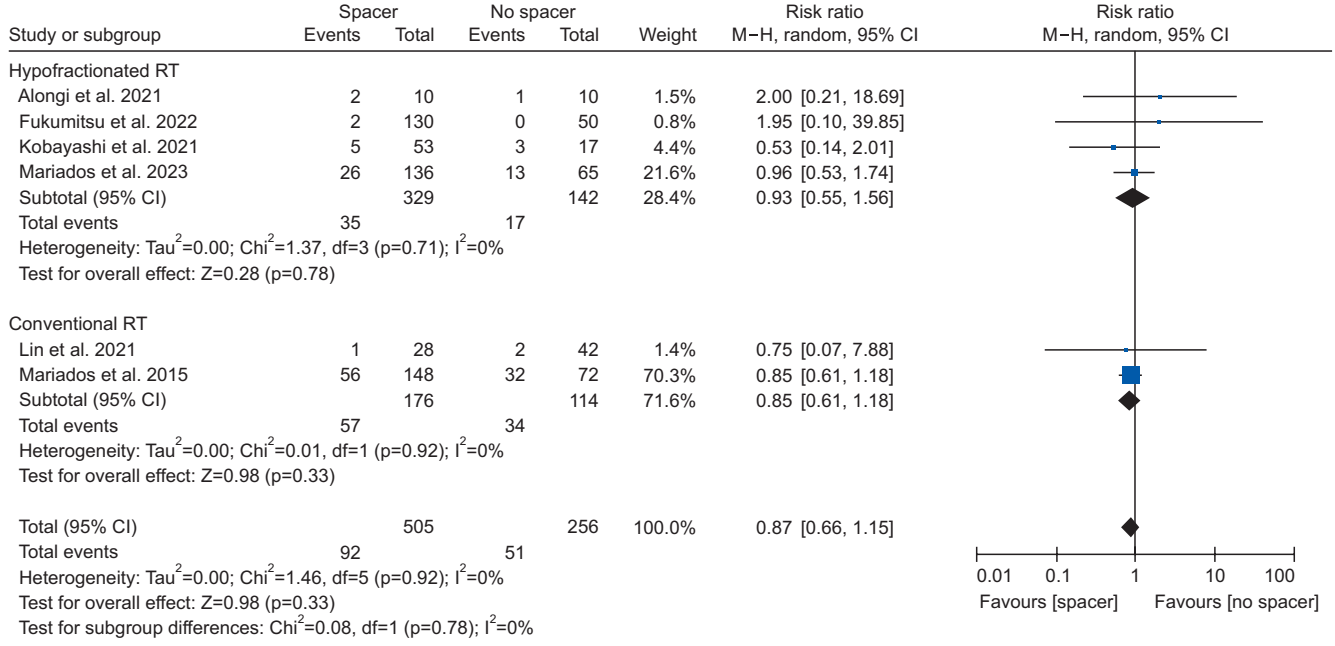


Fig. 3. Forest plots comparing acute and late genitourinary (GU) and gastrointestinal (GI) toxicities between spacer and no-spacer groups, including subgroup analysis based on conventional and hypofractionated radiotherapy. CI: confidence interval, M-H: Mantel–Haenszel.

fractionated RT had an RR of 0.93 (95% CI: 0.55–1.56, p=0.78, I^2= 0%), whereas conventional RT had an RR of 0.85 (95% CI: 0.61–1.18, p=0.33, I^2=0%). Again, no significant difference was noted between subgroups (p=0.78).

2) Late GU toxicity

Late GU toxicities (any grade and grade ≥2) did not significantly differ between the spacer and no-spacer groups (Fig. 3).

For any-grade late GU toxicity, the pooled RR was 0.86 (95% CI: 0.76–0.98, p=0.02), with no detected het-

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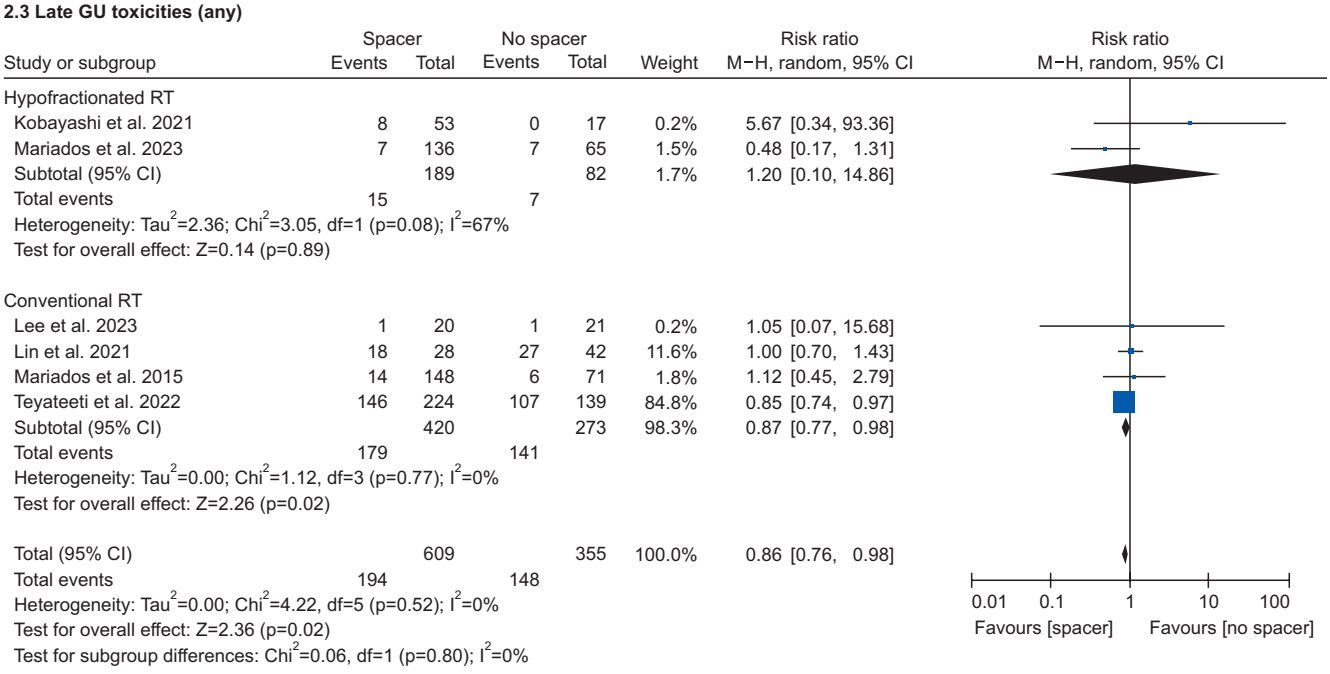


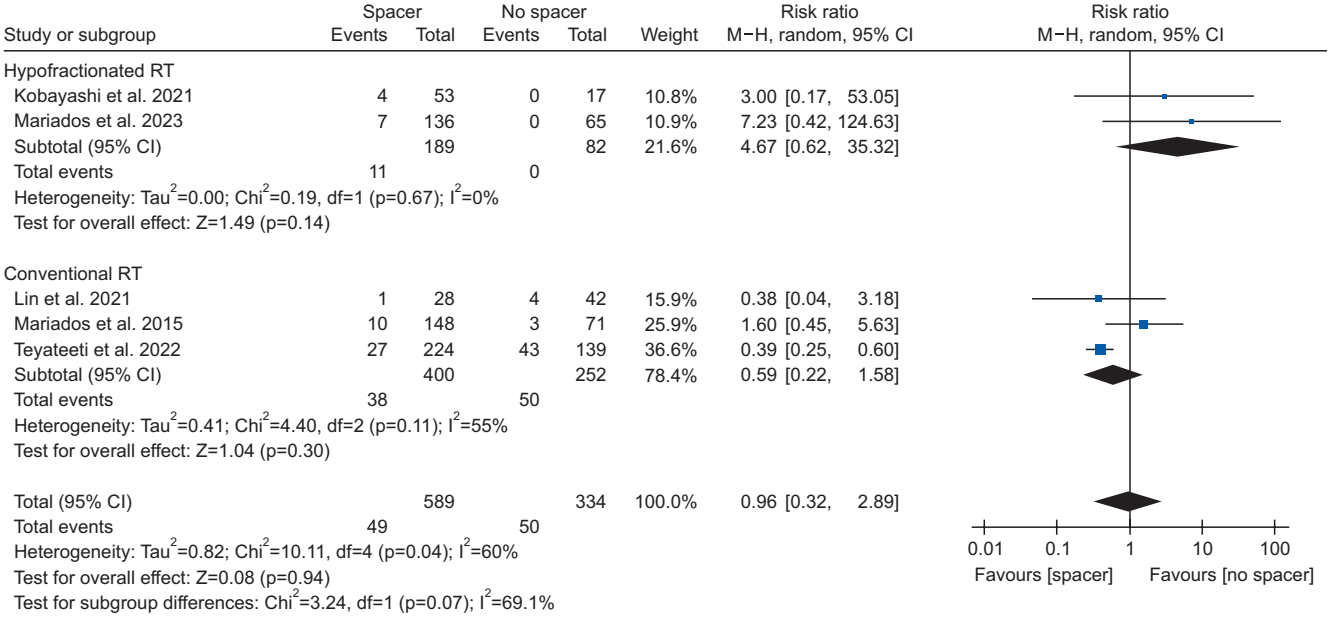


Fig. 3. Continued 1.

erogeneity (I^2=0%, p=0.52). When stratified by fractionation scheme, hypofractionated RT showed an RR of 1.20 (95% CI: 0.10–14.86, p=0.89, I^2=67%), while conventional RT had an RR of 0.87 (95% CI: 0.77–0.98, p=0.02, I^2=0%). No significant subgroup difference was observed (p=0.80).

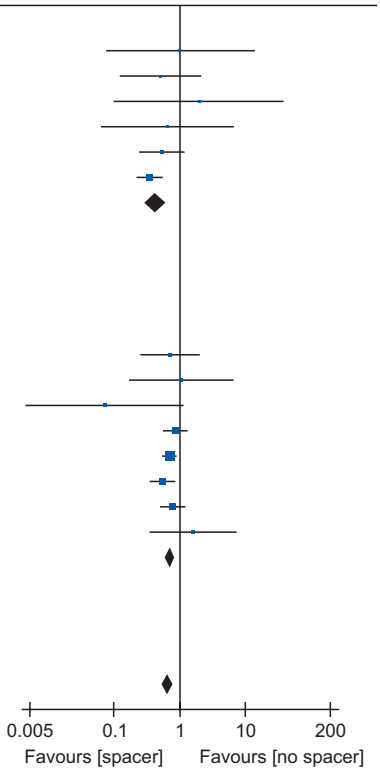
For grade ≥2 late GU toxicity, the pooled RR was 0.96 (95% CI: 0.32–2.89, p=0.94), with moderate heterogeneity (I^2=60%, p=0.04). In subgroup analysis, hypofractionated RT had an RR of 4.67 (95% CI: 0.62–35.32, p=0.14, I^2=0%), whereas conventional RT had an RR of 0.59 (95% CI: 0.22–1.58, p=0.30, I^2=55%). No significant difference was noted between subgroups (p=0.07).

3) Acute GI toxicity

Acute GI toxicities (any grade and grade ≥2) were

2.5 Acute GU toxicities (any)

Study or subgroup	Spacer Events	Spacer Total	No spacer Events	No spacer Total	Weight	Risk ratio M−H, random, 95% CI
Hypofractionated RT						
Alongi et al. 2021	1	10	1	10	0.5%	1.00 [0.07, 13.87]
Farjam et al. 2021	2	10	4	10	1.7%	0.50 [0.12, 2.14]
Fukumitsu et al. 2022	2	130	0	50	0.4%	1.95 [0.10, 39.85]
Kobayashi et al. 2021	2	53	1	17	0.7%	0.64 [0.06, 6.64]
Kundu et al. 2022	8	51	12	41	5.4%	0.54 [0.24, 1.19]
Mariados et al. 2023	21	136	29	65	12.9%	0.35 [0.21, 0.56]
Subtotal (95% CI)		390		193	21.7%	0.42 [0.29, 0.61]
Total events	36		47			
Heterogeneity: Tau^2=0.00; Chi^2=2.62, df=5 (p=0.76); I^2=0%						
Test for overall effect: Z=4.47 (p<0.00001)						
Conventional RT						
Kahn et al. 2020	5	40	7	40	3.2%	0.71 [0.25, 2.06]
Lee et al. 2023	2	20	2	21	1.1%	1.05 [0.16, 6.76]
Lin et al. 2021	0	28	10	42	0.5%	0.07 [0.00, 1.16]
Mariados et al. 2015	40	148	23	72	15.1%	0.85 [0.55, 1.30]
Navaratnam et al. 2020	32	51	19	21	28.9%	0.69 [0.54, 0.89]
Sagayanathan et al. 2024	19	80	36	82	13.5%	0.54 [0.34, 0.86]
Whalley et al. 2016	13	30	61	110	14.5%	0.78 [0.50, 1.22]
Wolf et al. 2015	5	30	2	19	1.6%	1.58 [0.34, 7.35]
Subtotal (95% CI)		427		407	78.3%	0.71 [0.60, 0.85]
Total events	116		160			
Heterogeneity: Tau^2=0.00; Chi^2=6.12, df=7 (p=0.53); I^2=0%						
Test for overall effect: Z=3.84 (p=0.0001)						
Total (95% CI)		817		600	100.0%	0.64 [0.53, 0.78]
Total events	152		207			
Heterogeneity: Tau^2=0.02; Chi^2=15.07, df=13 (p=0.30); I^2=14%						
Test for overall effect: Z=4.51 (p<0.00001)						
Test for subgroup differences: Chi^2=6.02, df=1 (p=0.01); I^2=83.4%						



2.6 Acute GI toxicities (grade ≥2)

Study or subgroup	Spacer Events	Spacer Total	No spacer Events	No spacer Total	Weight	Risk ratio M−H, random, 95% CI
Hypofractionated RT						
Alongi et al. 2021	0	10	0	10		Not estimable
Kobayashi et al. 2021	1	53	0	17	7.8%	1.00 [0.04, 23.47]
Kundu et al. 2022	2	51	2	41	13.1%	0.80 [0.12, 5.46]
Mariados et al. 2023	4	136	29	65	18.5%	0.07 [0.02, 0.18]
Subtotal (95% CI)		250		133	39.4%	0.28 [0.04, 2.14]
Total events	7		31			
Heterogeneity: Tau^2=2.18; Chi^2=6.88, df=2 (p=0.03); I^2=71%						
Test for overall effect: Z=1.22 (p=0.22)						
Conventional RT						
Kahn et al. 2020	0	40	0	40		Not estimable
Lee et al. 2023	1	20	1	21	9.4%	1.05 [0.07, 15.68]
Lin et al. 2021	0	28	0	42		Not estimable
Mariados et al. 2015	6	148	3	72	16.4%	0.97 [0.25, 3.78]
Navaratnam et al. 2020	1	51	0	21	7.8%	1.27 [0.05, 29.96]
Sagayanathan et al. 2024	7	80	6	82	18.2%	1.20 [0.42, 3.40]
Whalley et al. 2016	0	30	5	110	8.8%	0.33 [0.02, 5.73]
Wolf et al. 2015	0	30	0	19		Not estimable
Subtotal (95% CI)		427		407	60.6%	1.02 [0.49, 2.15]
Total events	15		15			
Heterogeneity: Tau^2=0.00; Chi^2=0.74, df=4 (p=0.95); I^2=0%						
Test for overall effect: Z=0.06 (p=0.95)						
Total (95% CI)		677		540	100.0%	0.56 [0.19, 1.69]
Total events	22		46			
Heterogeneity: Tau^2=1.45; Chi^2=20.79, df=7 (p=0.004); I^2=66%						
Test for overall effect: Z=1.03 (p=0.30)						
Test for subgroup differences: Chi^2=1.36, df=1 (p=0.24); I^2=26.7%						

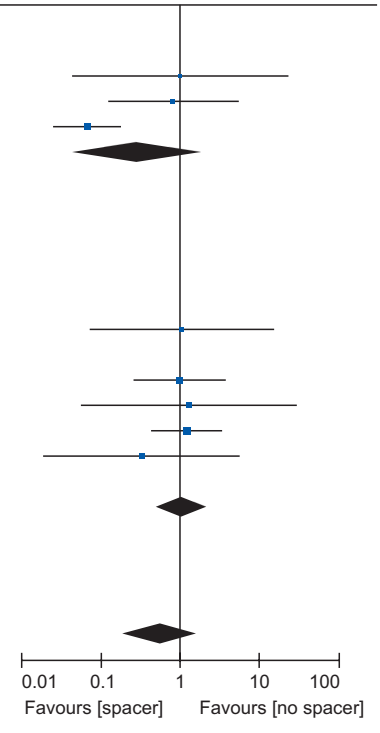
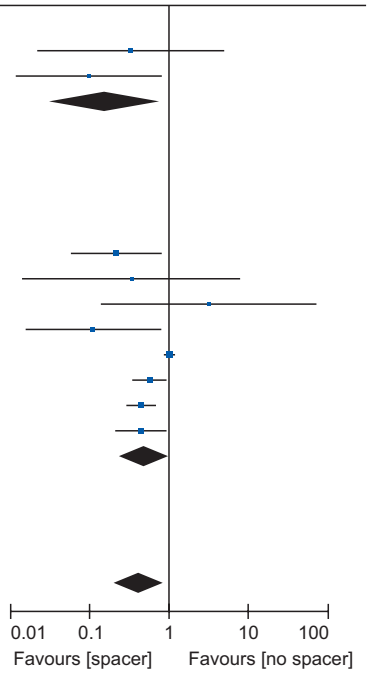


Fig. 3. Continued 2.

2.7 Late GI toxicities (any)

Study or subgroup	Spacer Events	Spacer Total	No spacer Events	No spacer Total	Weight	Risk ratio M−H, random, 95% CI
Hypofractionated RT						
Kobayashi et al. 2021	1	53	1	17	5.1%	0.32 [0.02, 4.86]
Mariados et al. 2023	1	136	5	65	6.9%	0.10 [0.01, 0.80]
Subtotal (95% CI)		189		82	12.0%	0.15 [0.03, 0.81]
Total events	2		6			
Heterogeneity: Tau^2=0.00; Chi^2=0.49, df=1 (p=0.49); I^2=0%						
Test for overall effect: Z=2.21 (p=0.03)						
Conventional RT						
Hamstra et al. 2017	3	149	7	73	10.8%	0.21 [0.06, 0.79]
Kahn et al. 2020	0	40	1	40	4.0%	0.33 [0.01, 7.95]
Lee et al. 2023	1	20	0	21	4.1%	3.14 [0.14, 72.92]
Lin et al. 2021	1	28	14	42	7.5%	0.11 [0.01, 0.77]
Navaratnam et al. 2020	36	39	13	14	16.4%	0.99 [0.84, 1.18]
Sagayanathan et al. 2024	17	80	31	82	15.4%	0.56 [0.34, 0.93]
Teyateeti et al. 2022	27	224	38	139	15.6%	0.44 [0.28, 0.69]
Whalley et al. 2016	6	30	50	110	14.2%	0.44 [0.21, 0.93]
Subtotal (95% CI)		610		521	88.0%	0.47 [0.22, 1.00]
Total events	91		154			
Heterogeneity: Tau^2=0.77; Chi^2=65.01, df=7 (p<0.00001); I^2=89%						
Test for overall effect: Z=1.96 (p=0.05)						
Total (95% CI)		799		603	100.0%	0.41 [0.20, 0.86]
Total events	93		160			
Heterogeneity: Tau^2=0.85; Chi^2=74.52, df=9 (p<0.00001); I^2=88%						
Test for overall effect: Z=2.37 (p=0.02)						
Test for subgroup differences: Chi^2=1.46, df=1 (p=0.23); I^2=31.7%						



2.6 Late GI toxicities (grade ≥2)

Study or subgroup	Spacer Events	Spacer Total	No spacer Events	No spacer Total	Weight	Risk ratio M−H, random, 95% CI
Hypofractionated RT						
Kobayashi et al. 2021	0	53	0	17		Not estimable
Mariados et al. 2023	1	136	0	65	8.0%	1.45 [0.06, 35.00]
Subtotal (95% CI)		189		82	8.0%	1.45 [0.06, 35.00]
Total events	1		0			
Heterogeneity: not applicable						
Test for overall effect: Z=0.23 (p=0.82)						
Conventional RT						
Hamstra et al. 2017	0	149	4	73	9.0%	0.05 [0.00, 1.00]
Kahn et al. 2020	0	40	1	40	8.0%	0.33 [0.01, 7.95]
Lee et al. 2023	1	20	0	21	8.1%	3.14 [0.14, 72.92]
Lin et al. 2021	0	28	0	42		Not estimable
Navaratnam et al. 2020	0	39	1	14	8.1%	0.13 [0.01, 2.90]
Sagayanathan et al. 2024	7	80	11	82	23.1%	0.65 [0.27, 1.60]
Teyateeti et al. 2022	4	224	8	139	20.6%	0.31 [0.10, 1.01]
Whalley et al. 2016	1	3	4	110	15.0%	9.17 [1.42, 59.31]
Subtotal (95% CI)		583		521	92.0%	0.62 [0.19, 1.98]
Total events	13		29			
Heterogeneity: Tau^2=1.25; Chi^2=14.90, df=6 (p=0.02); I^2=60%						
Test for overall effect: Z=0.81 (p=0.42)						
Total (95% CI)		772		603	100.0%	0.67 [0.23, 1.94]
Total events	14		29			
Heterogeneity: Tau^2=1.07; Chi^2=15.12, df=7 (p=0.03); I^2=54%						
Test for overall effect: Z=0.75 (p=0.46)						
Test for subgroup differences: Chi^2=0.24, df=1 (p=0.62); I^2=0%						

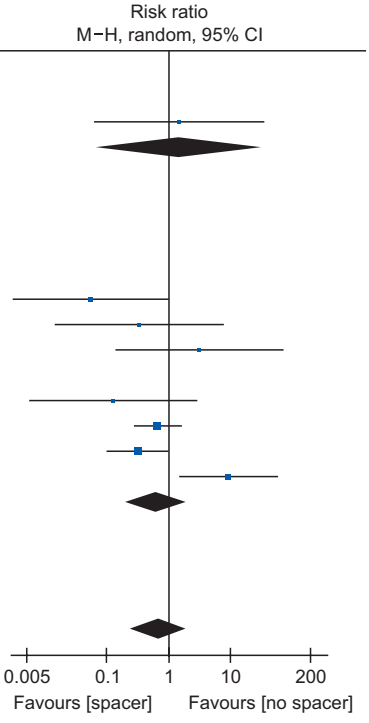


Fig. 3. Continued 3.

significantly lower in the spacer group compared to the no-spacer group (Fig. 3).

For any grade acute GI toxicity, the overall RR was 0.64 (95% CI: 0.53–0.78, p<0.00001), indicating a significant reduction in toxicity with the use of spacers. Heterogeneity was low (I^2=14%, p=0.30). In subgroup analy-

sis, hypofractionated RT showed an RR of 0.42 (95% CI: 0.29–0.61, p<0.00001, I^2=0%), while conventional RT had an RR of 0.71 (95% CI: 0.60–0.85, p=0.0001, I^2=0%). A significant difference between subgroups was observed (p=0.01), suggesting a potentially greater benefit of spacers in hypofractionated RT.

For grade ≥2 acute GI toxicity, the pooled RR was 0.56 (95% CI: 0.19–1.69, p=0.30), showing no statistically significant difference between the spacer and no-spacer groups. However, heterogeneity was moderate (I^2=54%, p=0.03). In subgroup analysis, hypofractionated RT had an RR of 0.28 (95% CI: 0.04–2.14, p=0.22, I^2=71%), while conventional RT had an RR of 0.62 (95% CI: 0.19–1.98, p=0.42, I^2=60%). No significant subgroup difference was observed (p=0.62).

4) Late GI toxicity

Late GI toxicities (any grade and grade ≥2) differed by fractionation regimen (Fig. 3).

For any grade late GI toxicity, the RR was 0.41 (95% CI: 0.20–0.86, p=0.02), with substantial heterogeneity (I^2=88%, p<0.00001). When stratified by fractionation, hypofractionated RT showed an RR of 0.15 (95% CI: 0.03–0.81, p=0.03, I^2=0%), while conventional RT had an RR of 0.47 (95% CI: 0.22–1.00, p=0.05, I^2=89%). No significant subgroup difference was observed (p=0.23).

For grade ≥2 late GI toxicity, the pooled RR was 0.67 (95% CI: 0.23–1.94, p=0.46), with moderate heterogeneity (I^2=54%, p=0.03). In subgroup analysis, hypofractionated RT had an RR of 1.45 (95% CI: 0.06–35.00, p=0.82), while conventional RT had an RR of 0.62 (95% CI: 0.19–1.98, p=0.42, I^2=60%). No significant subgroup difference was detected (p=0.62).

4. Quality assessment and qualitative risk of bias

A table summarizing the findings was generated using the GRADE approach to evaluate the certainty of evidence for each comparison. The certainty of evidence for comparison was determined to be very low or low for all parameters (Table 2, 3).

Funnel plots were created to assess the publication bias for the outcomes. The symmetry in the plots suggested no significant publication bias across all results (Supplement Fig. 3, 4).

The quality assessment results evaluated using the ROBINS-I and RoB 2 tools. All the non-randomized studies were assigned a "moderate risk" level in the overall assessment. Among the RCTs, three and five were rated as "low risk" and "some concerns" in the overall assessment, respectively (Supplement Fig. 5–8).

Supplement Fig. 7 and 8 present the quality assessment results evaluated using the ROBINS-I and RoB 2 tools. All the non-randomized studies were assigned a "moderate risk" level in the overall assessment. Among the RCTs, three and five were rated as "low risk" and "some concerns" in the overall assessment, respectively.

DISCUSSION

The present study revealed that spacers effectively reduced the average (Dmean) and maximum (Dmax) rectal radiation exposure, demonstrating their critical role in mitigating radiation-induced damage. The V-matrix parameter analyses further confirmed the consistent dose reduction effects of the spacers across various thresholds (V50 [mL], V70 [mL], V50 [%], and V70 [%]). Our results showed a reduction in late GU toxicity (any grade), as well as acute and late GI toxicity (any grade), with no significant differences observed in acute GU toxicity (any grade) or grade ≥2 GU and GI toxicities. Spacers significantly reduced acute GI toxicity, particularly in hypofractionated RT (p=0.01), while their effect on severe cases (grade ≥2) remained unclear. A protective effect against late GI toxicity was observed in conventional RT, but the impact in hypofractionated RT remains uncertain due to high variability. In contrast, spacers did not significantly affect acute or late GU toxicity, regardless of the fractionation regimen.

Miller et al. [19] conducted a systematic review and meta-analysis, reporting a 62.5% reduction in V70 (%), demonstrating the reliability and consistency of hydrogel spacers in reducing rectal radiation exposure across various dose levels. The substantial reduction observed at higher doses underscores the potential of hydrogel spacers to offer greater benefits in high-dose RT, highlighting their clinical significance in such settings. This aligns closely with our findings, further supporting the effectiveness of hydrogel spacers in minimizing rectal radiation exposure, particularly at higher doses. The key difference between the previous studies and our study lies in its expanded scope and depth. Our study incorporated more comprehensive evidence enriched by numerous new studies published since earlier research and delved deeper into rectal dosimetry and clinical

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Table 2. Grading of recommendations, assessments, developments, and evaluation (GRADE) quality assessment of direct evidence of each rectal dosimetric comparison

Certainty assessment							Number of patients		Effect	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spacer	No spacer	Absolute (95% CI)		
Rectal Dmax (n=3)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	Very strong association	229	222	MD 20.46 lower (37.8 lower to 3.12 lower)	⊕⊕◯◯ Low	Critical
Rectal Dmean (n=2)	Non-randomized studies	Serious[a]	Not serious	Not serious	Not serious	None	189	182	MD 8.33 lower (13.47 lower to 3.18 lower)	⊕◯◯◯ Very low	Critical
Rectal V50 (mL) (n=4)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	None	112	94	MD 9.34 lower (17.9 lower to 0.77 lower)	⊕◯◯◯ Very low	Critical
Rectal V60 (mL) (n=3)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	Strong association	96	59	MD 10.35 lower (15.58 lower to 5.13 lower)	⊕◯◯◯ Very low	Critical
Rectal V65 (mL) (n=2)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	None	66	29	MD 8.83 lower (17.49 lower to 0.17 lower)	⊕◯◯◯ Very low	Critical
Rectal V70 (mL) (n=5)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	None	166	154	MD 6.56 lower (10.72 lower to 2.4 lower)	⊕◯◯◯ Very low	Critical
Rectal V75 (mL) (n=3)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Seriousc	None	87	77	MD 0.11 lower (0.21 lower to 0)	⊕◯◯◯ Very low	Critical
Rectal V100 (mL) (n=10)	Non-randomized studies	Serious[a]	Serious[b]	Not serious	Not serious	None	1,159	1,330	MD 0.1 lower (0.14 lower to 0.05 lower)	⊕◯◯◯ Very low	Critical
Rectal V50 (%) (n=2)	Non-randomized studies +Randomized studies	Serious[d]	Serious[b]	Not serious	Not serious	Strong association	179	103	MD 15.66 lower (24.48 lower to 6.85 lower)	⊕◯◯◯ Very low	Critical
Rectal V70 (%) (n=3)	Non-randomized studies +Randomized studies	Serious[d]	Serious[b]	Not serious	Not serious	none	259	185	MD 8.76 lower (16.13 lower to 1.39 lower)	⊕◯◯◯ Very low	Critical

CI: confidence interval, MD: mean difference.
Explanations: [a]The overall risk of bias was all "moderate."; [b]The p-value was <0.05; [c]The result includes 0; [d]The overall risk of bias in the included studies was not "low."

Table 3. Grading of recommendations, assessments, developments, and evaluation (GRADE) quality assessment of direct evidence of each comparison of GI and GU toxicities

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spacer	No spacer	Relative (95% CI)	Absolute (95% CI)		
Acute GU toxicities (Any) (n=7)	Non-randomized studies +Randomized studies	Serious[a]	Not serious	Not serious	Serious[b]	None	264/405 (65.2%)	162/237 (68.4%)	RR 0.99 (0.92 to 1.07)	7 fewer per 1,000 (from 55 fewer to 48 more)	⊕◯◯◯ Very low	Critical
Acute GU toxicities (Grade≥2) (n=6)	Non-randomized studies +Randomized studies	Serious[a]	Not serious	Not serious	Serious[b]	None	92/505 (18.2%)	51/256 (19.9%)	RR 0.87 (0.66 to 1.15)	26 fewer per 1,000 (from 68 fewer to 30 more)	⊕◯◯◯ Very low	Critical
Late GU toxicities (Any) (n=6)	Non-randomized studies +Randomized studies	Serious[a]	Not serious	Not serious	Not serious	None	194/609 (31.9%)	148/355 (41.7%)	RR 0.86 (0.76 to 0.98)	58 fewer per 1,000 (from 100 fewer to 8 fewer)	⊕◯◯◯ Very low	Critical
Late GU toxicities (Grade≥2) (n=5)	Non-randomized studies +Randomized studies	Serious[a]	Serious[c]	Not serious	Serious[b]	None	49/589 (8.3%)	50/334 (15.0%)	RR 0.96 (0.32 to 2.89)	6 fewer per 1,000 (from 102 fewer to 283 more)	⊕◯◯◯ Very low	Critical
Acute GI toxicities (Any) (n=14)	Non-randomized studies +Randomized studies	Serious[a]	Not serious	Not serious	Not serious	None	152/817 (18.6%)	207/600 (34.5%)	RR 0.64 (0.53 to 0.78)	124 fewer per 1,000 (from 162 fewer to 76 fewer)	⊕◯◯◯ Very low	Critical
Acute GI toxicities (Grade≥2) (n=12)	Non-randomized studies +Randomized studies	Serious[a]	Serious[c]	Not serious	Serious[b]	None	22/677 (3.2%)	46/540 (8.5%)	RR 0.56 (0.19 to 1.69)	37 fewer per 1,000 (from 69 fewer to 59 more)	⊕◯◯◯ Very low	Critical
Late GI toxicities (Any) (n=10)	Non-randomized studies +Randomized studies	Serious[d]	Serious[c]	Not serious	Not serious	None	93/799 (11.6%)	160/603 (26.5%)	RR 0.41 (0.20 to 0.86)	157 fewer per 1,000 (from 212 fewer to 37 fewer)	⊕◯◯◯ Very low	Critical
Late GI toxicities (Grade≥2) (n=10)	Non-randomized studies +Randomized studies	Serious[d]	Serious[c]	Not serious	Serious[b]	None	14/772 (1.8%)	29/603 (4.8%)	RR 0.67 (0.23 to 1.94)	16 fewer per 1,000 (from 37 fewer to 45 more)	⊕◯◯◯ Very low	Critical

CI: confidence interval, RR: risk ratio, GI: gastrointestinal, GU: genitourinary.

Explanations: [a]The overall risk of bias was all "moderate" or "some concerns"; [b]The 95% confidence interval includes 0; [c]The p-value was <0.05; [d]The overall risk of bias in the included studies was not "low."

outcomes. This broader and more detailed analysis enhanced the robustness and clinical relevance of our findings, offering significant advancements over previous studies [19].

The reduction in overall GI toxicities was evident, but the difference in grade ≥2 severe toxicities between spacer and non-spacer groups was less pronounced. This discrepancy may be attributed to the inherently low incidence of severe toxicities, which reduced the statistical power of the analyses. Additionally, patient-specific anatomical variations, such as rectal shape and position, influence the radiation dose distribution and the subsequent risk of toxicity [29]. The physical limitations of hydrogel spacers in attenuating high-dose radiation (>70 Gy) may also contribute to the smaller differences observed in severe toxicity [30]. While spacers increase the rectum-prostate distance and reduce radiation exposure by expanding the boundary where the radiation intensity sharply declines, their attenuation effect diminishes at higher dose levels because of the limitations of radiation decay over short distances [31]. This may explain the smaller-than-expected differences in severe GI toxicity. However, the mismatch between reduced V70 values, a key factor in severe GI toxicities, and the analysis results for severe toxicities highlights the need for further research to clarify their clinical impact.

Regarding GU toxicities, our findings indicate a modest reduction in overall mild-to-moderate toxicities, while severe GU toxicities remain statistically insignificant. This contrast with GI toxicities can be attributed to the physical placement of spacers, which effectively increases the distance between the rectum and the prostate but does not directly reduce bladder exposure itself. Consequently, the impact on bladder-related GU toxicities is inherently limited. Although spacers may indirectly lower radiation to parts of the urethra, including the penile bulb, their overall effect on GU toxicities is likely less pronounced than on GI toxicities [32]. The high heterogeneity in bladder-specific dosimetric parameters (*e.g.,* V70 [mL]) across studies further underscores the complexity of spacer impact on GU outcomes, particularly in severe toxicity contexts [13,33].

Spacers clearly hold promise in reducing rectal radiation exposure and long-term complications in prostate cancer RT. However, their effectiveness may vary due to individual anatomical differences, sometimes causing spacer displacement and suboptimal outcomes. In some cases, physical pressure from the spacer may trigger localized symptoms [34,35]. Although spacers naturally biodegrade, introducing foreign material still raises concerns about chronic inflammation and tissue changes that could lead to long-term complications [35]. Personalized treatment plans considering individual characteristics and potential risks are crucial and careful patient selection helps ensure maximum benefits with minimal complications. Recent studies, including the latest findings by Mariados et al [13], have suggested a potential role for spacers in hypofractionated RT. However, as demonstrated in the present study, further high-quality research is needed to establish more definitive conclusions. Additional investigations will be essential to build upon the accumulating evidence and refine the clinical application of spacers in this setting.

The strength of our study lies in its inclusion of a larger number of studies compared to previous research and its deeper exploration of rectal dosimetry and clinical outcomes. Compared to the previous meta-analysis, which primarily assessed V70 and certain QoL improvements, this study offers a more comprehensive evaluation by analyzing V50, V60, V70, and V75, along with a detailed assessment of grade ≥2 toxicity. Furthermore, by comparing both acute and late GU/GI toxicities and emphasizing the clinical relevance of severe toxicities, our findings provide a more refined perspective on the impact of hydrogel spacer placement. Additionally, while previous studies primarily focused on conventional fractionated RT, this study incorporates six recently published studies on hypofractionated RT and SBRT, further evaluating the potential benefits of hydrogel spacers in high-dose radiation settings.

Despite these advantages, this study has certain limitations. One limitation was the variability in study designs and treatment protocols among the included studies, which may have influenced the outcomes. Additionally, the number of studies on hypofractionated RT was limited, with only a few studies falling into this category. This small sample size restricts the ability to draw definitive conclusions. Additionally, investigating spacer efficacy in treatment contexts, such as stereotactic body RT or re-irradiation settings, could provide valuable insights into their roles in mitigating severe toxicities. Furthermore, most of the included studies were non-RCTs; thus, the evidence levels of

our results were predominantly classified as very low. Another major limitation of this meta-analysis is the inclusion of a substantial number of non-randomized studies, which may introduce selection bias and confounding variables. Although observational studies provide valuable real-world insights, their inherent limitations reduce the overall level of evidence. To mitigate this issue, we applied rigorous risk of bias assessment tools to evaluate the robustness of our findings. Risk of bias was evaluated using RoB 2 for RCTs and ROBINS-I for non-randomized studies (Supplement Fig. 7, 8). Sensitivity analyses showed consistency in acute and late GU toxicity, but variability in late GU (grade ≥2) and late GI toxicity suggests study influence. Despite high heterogeneity in some dosimetric outcomes and GI toxicity, sensitivity analyses did not significantly alter the overall conclusions, affirming the validity of the pooled results. The high heterogeneity observed in late GU toxicity and the inconclusive findings on severe GI/GU toxicity (grade ≥2) likely stem from inconsistencies across study designs (RCTs *vs.* retrospective studies), variations in radiation fractionation schemes (conventional, hypofractionated RT, brachytherapy, or combined), and differences in toxicity grading systems (CTCAE v4.0 *vs.* v5.0). Additionally, variations in patient follow-up durations, baseline urinary function, and spacer placement techniques further contribute to the observed discrepancies. Given that late toxicities often manifest years after treatment, standardized toxicity assessment criteria and stratified patient analysis are crucial. However, the availability of data in existing studies limits further subgroup analysis. Therefore, future research with more comprehensive toxicity reporting and extended follow-up is warranted to derive more definitive conclusions. Further RCTs with larger sample sizes, longer follow-up periods, and varied clinical settings are needed to validate these findings and assess radiation reduction and toxicities.

CONCLUSIONS

Hydrogel spacers are a valuable innovation in prostate cancer RT, significantly reducing rectal radiation exposure and overall GI toxicities. These benefits improve the therapeutic index by enhancing safety and tolerability, particularly during dose-escalated treatments. While some evidence supports their role in mitigating toxicities in hypofractionated RT, further research is needed to confirm these effects. Ongoing studies focusing on spacer design, integration with advanced techniques like stereotactic RT, and long-term outcomes will be essential to optimize their clinical utility. Overall, hydrogel spacers hold strong potential to improve treatment outcomes and patient quality of life in prostate cancer care.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: JKK, DKK. Data curation: JKK, DKK. Formal analysis: JKK, JKK. Funding acquisition: none. Investigation: JKK, DKK. Methodology: JKK, DKK, KSC. Project administration: JKK, DKK, KSC. Resources: JKK, DKK, JJ Software: DKK, KCK, SB. Supervision: KSC, KCK. Validation: KCK, SB, JJ. Visualization: JKK, DKK. Writing – original draft: JKK, DKK. Writing – review & editing: JKK, DKK.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.250043.

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