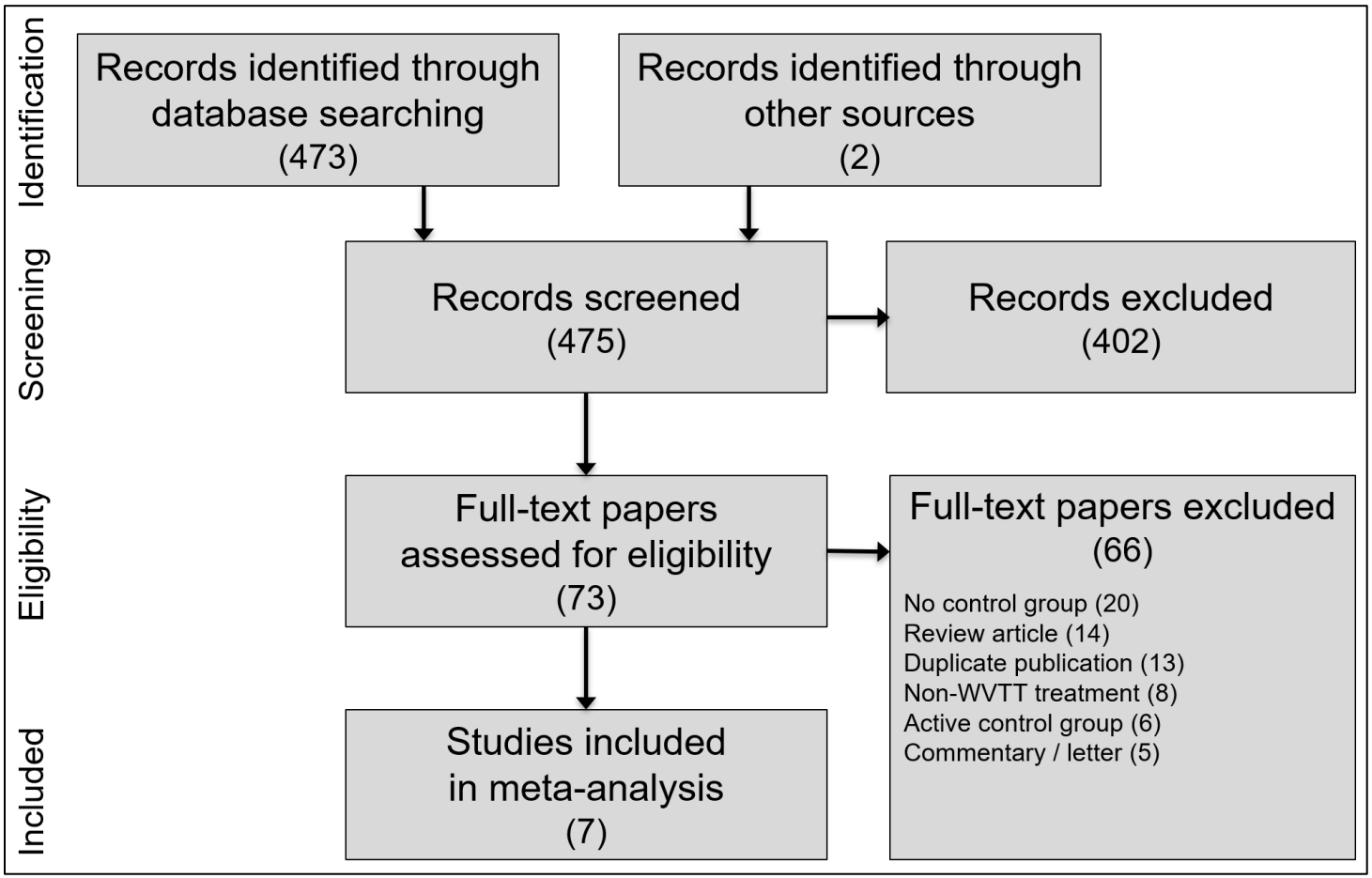
Supplementary Online Content

Miller LE, Efstathiou JA, Bhattacharyya SK, Payne HA, Woodward E, Pinkawa M. Association of the placement of a perirectal hydrogel spacer with the clinical outcomes of men receiving radiotherapy for prostate cancer: a systematic review and meta-analysis. *JAMA Netw Open.* 2020;3(6):e208221. doi:10.1001/jamanetworkopen.2020.8221

This supplementary material has been provided by the authors to give readers additional information about their work.

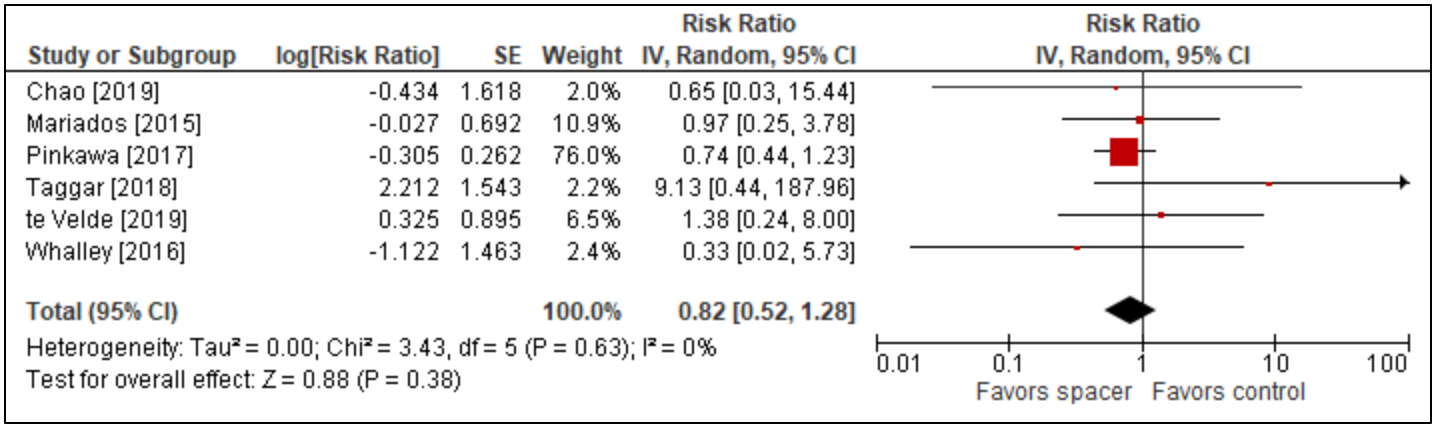


eFigure 1. PRISMA Flow Diagram

eTable 1. Cochrane Risk of Bias Assessment Among Individual Studies

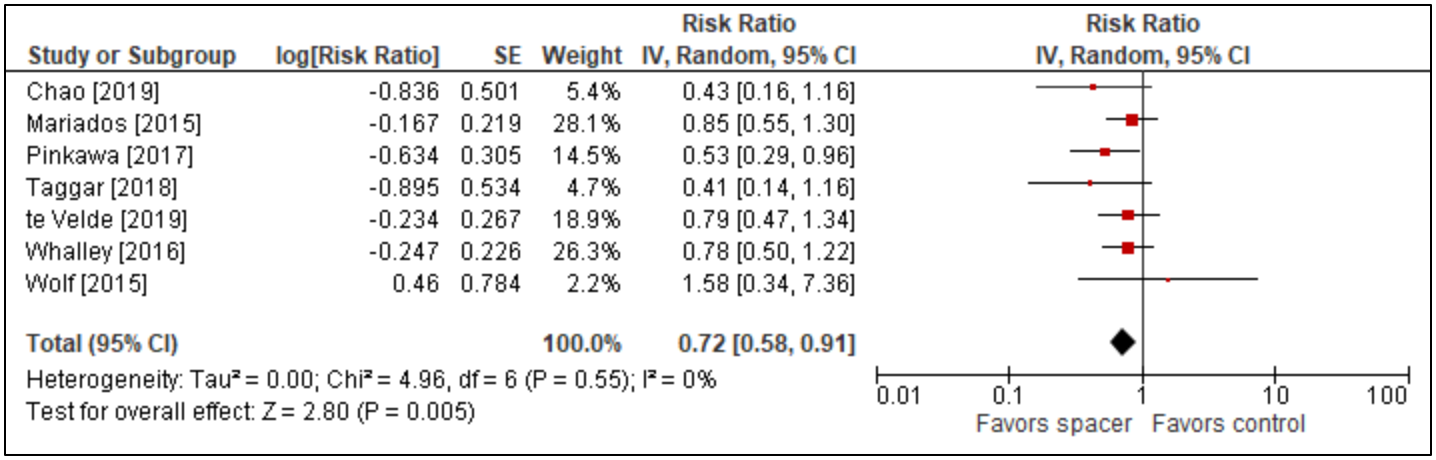
Primary Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Other Sources of Bias Description
Chao, 2019 [1]	H	H	H	H	H	H	H	L	
Mariados, 2015 [2]	U	U	L	H	H	U	L	U	Industry funding
Pinkawa, 2017 [3]	H	H	H	H	H	H	U	U	Industry funding
Taggar, 2018 [4]	H	H	H	H	H	H	U	U	BT +/- EBRT; industry funding
te Velde, 2019 [5]	H	H	H	H	H	H	H	L	
Whalley, 2016 [6]	H	H	H	H	H	U	U	L	
Wolf, 2015 [7]	H	H	H	H	H	U	H	U	Baseline patient characteristics not reported

Abbreviations: BT, brachytherapy; EBRT, external beam radiotherapy; H, high risk of bias; L, low risk of bias; U, uncertain risk of bias.



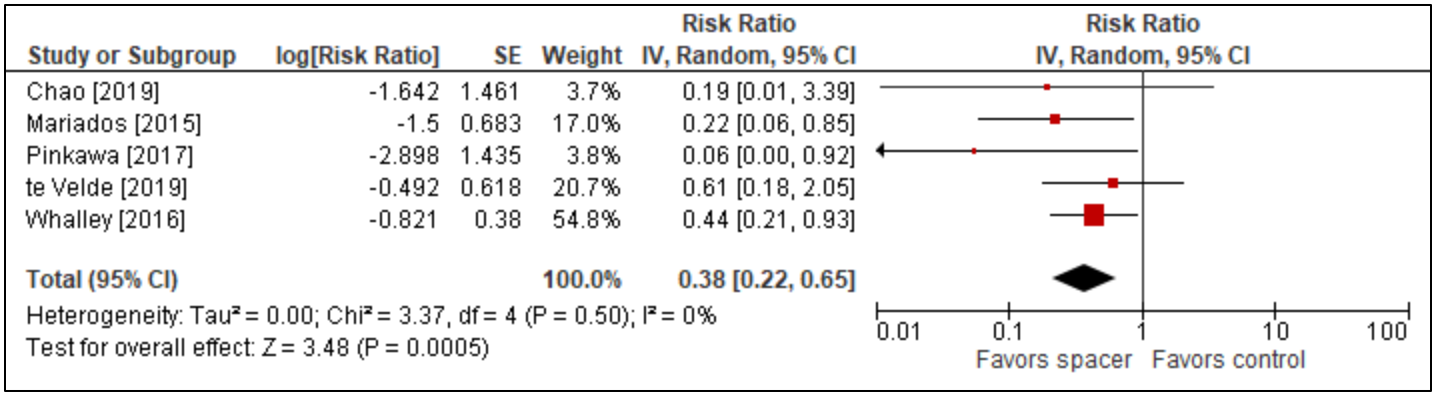
eFigure 2. Early Grade ≥2 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio and 95% confidence interval between hydrogel spacer and control groups are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with controls. A pooled risk ratio of less than 1 indicates lower risk with hydrogel spacer. Early grade ≥2 rectal toxicity was not statistically different between groups (4.5% vs. 4.1%; risk ratio=0.82, *P* = .38). Significant heterogeneity among studies was not identified (I^2=0%, *P* = .63).



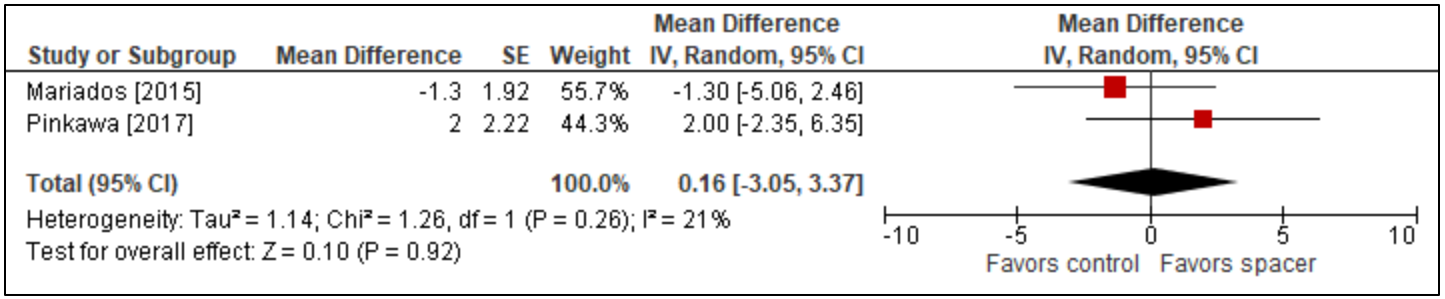
eFigure 3. Early Grade ≥1 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio and 95% confidence interval between hydrogel spacer and control groups are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with controls. A pooled risk ratio of less than 1 indicates lower risk with hydrogel spacer. Early grade ≥1 rectal toxicity was significantly lower in the hydrogel spacer group (20.5% vs. 29.5%; risk ratio=0.72, *P* = .005). Significant heterogeneity among studies was not identified (I^2=0%, *P* = .55).



eFigure 4. Late Grade ≥1 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio and 95% confidence interval between hydrogel spacer and control groups are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with controls. A pooled risk ratio of less than 1 indicates lower risk with hydrogel spacer. Late grade ≥1 rectal toxicity was significantly lower in the hydrogel spacer group (4.8% vs. 16.2%; risk ratio=0.38, $P < .001$). Significant heterogeneity among studies was not identified (I^2=0%, $P = .50$).



eFigure 5. Change in Early Bowel Quality of Life (QoL) With vs Without Perirectal Hydrogel Spacer

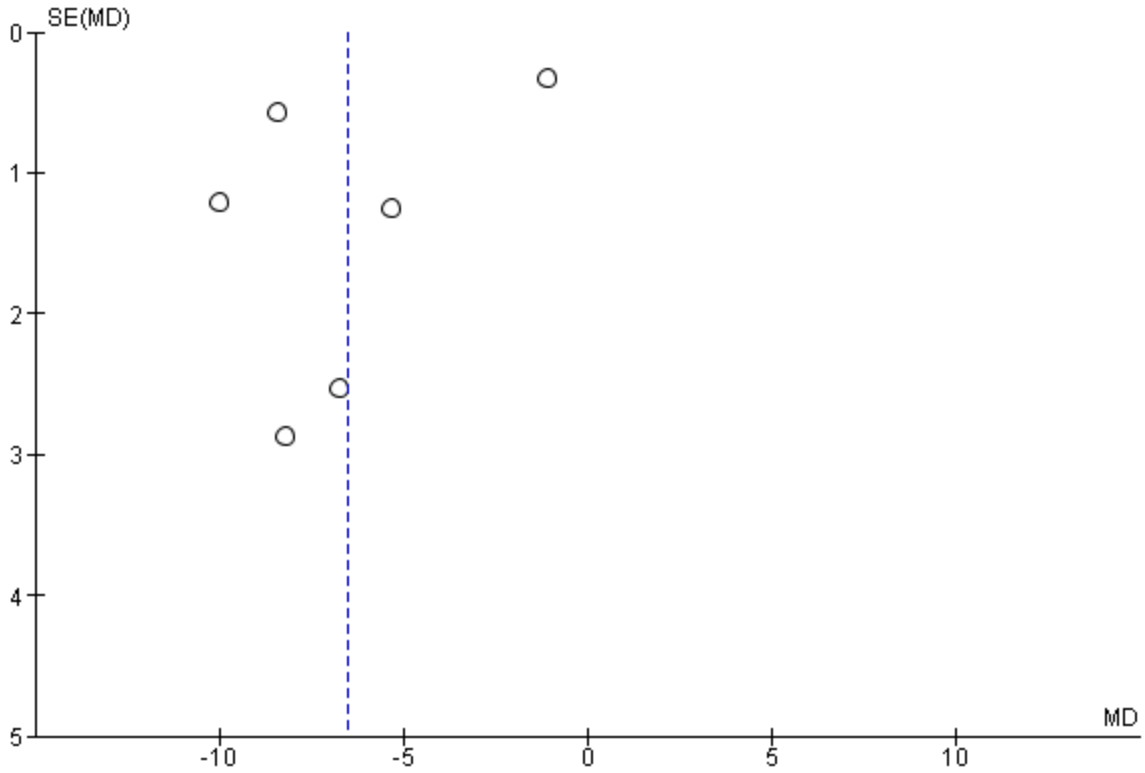
The mean difference and 95% confidence interval between hydrogel spacer and control groups are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled mean difference denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled mean difference of less than 0 indicates lower bowel QoL with hydrogel spacer; a value greater than 0 indicates higher bowel QoL with hydrogel spacer. Bowel QoL reported on a 0 to 100 scale where higher values indicate better QoL. Early bowel QoL was not statistically different between groups (mean difference=0.2, *P* = .92). Significant heterogeneity among studies was not identified (I^2=21%, *P* = .26).

eTable 2. Subgroup Analysis of Study-Level Factors on Rectal Irradiation (v70) During External Beam Radiotherapy With vs Without Hydrogel Spacer for Prostate Cancer

Study Characteristics	No. Studies	Mean Difference [a]	95% CI	*P*-value between subgroups
Random treatment allocation				
No	5	-6.1%	-10.5, -1.7	.31
Yes	1	-8.4%	-9.5, -7.3	
Sample size (HGS arm) [b]				
≥65	3	-8.0%	-10.2, -5.8	.26
<65	3	-4.8%	-9.9, 0.3	
Multicenter study				
No	4	-6.4%	-12.2, -0.5	.83
Yes	2	-7.1%	-10.1, -4.0	
Prospective enrollment (HGS arm)				
No	3	-5.4%	-11.0, 0.2	.32
Yes	3	-8.3%	-9.4, -7.2	

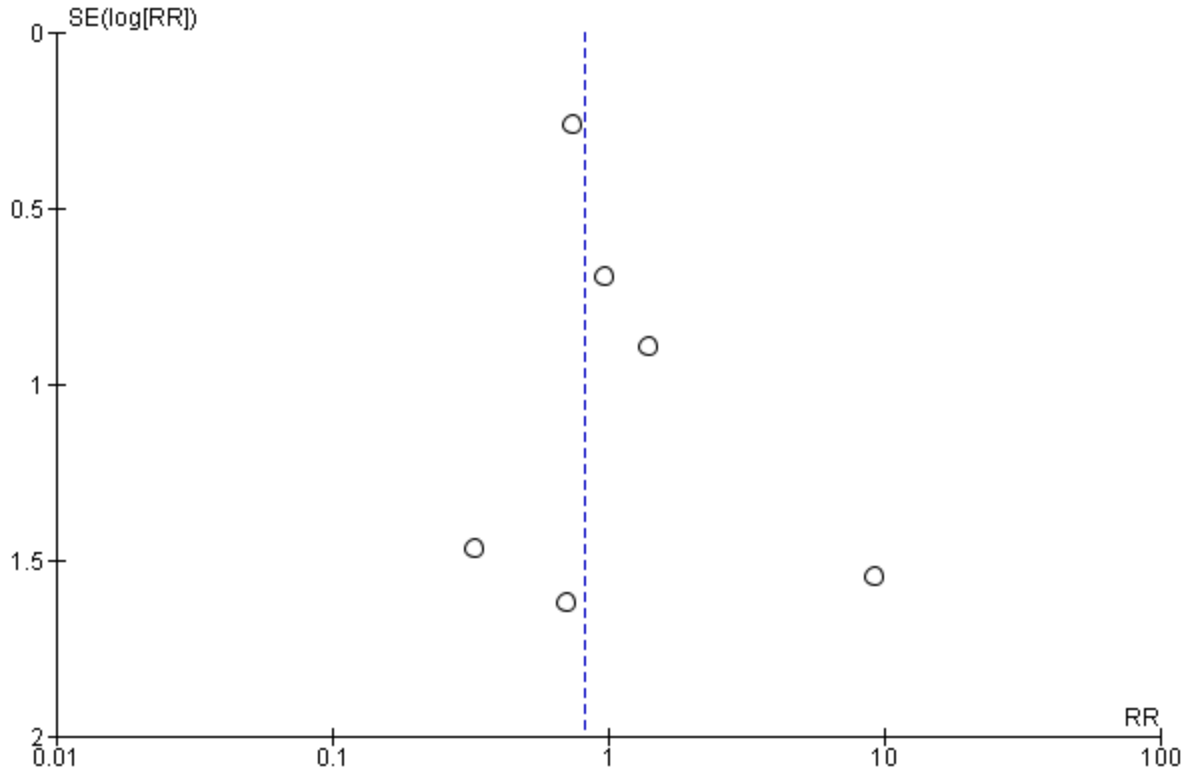
Abbreviations: HGS, hydrogel spacer.

[a]Mean difference values indicate the difference between hydrogel spacer and control groups in the percentage of rectal volume receiving at least 70 Gy radiation (v70).
[b]Categorized by median value.



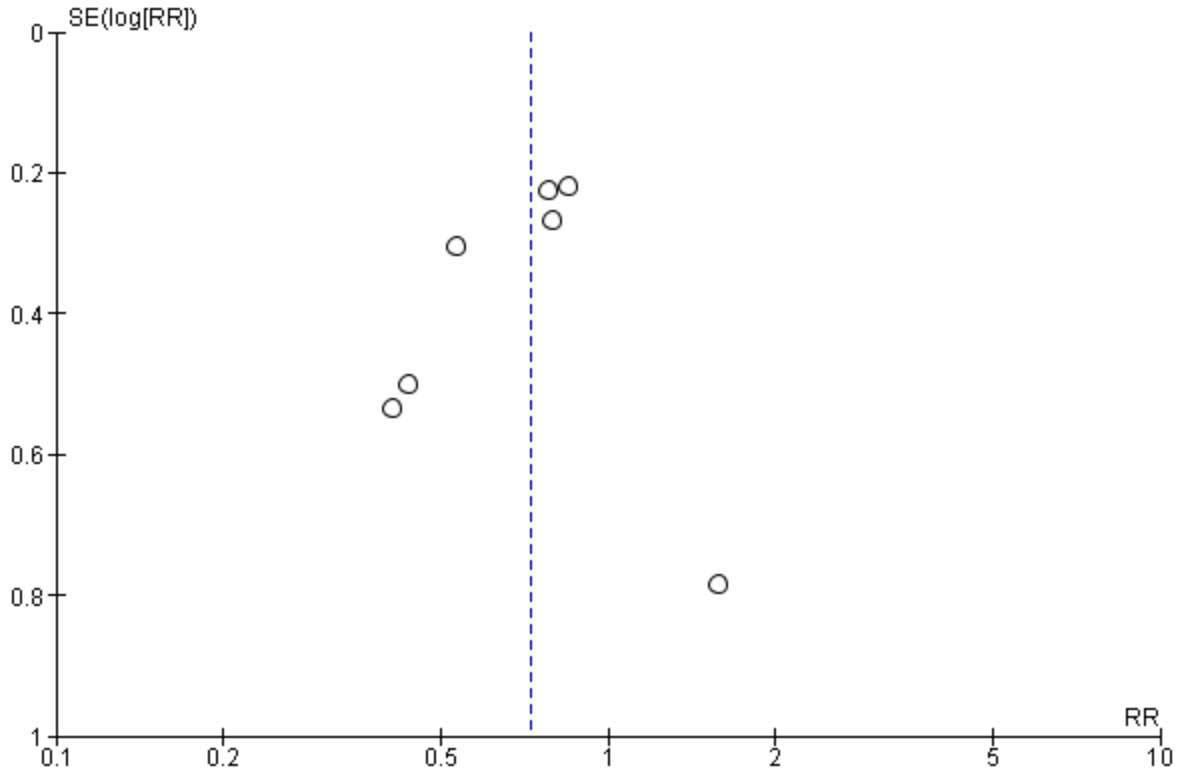
eFigure 6. Funnel Plot for the Meta-Analysis of Rectal Irradiation With vs Without Perirectal Hydrogel Spacer

The mean difference (MD) between hydrogel spacer and control groups relative to the precision of the study, denoted as the standard error (SE) of the MD, is plotted for each study. Asymmetry was not evident by visual assessment or by Egger's regression test (*P* = .18).



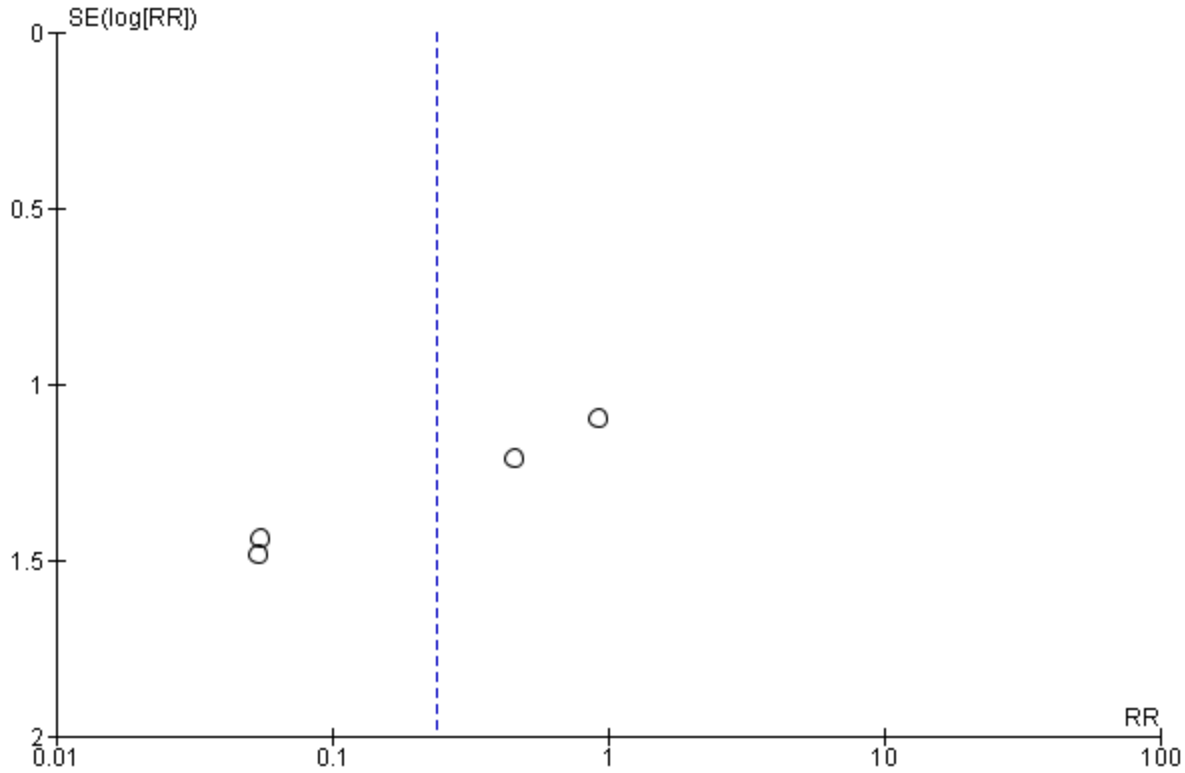
eFigure 7. Funnel Plot for the Meta-Analysis of Early Grade ≥2 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio (RR) between hydrogel spacer and control groups relative to the precision of the study, denoted as the standard error (SE) of the log of the RR, is plotted for each study. Asymmetry was not evident by visual assessment or by Egger's regression test (*P* = .37).



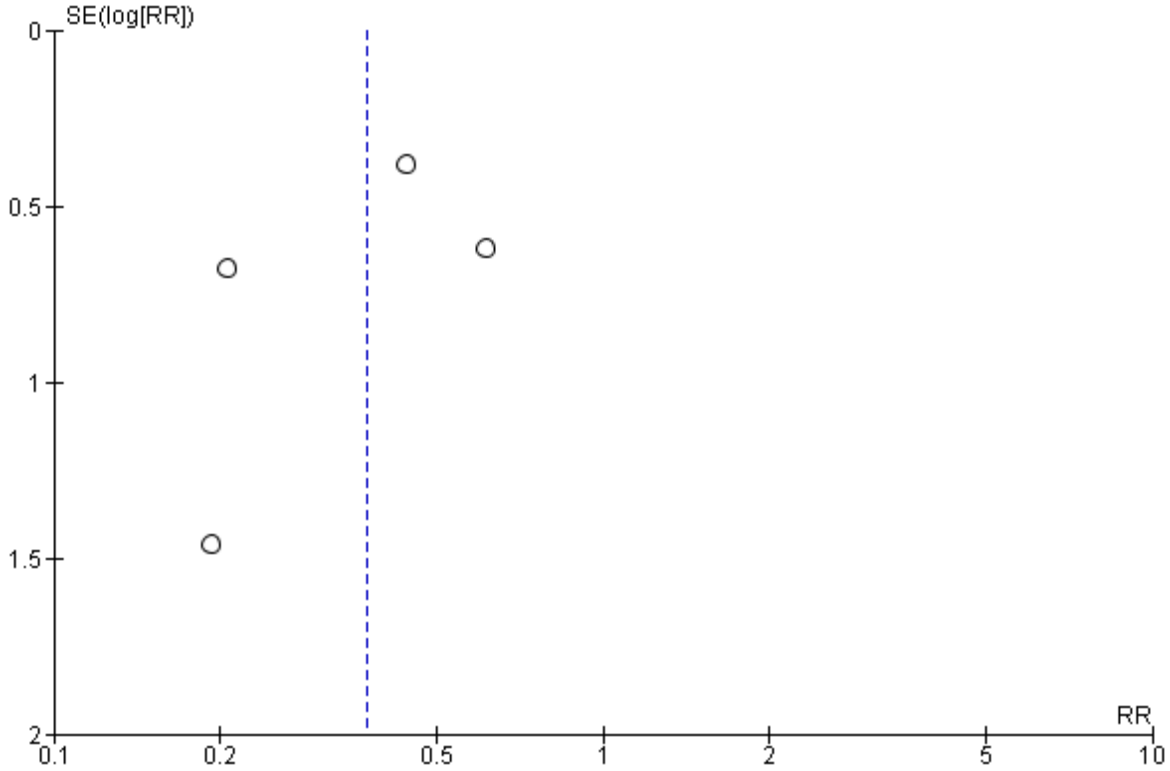
eFigure 8. Funnel Plot for the Meta-Analysis of Early Grade ≥1 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio (RR) between hydrogel spacer and control groups relative to the precision of the study, denoted as the standard error (SE) of the log of the RR, is plotted for each study. Asymmetry was not evident by visual assessment or by Egger's regression test (*P* = .49).



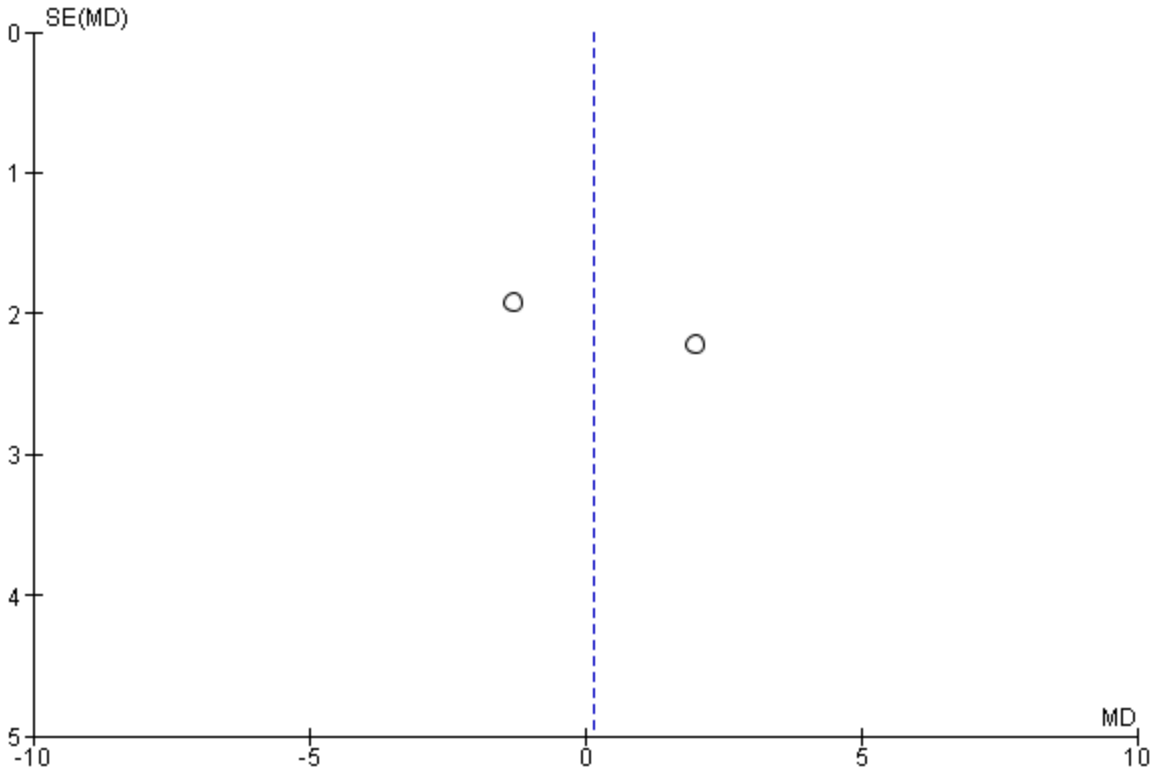
eFigure 9. Funnel Plot for the Meta-Analysis of Late Grade ≥2 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio (RR) between hydrogel spacer and control groups relative to the precision of the study, denoted as the standard error (SE) of the log of the RR, is plotted for each study. Asymmetry was not evident by visual assessment or by Egger's regression test (*P* = .60).



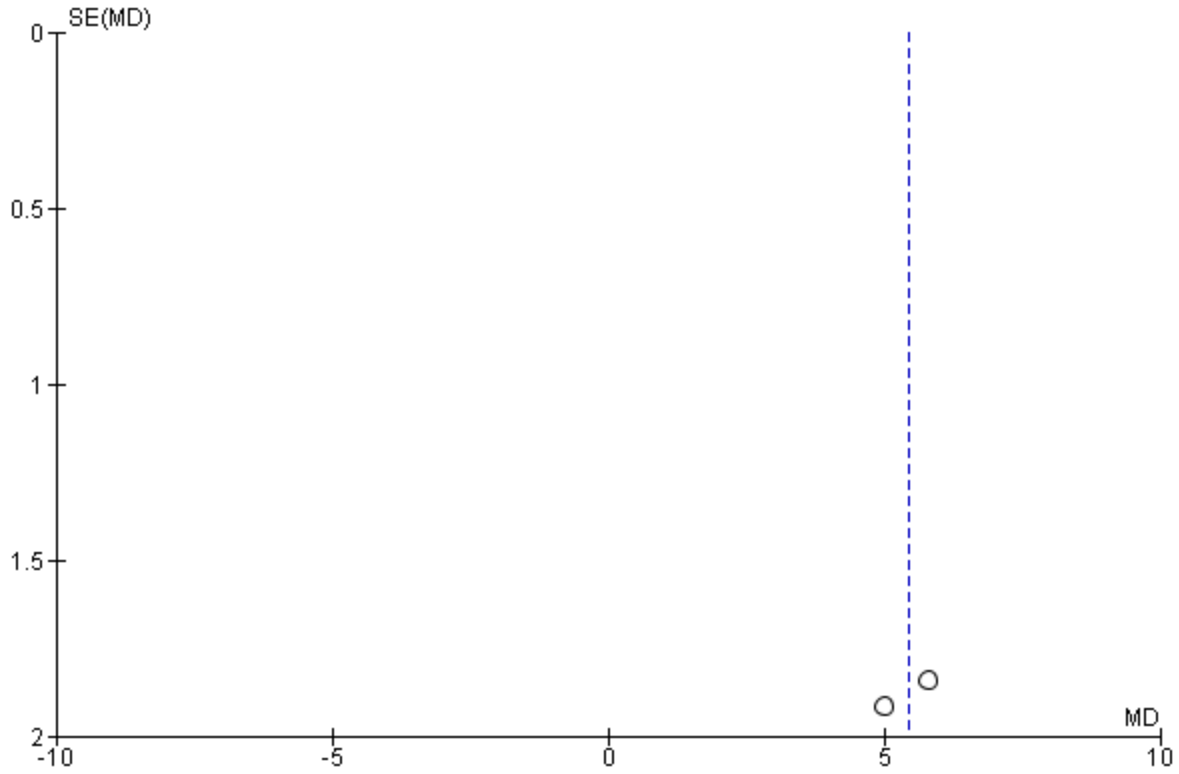
eFigure 10. Funnel Plot for the Meta-Analysis of Late Grade ≥1 Rectal Toxicity With vs Without Perirectal Hydrogel Spacer

The risk ratio (RR) between hydrogel spacer and control groups relative to the precision of the study, denoted as the standard error (SE) of the log of the RR, is plotted for each study. Asymmetry was not evident by visual assessment or by Egger's regression test (*P* = .30).



eFigure 11. Funnel Plot for the Meta-Analysis of Change in Early Bowel Quality of Life (QoL) With vs Without Perirectal Hydrogel Spacer

Asymmetry could not be assessed owing to an insufficient number of studies.



eFigure 12. Funnel Plot for the Meta-Analysis of Change in Late Bowel Quality of Life (QoL) With vs Without Perirectal Hydrogel Spacer

Asymmetry could not be assessed owing to an insufficient number of studies.

eTable 3. One-Study-Removed Sensitivity Analyses of Radiotherapy With vs Without Hydrogel Spacer for Prostate Cancer

Outcome	Statistic	No. Studies	Main Analysis			One Study Removed [a]			
			Estimate	*P*-value		Worst Estimate	*P*-value	Best Estimate	*P*-value
Rectal irradiation (v70)	Mean difference	6	-6.5%	.001		-5.8%	.009	-7.9%	< .001
Rectal toxicity, early grade ≥1	Risk ratio	7	0.72	< .01		0.76	.03	0.68	< .01
Rectal toxicity, early grade ≥2	Risk ratio	6	0.82	.38		1.15	.77	0.78	.27
Rectal toxicity, late grade ≥1	Risk ratio	5	0.38	< .001		0.31	.005	0.42	< .01
Rectal toxicity, late grade ≥2	Risk ratio	4	0.23	< .05		0.13	< .01	0.35	.18
Bowel quality of life, early	Mean difference	2	0.2	.92		-1.3	.50	2.0	.37
Bowel quality of life, late	Mean difference	2	5.4	< .001		5.0	< .01	5.8	< .01

[a]Data derived from a one-study removed sensitivity analysis in which we iteratively removed one study at a time to determine whether conclusions were influenced by any single study. The worst (most favorable to controls) and best (most favorable to hydrogel spacer) estimates demarcate the range of values derived from the analysis of each outcome.

eReferences

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7. Wolf F, Gaisberger C, Ziegler I, et al. Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiother Oncol.* 2015;116:221-225.