Supplementary File

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Reported below
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary File 1/C
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods; Supplementary File 1/F
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary File 1/D
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary File 1/E
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary File 1/F
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Results
	23b	Discuss any limitations of the evidence included in the review.	Results
	23c	Discuss any limitations of the review processes used.	Results
	23d	Discuss implications of the results for practice, policy, and future research.	Results
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO: CRD42024506380
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	PROSPERO: CRD42024506380
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	PROSPERO: CRD42024506380
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements
Competing interests	26	Declare any competing interests of review authors.	Acknowledgements

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Acknowledgements

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 for Abstracts checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71



PRISMA 2020 Checklist

2. PICOS Framework

(P) Patients undergoing radiation therapy for localised prostate cancer.

(I) Implantation of a rectal spacer to reduce radiotherapy dose delivered to the rectum.

(C) Standard-of-care radiotherapy without the use of a rectal spacer.

(O) Success rate of spacer implantation, periprocedural complications, rates of early (<90 days) and late (>90 days) adverse events. Robustness of findings and practical effectiveness of interventions described in randomised trials.

(S) Randomised controlled trials.

Non-randomised prospective studies, inclusive of data from prospectively maintained registry studies, will also be retrieved and reported separately.

3. Search strategy

MEDLINE database (via PubMed)

The search strategy was conducted on 14/03/2024 without filters, including language or date.

#	Argument	Results
#1	SpaceOAR[TIAB] OR ((rectal[TIAB] OR rectum[TIAB] OR perirectal[TIAB]) and (spacer[TIAB] OR hydrogel[TIAB] OR “polyethylene glycol”[TIAB]))	658
#2	"prostatic neoplasms"[MeSH Terms] OR (prostat*[TIAB] AND (cancer[TIAB] OR carcinoma[TIAB]))	211,145
#3	radiotherapy [MeSH Terms] OR radiotherapy[TIAB] OR “radiation therapy”[TIAB] OR irradiation[TIAB] OR IMRT[TIAB] OR VMAT[TIAB] OR SBRT[TIAB] OR proton[TIAB] OR “heavy ion”[TIAB] OR “carbon ion”[TIAB] OR “particle therapy”[TIAB]	686,899
#4	#1 #2 #3	265

The search strategy was updated on 18/08/2024 with date filter, to identify articles published since the beginning of March 2024. The numbers below are reported with the use of ("2024/03/01"[PDAT] : "2024/08/18"[PDAT]) filter:

#	Argument	Results
#1	SpaceOAR[TIAB] OR ((rectal[TIAB] OR rectum[TIAB] OR perirectal[TIAB]) and (spacer[TIAB] OR hydrogel[TIAB] OR “polyethylene glycol”[TIAB]))	41
#2	"prostatic neoplasms"[MeSH Terms] OR (prostat*[TIAB] AND (cancer[TIAB] OR carcinoma[TIAB]))	5,499
#3	radiotherapy [MeSH Terms] OR radiotherapy[TIAB] OR “radiation therapy”[TIAB] OR irradiation[TIAB] OR IMRT[TIAB] OR VMAT[TIAB] OR SBRT[TIAB] OR proton[TIAB] OR “heavy ion”[TIAB] OR “carbon ion”[TIAB] OR “particle therapy”[TIAB]	16,922
#4	#1 #2 #3	24

Embase database (via Embase.com)

The search strategy was conducted on 14/03/2024 without filters, including language or date.

#	Argument	Results

#1	'SpaceOAR':ti,ab OR ((‘rectal’:ti,ab OR 'rectum':ti,ab OR ‘perirectal’:ti,ab) AND ('spacer':ti,ab OR 'hydrogel':ti,ab OR ‘polyethylene glycol’:ti,ab))	1,266
#2	'prostate cancer'/exp OR (prostat*:ti,ab AND (cancer:ti,ab OR carcinoma:ti,ab))	339,597
#3	'radiotherapy'/exp OR radiotherapy:ti,ab OR ‘radiation therapy’:ti,ab OR irradiation:ti,ab OR IMRT:ti,ab OR VMAT:ti,ab OR SBRT:ti,ab OR proton:ti,ab OR ‘heavy ion’:ti,ab OR ‘carbon ion’:ti,ab OR ‘particle therapy’:ti,ab	1,124,418
#4	[embase]/lim	N/A
#5	(#1) AND (#2) AND (#3) AND (#4)	538

The search strategy was updated on 18/08/2024 with date filter, to identify articles added to Embase since the beginning of March 2024 (01-03-2024 to 18-08-2024). The numbers below are reported with the use of this filter:

#	Argument	Results
#1	'SpaceOAR':ti,ab OR ((‘rectal’:ti,ab OR 'rectum':ti,ab OR ‘perirectal’:ti,ab) AND ('spacer':ti,ab OR 'hydrogel':ti,ab OR ‘polyethylene glycol’:ti,ab))	47
#2	'prostate cancer'/exp OR (prostat*:ti,ab AND (cancer:ti,ab OR carcinoma:ti,ab))	10,999
#3	'radiotherapy'/exp OR radiotherapy:ti,ab OR ‘radiation therapy’:ti,ab OR irradiation:ti,ab OR IMRT:ti,ab OR VMAT:ti,ab OR SBRT:ti,ab OR proton:ti,ab OR ‘heavy ion’:ti,ab OR ‘carbon ion’:ti,ab OR ‘particle therapy’:ti,ab	34,024
#4	[embase]/lim	N/A
#5	(#1) AND (#2) AND (#3) AND (#4)	26

Scopus database (via Scopus)

The search strategy was conducted on 14/03/2024 without filters, including language or date.

#	Argument	Results
#1	TITLE-ABS-KEY (spaceoar) OR ((TITLE-ABS-KEY (rectal) OR TITLE-ABS-KEY (rectum) OR TITLE-ABS-KEY (perirectal)) AND (TITLE-ABS-KEY (spacer) OR TITLE-ABS-KEY (hydrogel) OR TITLE-ABS-KEY ("polyethylene glycol")))	1,356
#2	TITLE-ABS-KEY ("prostatic neoplasms") OR (TITLE-ABS-KEY (prostat*) AND (TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (carcinoma)))	295,190
#3	TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY ("radiation therapy") OR TITLE-ABS-KEY (irradiation) OR TITLE-ABS-KEY (imrt) OR TITLE-ABS-KEY (vmat) OR TITLE-ABS-KEY (sbrt) OR TITLE-ABS-KEY (proton) OR TITLE-ABS-KEY ("heavy ion") OR TITLE-ABS-KEY ("carbon ion") OR TITLE-ABS-KEY ("particle therapy")	1,836,757
#4	(TITLE-ABS-KEY (spaceoar) OR ((TITLE-ABS-KEY (rectal) OR TITLE-ABS-KEY (rectum) OR TITLE-ABS-KEY (perirectal)) AND (TITLE-ABS-KEY (spacer) OR TITLE-ABS-KEY (hydrogel) OR TITLE-ABS-KEY ("polyethylene glycol")))) AND (TITLE-ABS-KEY ("prostatic neoplasms") OR (TITLE-ABS-KEY (prostat*) AND (TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (carcinoma)))) AND (TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY ("radiation therapy") OR TITLE-ABS-KEY (irradiation) OR TITLE-ABS-KEY (imrt) OR TITLE-ABS-KEY (vmat) OR TITLE-ABS-KEY (sbrt) OR TITLE-ABS-KEY (proton) OR TITLE-ABS-KEY ("heavy ion") OR TITLE-ABS-KEY ("carbon ion") OR TITLE-ABS-KEY ("particle therapy"))	335

The search strategy was updated on 18/08/2024 with date filter, to identify articles published since the beginning of March 2024: (PUBDATETXT(March 2024) OR PUBDATETXT(April 2024) OR PUBDATETXT(May 2024) OR PUBDATETXT (June 2024) OR PUBDATETXT (July 2024) OR PUBDATETXT(August 2024)). The numbers below are reported with the use of this filter:

#	Argument	Results

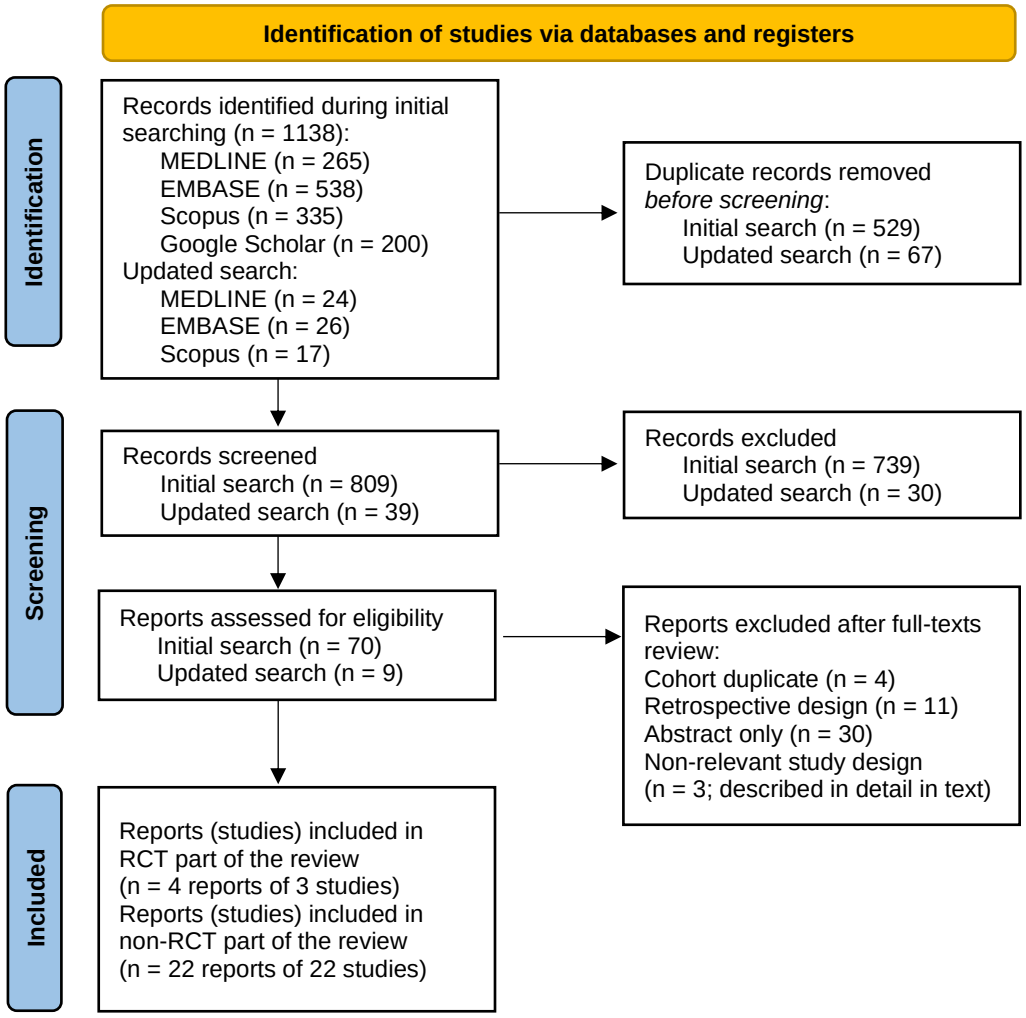
#1	TITLE-ABS-KEY (spaceoar) OR ((TITLE-ABS-KEY (rectal) OR TITLE-ABS-KEY (rectum) OR TITLE-ABS-KEY (perirectal)) AND (TITLE-ABS-KEY (spacer) OR TITLE-ABS-KEY (hydrogel) OR TITLE-ABS-KEY ("polyethylene glycol")))	43
#2	TITLE-ABS-KEY ("prostatic neoplasms") OR (TITLE-ABS-KEY (prostat*) AND (TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (carcinoma)))	4,864
#3	TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY ("radiation therapy") OR TITLE-ABS-KEY (irradiation) OR TITLE-ABS-KEY (imrt) OR TITLE-ABS-KEY (vmat) OR TITLE-ABS-KEY (sbrt) OR TITLE-ABS-KEY (proton) OR TITLE-ABS-KEY ("heavy ion") OR TITLE-ABS-KEY ("carbon ion") OR TITLE-ABS-KEY ("particle therapy")	30,354
#4	(TITLE-ABS-KEY (spaceoar) OR ((TITLE-ABS-KEY (rectal) OR TITLE-ABS-KEY (rectum) OR TITLE-ABS-KEY (perirectal)) AND (TITLE-ABS-KEY (spacer) OR TITLE-ABS-KEY (hydrogel) OR TITLE-ABS-KEY ("polyethylene glycol")))) AND (TITLE-ABS-KEY ("prostatic neoplasms") OR (TITLE-ABS-KEY (prostat*) AND (TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (carcinoma)))) AND (TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY ("radiation therapy") OR TITLE-ABS-KEY (irradiation) OR TITLE-ABS-KEY (imrt) OR TITLE-ABS-KEY (vmat) OR TITLE-ABS-KEY (sbrt) OR TITLE-ABS-KEY (proton) OR TITLE-ABS-KEY ("heavy ion") OR TITLE-ABS-KEY ("carbon ion") OR TITLE-ABS-KEY ("particle therapy"))	17

Google Scholar search engine

The search strategy was conducted on 14/03/2024 without filters, including language or date. Top 200 hits were retrieved.

(SpaceOAR|(rectal|rectum|perirectal spacer|hydrogel|"polyethylene glycol")) (prostat* cancer|carcinoma) (“radiation therapy”|radiotherapy|irradiation|IMRT|VMAT|SBRT|proton|”heavy ion”|”carbon ion”|”particle therapy”)

4. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

5. Studies that appeared relevant to the inclusion criteria, but were excluded after full-text screening due to the study design:

Hamstra DA, Mariados N, Sylvester J, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys. 2017;97(5):976-985.

The authors present the outcomes as the final results of a randomised controlled trial. However, the final primary outcomes were measured at 6 months, and the last pre-specified secondary endpoint was measured at 15 months (ClinicalTrials.gov: NCT01538628). As described in the manuscript, the 3-year outcome data was gathered during additional voluntary patient visits in centres which voluntary agreed to participate, and received IRB approval. This resulted in less than two thirds of the initial study group being available for analysis (n = 140; 63%). Considering that the investigators were aware of the primary trial outcomes at the time of designing this analysis, we believe that this should be regarded as an explorative analysis of subset of patients previously treated in a clinical trial, and the presentation of data as final randomised clinical trial outcomes is misleading. [1]

Hamstra DA, Mariados N, Sylvester J, et al. Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: Secondary analysis of a phase 3 trial. Pract Radiat Oncol. 2018;8(1):e7-e15. doi:10.1016/j.prro.2017.07.008

Similarly to the study described above, the analysis was performed post-hoc based on a subset of patients previously treated in NCT01538628 trial. In this case, the authors based patient-reported outcomes on three-year results reported in 88 out of the 222 initially randomised patients (41%). Considering that the analysis did not adhere to the analysis plan specified before randomisation, which comprised evaluation of changes in the Expanded Prostate Cancer Index Composite score inclusive of sexual domain up to 15 months after treatment, we believe that it should also be considered only as an hypothesis-generating explorative analysis of subset of patients previously treated in a randomised clinical trial. [2]

Pinkawa M, Berneking V, Schlenter M, Krenkel B, Eble MJ. Quality of Life After Radiation Therapy for Prostate Cancer With a Hydrogel Spacer: 5-Year Results. Int J Radiat Oncol Biol Phys. 2017;99(2):374-377. doi:10.1016/j.ijrobp.2017.05.035

Although this trial might initially appear as relevant to the inclusion criteria, this is a report of retrospective cohort of patients receiving radiotherapy with or without perirectal spacer in real-world setting. No randomisation between groups was performed. [3]

6. Quality assessment – risk of bias analysis

	Risk of Bias domain:					
Study:	Randomisation process	Deviations from the intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall judgement
Mariados et al. (2015) [4] / Pieczonka et al. (2016) [5]	Low	Some concerns	Low	Low	Low	Some concerns
Mariados et al. (2023) [6]	Low	Some concerns	Low	Low	Low	Some concerns
Song et al. (2024) [7]	Low	Some concerns	Low	Low	Low	Some concerns

Each of the three included randomised controlled trials was well-conducted, and the four corresponding publications did not present with any substantial concerns regarding reporting of the results. There were some concerns with regard to 'deviations from the intended intervention' domain inherent to the trial design and the nature of the intervention. In each of the three RCTs, the investigators were aware of the allocated intervention, and the patients could theoretically verify the allocation using non-sophisticated methods, which could cause a positive bias towards the study group.

7. Summary of reductions in radiotherapy dose delivered to the rectum

This summary compares the reductions in radiotherapy doses delivered to the rectum after spacer implantation against baseline assessments. The estimations are based on radiotherapy treatment-planning system calculations, using pre- and post-spacer implantation treatment-planning computed tomographies. The VX value indicates the percentage of the rectum receiving a dose of X Gy or higher.

Mariados et al. (2015) [4], Pieczonka et al. (2015) [5] (n = 148)

Parameter	V50	V60	V70	V80
Baseline [%]	25.7	18.4	12.4	4.6
Post-spacer [%]	12.2	6.8	3.3	0.6
Absolute reduction [%]	13.4	11.6	9.1	3.9
Relative reduction	52.3%	62.9%	73.3%	86.3%

Mariados et al. (2023) [6] (n = 135)

Parameter	V38	V45	V49	V53	V54	V57
Baseline [%]	20.2	15	12.4	9.8	9.2	7
Post-spacer [%]	8	4.3	2.9	1.7	1.5	0.9
Absolute reduction [%]	12.3	10.7	9.6	8.1	7.7	6.1
Relative reduction	62.4%	73.2%	78.6%	83.7%	85%	88.6%

Song et al. (2024) [7] (n = 139)

Parameter	V40	V50	V60	V70	V80
Baseline [%]	22.2	15.6	11	7	2.8
Post-spacer [%]	10.1	5.1	2.5	1.1	0.3
Absolute reduction [%]	12.1	10.6	8.5	5.9	2.5
Relative reduction	55.5%	68.4%	78%	84.8%	91.4%

8. Summary of non-randomized controlled studies investigating the clinical effect of rectal spacer implantation before radiotherapy of prostate cancer

Author, year	N	Number of centres and location	Device	PCa setting	RT setting	RT details	Procedural success [%]	Periprocedural spacer related toxicity
Pinkawa et al. (2012) [8]	30	1, Germany	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 76 Gy in 38 fractions	100	None reported
Eckert et al. (2013) [9]	11	1, Germany	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 78 Gy in 39 fractions	90.9	40% pelvic discomfort
Uhl et al. (2014) [10]	52	4,Germany, Netherlands, Switzerland	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 78 Gy in 39 fractions	92.3	1.9% rectal mucosal necrosis, 1.9% improper polymer reconstitution
Chapet et al. (2015) [11]	36	2, France	NASHA Spacer Gel Q-Med AB	Localised PCa	Primary tx, Prostate only	Hypofractionated IMRT, 62 Gy in 20 fractions	97.2	2.8% hematoma requiring surgical intervention (G3), 2.8% lower abdominal pain, 2.8% haematuria, 2.8% asthenia
Whalley et al. (2016) [12]	30	1, Australia	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT or VMAT, 80 Gy in 40 fractions	96.7	3.3% rectal wall injection
Chao et al. (2018) [13]	76	1, Australia	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT or VMAT, 78 Gy in 39 fractions	100	None reported
Chao et al. (2019) [14]	31	n/a, Australia	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 78 Gy in 39 fractions	100	None reported

Seymour et al. (2020) [15]	245	20, USA	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 79.2 Gy in 44 fractions or 76 Gy in 38 fractions or 78 Gy in 39 fractions	n/a	n/a
Folkert et al. (2021) [16]	43	2, USA	SpaceOAR™	LR/IR PCa	Primary tx, Prostate only	Ultra-hypofractionated RT, 45 Gy in 5 fractions;	100	n/a
Latorzeff et al. (2021) [17]	24	1, France	ProSpace™	IR PCa	Primary tx, Prostate only	Conv. IMRT or VMAT, 78 Gy in 39 fractions	100	n/a
Magli et al. (2021) [18]	59	3, Italy	Hydrogel spacer (unspecified)	LR/IR PCa	Primary tx, Prostate only	Ultra-hypofractionated VMAT or Tomotherapy, 40 Gy in 3 fractions	100	n/a
Newman et al. (2021) [19]	59	1, USA	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Ultra-hypofractionated RT, hypofractionated RT/LDR BT	100	n/a
Ogita et al. (2021) [20]	40	1, Japan	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Ultra-hypofractionated IMRT, 36.25 Gy in 5 fractions	98	2.5% prostatitis and seminal vasculitis (G2), 20% urinary tract pain (G1), 7.5% urinary frequency (G1), 7.5% haematuria (G1), 5% urinary retention (G1), 10% rectal pain (G1), 5% abdominal pain (G1), 5% anal pain (G1)
Hannoun-Levi et al. (2022) [21]	33	1, France	Macrolane VRF30 Q-Med Galderma™	Localised PCa	Primary tx, Prostate only	HDR BT, 20 Gy in single fraction	94.3	n/a
See et al. (2022) [22]	70	1, Australia	SpaceOAR™	Localised PCa	Primary tx, Prostate only	Conv. IMRT, 82 Gy in 41 fractions (n=64) or 78 Gy in 39 fractions (n=6)	100	1.4% rectal discomfort pain (G3), 1.4% rectal pain and ulcer (G3)
Björeland et al. (2023) [23]	68	1, Sweden	Macrolane VRF30 Q-Med Galderma™	Localised PCa	Primary tx, Prostate only	Conv. 3D-CRT, 78 Gy in 39 fractions;	96.3	13.7% anal fulness, 2% pain with HA, 2% fever with HA, 3.9% rectal bleeding > 3 days, 7.8% urinary frequency
Cloitre et al. (2023) [24]	33	1, Switzerland	BioProtect Balloon Implant system™	IR/HR PCa	Primary tx, Prostate only	Ultra-hypofractionated CyberKnife or VMAT, 36.25 Gy in 5 fractions and 50 Gy dominant lesion boost	100	n/a
Pinkawa et al. (2024) [25]	30	3, Germany	RVS TraceIT™	Localised PCa	Primary tx, Prostate only	Conv. RT or hypofractionated RT or BT boost;	100	None reported
Poon et al. (2024) [26]	34	1, Hong Kong	Barrigel™ (n=31); SpaceOAR™ (n=3)	Localised PCa	Primary tx, Prostate and pelvis in high-risk patients	MRgSBRT, 36.25 Gy or 40 Gy in 4 fractions and dominant lesion boost (40-42.5Gy); 25 Gy in 5 fractions for pelvis in high-frisk patients	100	2.9% rectal bleeding
Fredman (2024) [27]	20	1, Israel	Hydrogel spacer (unspecified)	LR/IR PCa	Primary tx, Prostate only	27 Gy in 2 fractions to the prostate with optional SIB up to 30 Gy to the dominant lesion, and 23 Gy to the seminal vesicles	100	None reported

Janoray (2024) [28]	16	1, France	ProSpace	LR/IR PCa	Primary tx, Prostate and pelvis in two patients (13%)	Conv. IMRT, 78 Gy in 39 fractions, with optional pelvic irradiation up to 46 Gy	100%	None reported
Kobayashi (2024) [29]	100	1, Japan	SpaceOAR	LR/IR PCa	Primary tx, Prostate only	Ultra-hypofractionated CyberKnife, 36.25 Gy in 5 fractions	n/a	n/a

Abbreviations: 3D-CRT - 3-dimensional conformal technique; BT – brachytherapy; conv – conventionally fractionated; HR – high risk group; IG – image-guided; IMRT – intensity-modulated radiation therapy; IR – intermediate risk group; LR – low risk group; MRgSBRT - Stereotactic body radiation therapy with magnetic resonance imaging online guidance; N – number of patients; n/a – data not available; PCa – prostate cancer; RT – radiotherapy; tx – treatment; VMAT - volumetric modulated arc therapy.

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