Review

SpaceOAR Hydrogel Spacer for Reducing Radiation Toxicity During Radiotherapy for Prostate Cancer. A Systematic Review

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OBJECTIVE To evaluate the association between SpaceOAR and radiation dosing, toxicity and quality-of-life vs no spacer across all radiotherapy modalities for prostate cancer.

METHODS A systematic search of the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase was performed from database inception through May 2020. Two reviewers independently screened titles/abstracts and full papers. Data extraction was performed, and quality assessed by 1 reviewer and checked by a second, using a third reviewer as required. The synthesis was narrative.

RESULTS 19 studies (3,622 patients) were included (only 1 randomized controlled trial, in image-guided intensity-modulated radiotherapy (IG-IMRT), 18 comparatives non−randomized controlled trials in external-beam radiotherapy (EBRT), brachytherapy, and combinations thereof). No hypofractionation studies were found. Regardless of radiotherapy type, SpaceOAR significantly reduced rectal radiation dose (eg, V40 average difference -6.1% in high dose-rate brachytherapy plus IG-IMRT to -9.1% in IG-IMRT) and reduced gastrointestinal and genitourinary toxicities (eg, late gastrointestinal toxicity 1% vs 6% (P = .01), late genitourinary toxicity of 15% vs 32% (P < .001) in stereotactic body radiotherapy). Improvements were observed in most Expanded Prostate Cancer Index Composite quality-of-life domains (eg, bowel function score decrease at 3 and 6 months: Average change of zero vs -6.25 and -3.57 respectively in low dose-rate brachytherapy plus EBRT).

CONCLUSION The randomized controlled trial in IG-IMRT demonstrated that SpaceOAR reduces rectal radiation dose and late gastrointestinal and genitourinary toxicities, with urinary, bowel, and sexual quality-of-life improvement. These advantages were verified in observational studies in various radiotherapy types. Further research is required in hypofractionation. UROLOGY 156: e74−e85, 2021. © 2021 Elsevier Inc.

In the USA and Europe, prostate cancer (PC) is the most common cancer in men, accounting for, respectively, 450,000 and 260,000 new cases annually.[1] Age-adjusted 5-year survival is high (100% for localized or locally advanced in the USA).[2]

Radiotherapy (RT) is an effective treatment for localized and locally advanced PC and is continually advancing. It can be either applied internally as brachytherapy (BT), which can be high dose rate (HDR) or low dose rate (LDR) or externally delivered as external beam RT (EBRT).[3] EBRT can take a number of forms: Intensity-modulated radiation therapy (IMRT) is where each RT beam is divided into many small beamlets that can vary the intensity of radiation, which allows different doses of radiation to be given across the tumour; stereotactic body radiotherapy (SBRT) gives RT from many different angles around the body. IMRT is referred to as image guided RT (IGRT) if it uses scans and x-rays to ensure the correct position for the RT. Proton beam therapy (PBT) uses high energy or low energy proton beams instead of high energy x-rays (photons). BT can also be given in

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combination with EBRT, when it is often referred to as 'BT boost'. However, due to the proximity of the rectum and other structures to the prostate, radiation toxicity remains a significant problem.[4] Side effects, including rectal bleeding, diarrhea, proctitis, and faecal incontinence may persist for many years or be permanent.

Rectal spacers have been increasingly adopted into clinical practice to address radiation toxicity. SpaceOAR (OAR = organs at risk) is an absorbable polyethylene glycol (PEG) hydrogel spacer that is injected into the perirectal space to temporarily position the anterior rectal wall away from the prostate during RT, thereby reducing the radiation dose to the rectum. The spacer material remains intact during the course of the patient's radiation therapy (approximately 3 months), after which it is absorbed into the body and cleared in the urine.

There is a growing interest in rectal spacers, and several systematic reviews have confirmed the efficacy of SpaceOAR in intensity-modulated radiotherapy (IMRT).[5,6] However, until now there has not been a comprehensive review including the full range of RT employed in clinical practice including hypofractionation, high, and low dose-rate brachytherapy (BT) and combinations thereof. This systematic review therefore evaluates the association between use of SpaceOAR and radiation toxicity across the full range of RT modalities.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the best methodological guidance.[7-9] The protocol registered on PROSPERO is: CRD42020196459.

Inclusion Criteria

The inclusion criteria are shown in Supplementary Table 1. All RT types were included and any of a number of outcomes including radiation dose, toxicity, and quality of life. Dosing is measured in many different ways, including:[10]

- Vx is the volume of the organ receiving at least x % or Grays (Gy) of prescription dose.
- Dmax = Maximum radiation dose in Gy.
- Dx = minimum dose received by the "hottest" x% (or x cc) of the organ.

Only studies comparing SpaceOAR to no spacer were included, both randomized and non−randomized.

Literature Searches

Electronic searches were undertaken in May 2020 to identify published and unpublished reports of randomized controlled trials (RCT) and observational studies that reported on the clinical effectiveness of rectal spacers. The following databases were searched: MEDLINE (Ovid), MEDLINE In-Process Citations, Daily Update & Epub Ahead of Print (Ovid), EMBASE (Ovid), PubMed (NLM), Cochrane Database of Systematic Reviews (CDSR) (Wiley), Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley), Database of Abstracts of Reviews of Effects (DARE) (CRD), Health Technology Assessment Database (HTA)(CRD), KSR Evidence (www.ksrevidence.com), Econlit (EBSCO), and NHS EED (CRD). HTA Agency websites, clinical trials registers, conference abstracts databases and reference lists of included articles were also searched. No restrictions on language or publication status were applied. Database details and search strategies are provided in Supplementary Appendix e1 and e2.

Methods of Study Selection, Data Extraction and Quality Assessment

Two reviewers, working independently, screened the titles/abstracts and full papers. Data extraction was performed, and methodological quality assessed by 1 reviewer and checked by the second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer. Study quality of RCT was assessed using the Cochrane Risk of Bias Tool.[11] Study quality of comparative non−RCT was assessed using the JBI Critical Appraisal Checklist for Cohort Studies.[12]

RESULTS

Included Studies

The search strategies identified 4897 references. Of these, 222 were selected for further assessment (Supplementary Figure 1). 28 references met the inclusion criteria. These included 1 RCT reported in 10 references (Supplementary Table 2), 18 references to 18 non−RCT comparative studies, which compared SpaceOAR to no spacer with 1 also comparing to balloon spacer (Supplementary Table 3). None of the studies, apart from those by Pinkawa[13-16] recruited patients to either the intervention or comparator at the same time and so could not be regarded as cohort studies, which is why the term 'non−randomized controlled trial' was adopted. This paper reports on the following outcomes: Dosimetry, toxicity and quality of life (QoL).[10]

RCT

One RCT, which was single blinded (initial follow-up 15 months) and conducted in the USA, compared SpaceOAR to no spacer in Image-Guided, Intensity-Modulated Radiation Therapy (IGRT).[17] The quality assessment showed that the trial was well designed with overall low risk of bias (Supplementary Table 4).[11] SpaceOAR substantially reduced irradiation to the rectum: The primary endpoint of at least 25% reduction in rV70 was achieved in 97.3% of SpaceOAR patients ($P < .0001$) (Supplementary Table 5). The primary safety endpoint was the reduction in rectal or procedure-related adverse events (AE) in the first 6 months, and showed no statistically significant difference (34.2% and 31.5% for SpaceOAR and no spacer respectively ($P = .7$).[17] Late rectal toxicity was significantly lower with SpaceOAR (15 months) with no increase in urinary toxicity (Supplementary Table 6). At 36-month follow-up, Grade ≥1 rectal toxicity was 2.0% vs 9.2% ($P = .028$) and Grade ≥2, 0% vs 5.7% ($P = .012$) favoring the spacer arm.[18] From 6 to 36 months, fewer men experienced clinically significant declines in all 3 EPIC-QoL domains, ie bowel, urinary, and sexual (2.5% vs. 20%, $P = .002$) (Supplementary Table 7).[18] Changes in bowel QoL statistically significantly and consistently favored SpaceOAR from 6 months ($P = .002$). At 36 months the difference between control and SpaceOAR was 5.8 points ($P < .05$), ie greater than the minimally important difference (5 points) (Supplementary Table 7).[18]

Comparative Non−Rct Studies

Study and Patient Characteristics. Seven of the 18 comparative non−RCT studies were in non−hypofractionated IMRT (Table 1).[13-16,19-21] Two studies used ultra-hypofractionation in the form of stereotactic body radiation therapy (SBRT).[22,23] One study was in PBT and one was in high dose rate brachytherapy (HDR-BT) monotherapy.[24,25] The other 7 studies included some BT plus EBRT combination, 5 with BT first (2 HDR-BT[26,27] and 3 LDR-BT[28-30]) and 2 with BT second (1 HDR-BT[31] and 1 LDR-BT[19]). Very few studies provided a comprehensive list of baseline characteristics, although there was little difference in age between arms, where reported (Supplementary Table 8). The quality assessment showed that, whilst outcome measurement was valid and follow-up sufficient for most studies, the main problem was risk of selection bias (Supplementary Table 9). This risk is often seen in retrospective studies that lack randomization; treatment is usually allocated based on clinician/patient preference (Supplementary Table 10). Three studies attempted to mitigate bias by using matching.[15,19,30]

Rectal Dosimetry. SpaceOAR decreased rectal dose across all 13 studies were reported regardless of RT type and for all dosimetry outcomes, statistically significantly in all but 4 reported outcomes (See Table 2). This decrease therefore applied to all measures of dosimetry in all 5 EBRT studies. Nearly all reported differences were statistically significant.[14,20-22,24] It also applied to BT, although there was only 1 study, evaluating HDR-BT as monotherapy. [25] Finally, SpaceOAR decreased dose in all 7 BT plus EBRT studies, including 2 of the studies using matching.[19,26-31] Variation in outcome hindered any judgment as to the effect of RT type on size of the difference in dosimetry outcome. Indeed, the higher the Vxx the lower the volume or percentage of the organ exposed to that level of radiation. For example, the outcome V90 is the volume of the organ receiving at least 90% of the target dose, which must be less than V40 because V40 includes all values of Vxx greater than V40. Therefore, it is not surprising that generally the difference between SpaceOAR and no spacer decreased. For example, in Chao 2019[27] values varied between -0.2% for V80 and -6.1% for V40. Some studies did report the same outcome eg the V40 mean/median difference ranged between -6.1% in HDR-BT plus IGRT in Chao 2019[27] to -9.1% in IMRT in Whalley 2016.[20] However, it is unclear that this variation can be attributed to RT type.

Other Dosimetry. Dosing to other organs was reported in 6 studies.[13,22,27-29,31] Differences between SpaceOAR and no spacer were most often not statistically significant: Exceptions were to the penile bulb in the only study in SBRT,[22] and to the neurovascular bundle in BT plus EBRT combinations,[31] where SpaceOAR was favored (Supplementary Table 11).

Toxicity. SpaceOAR generally reduced toxicity risk across all 7 studies where reported regardless of RT type (Table 3).[20,21,23,24,27,29,32] In all EBRT studies the point estimate of the odds ratio (OR) was lower than 1 (indicating a lower risk for SpaceOAR), except during RT and only for proctitis and haemorrhoids.[20,21,23,24,32] One study using IMRT reported that acute and late rectal toxicity was lower with SpaceOAR, statistically significantly for Grade 1 at a median of 26 months, 16.6% vs 41.8% (P = .04).[20] In another study using IMRT, risk of diarrhea, fecal incontinence, proctitis, and hemorrhoids were lower with SpaceOAR or zero in both arms up 36 months, except for hemorrhoids and Grade 1 proctitis during RT.[21] Although one IMRT study did show a higher rate of grade 2 acute GU toxicity, there were no grade 2 rectal and no grade 3 rectal or GU events.[32] In PBT, risk was higher for SpaceOAR only for Grade 1 or 2 events during RT, but lower for grade 2 late rectal toxicity for at least 7.5 months follow-up.[24] In SBRT, SpaceOAR decreased the risk of Grade 2+ acute and late gastrointestinal (GI)/rectal and genitourinary (GU) toxicity, with late GI toxicity of 1% vs 6% (P = .01) and late GU toxicity of 15% vs 32% (P < .001).[23]

In the only study in HDR-BT plus IGRT, SpaceOAR reduced the risk of all grades of toxicity, acute and late, except grade 1+ late GU toxicity, although not statistically significantly.[27] The only study involving LDR-BT showed that the risk of rectal/GI toxicity, proctitis and rectal bleeding was lower for SpaceOAR for LDR-BT, regardless of whether combined with EBRT. Only diarrheadiarrhea was more frequently reported in LDR-BT + EBRT and LDR-BT salvage, and rectal discomfort was higher in LDR + EBRT and LDR monotherapy, although no differences were statistically significant.[29]

HRQoL. Four studies, using the EPIC-QoL tool, measured QoL following perirectal spacer implantation, 3 of which were in IMRT from the same institution (see Supplementary Table 12). In most domains across the 3 IMRT studies and up to 60 months follow-up, difference in QoL favored SpaceOAR although largely not statistically significantly.[17-19] Pinkawa 2017 reported clinically meaningful differences in EPIC−bowel bother scores at 18 and 60 months (6-point and 5-points respectively, p>0.05).[14] The fourth study, in EBRT plus LDR-BT, showed that EPIC bowel function score decrease at 3 months and 6 months follow up was lower in and therefore favored the SpaceOAR hydrogel group (median of zero change vs -6.25 and -3.57 respectively).[19] There were no studies reporting QoL in EBRT plus HDR-BT, BT monotherapy or hypofractionated EBRT.

COMMENT

Our findings from all included studies suggest that SpaceOAR hydrogel, regardless of RT type, reduces radiation-exposure in comparison with no spacer (Table 2). Although most odds ratios of rectal toxicity were not statistically significant, most point estimates favored SpaceOAR (less than 1), regardless of RT type (Table 3). In this review, we reported on the published data from 1 RCT[17] and 18 non−RCT studies (Table 1) that compared the dosimetric and clinical effects of SpaceOAR hydrogel in men undergoing RT in comparison with no spacer. We incorporated results from a total of 3,622 patients receiving a variety of RT types, including IMRT, SBRT, BT plus EBRT (including HDR-BT and LDR-BT), brachytherapy and proton therapy. No hypofractionation studies were found. Also, LDR monotherapy was only included in 1 study,[29] in which Pd-103 instead of the more usual I-125 was used as the isotope and, despite a lower rectal dose with SpaceOAR, there was no statistically significant difference in toxicity.[33] In addition, the RCT showed a clinically meaningful and statistically

Table 1. Study population, Comparative non—RCT

Study ID	No. of patients, follow-up mo	RT 1	RT 1 dose - per fraction (Gy)	RT dose - total (Gy)	RT 1 —fraction number	Radiotherapy 1 — other	RT type 2	RT 2 dose - total (Gy)	RT 2 - fraction number	RT 2 - other	T class	Risk status
Baghwala 2019[1]	36, NR	HDR BT	13.5	27	2	NA	NA	NA	NA	NA	NR	Low /intermediate risk
Chao 2019[2]	97, 60 (median)		3/2	18/16	NR	Iridium 192. N = 24 patients received an initial dose of 18 Gy in 3 fractions from 2010—2011, n = 71 patients received 16 Gy in 2 fractions from 2012 onwards as per our departmental protocol.	IG-IMRT	50.4	28		T1-T3	Intermediate /high risk
Fried 2017[3]	94, NR	SBRT	7.25	36.25	5	NA	NA	NA	NA		NR	Low /favourable intermediate
Liu 2020[4]	162, NR	LDR BT +/- EBRT	NR	NR	NR	Out of 81 spacer patients, 21 received EBRT only, 7 received combined EBRT and Iodine-125 LDR, and 53 received Iodine-125 LDR only.	LDR BT +/- EBRT	NR	NR	NR		Low /intermediate risk
Morita 2020[5]	300, NR	LDR BT	NA		NA	I-125 seeds were implanted as free seeds using Mick applicator.	IMRT	45	25	NA	T1-4	very low to very high
							NA	NA	NA			very low to very high
Navaratnam 2020[6]	72, 9.5 (median)	PBT	NR	67.5-79	25-44	NR					T1-T3	NR
Patel 2018[7]	57, 6	EBRT	NR	NR	NR		LDR-BT	NR			NR	NR
Pinkawa 2012[8]	56, 3	IMRT	2	78 (median)/ 76		Spacer: 78 Gy for 16 and 76 Gy for 12 patients; no spacer: 76 Gy.	NA	NA				low to high risk
Pinkawa 2016[9]	202, 17	IMRT	NR	76-78		"Only for patients with a spacer the prescription dose was increased from 76Gy to 78Gy,	NA	NA				NR

Continue

Table 1. Continued

Study ID	No. of patients, follow-up mo	RT 1	RT 1 dose - per fraction (Gy)	RT dose - total (Gy)	RT 1 –fraction number	Radiotherapy 1 – other	RT type 2	RT 2 dose - total (Gy)	RT 2 - fraction number	RT 2 - other	T class	Risk status
Pinkawa 2017[10]	114, 63276/78	"Fractions of 2 Gy up to a total dose pf 76 Gy (n = 96) or 78 Gy (n = 18, all with hydrogel). "low to high risk										
Pinkawa 2017[11]	167, 17 (median)	76-78	"The prescription dose increased from 76 to 78Gy, subsequently to 80Gy, only for patients with a spacer. "									
NRSaigal 2019[12]	117, NR	EBRT	NR	NR	45, 37.5-50.4 (median, range)	NA	HDR-BT	15	NR	NR	T1-T3	NR
RT-Velde 2019[14]	125, 36	IMRT	1.8	81	45	NA	Low to high risk	Whalley 2016[15]	140, 26 (median)	28	40	Intermediate / high risk
Wolf 2015[16]	78, 61	IMRT	1.85	75.85	41	NA	NR	Wolf 2015[16]	Wu 2018[17]	54, 14.4	HDR BT +/- EBRT	NA
15,18,19-21	NA	15 Gy boost in conjunction with external beam radiation; 18 Gy as salvage brachytherapy; 19-21 Gy brachytherapy monotherapy.	HDR BT +/- EBRT	NR	NR	T1-T3	NR	Zelefsky 2019[18]	551, 17	SBRT	8 (most patients)	37.5/405 (most patients)
Ultrahypofractionated, most patients received 40.0 Gy (85.5%; 471/551) in 8 Gy. fractions	NA	NA	NA	T1/2	Low / intermediate risk							

significant advantage to SpaceOAR in QoL using the EPIC tool,[18] and the 4 non−RCT studies that reported EPIC QoL also indicated the possibility of improvement in all QoL domains, especially in later follow-up (Supplementary Table 12).[13,15,16,19] There were also no significant safety concerns in the RCT.[17]

Over the last decade, there have been significant improvements in the way RT is planned and delivered such as the use of dose escalation, IGRT and hypofractionation, including SBRT. These RT advancements give the ability to reduce the overall treatment time, through the delivery of larger doses of RT per fraction in comparison to usual (or 'conventional') external beam RT treatment. The only RCT used dose escalated IGRT with conventional fractionation.[17] Several published studies report on the shift from conventional hypofractionation (1.8 - 2 Gy per fraction) to moderate hypofractionation (2.5-4 Gy per fraction) and the subsequent emerging shift to ultra-hypofractionation (>3.4 Gy) using SBRT.[34] Moderate and ultra-hypofractionation are attractive to both healthcare providers and patients as treatment can be delivered more conveniently in fewer hospital visits. While randomized controlled trials have shown that moderate hypofractionation results in higher acute and similar late toxicity rates when compared with conventional fractionation, there are still concerns on the long-term toxicity effects of ultra-hypofractionation.[4,34] Furthermore, prostate cancer national audits suggest that GI events are more frequently reported than what is reported in randomized published trials. The 2020 UK National Prostate Cancer Audit reported that 11% of men experienced at least 1 severe bowel complication within 2 years of RT in mainly intermediate risk with hypofractionation RT modalities without a rectal spacer.[35] This systematic literature review (SLR) includes data on the use of SpaceOAR with ultra-hypofractionation for the first time.[22,23] With the use of SBRT in Zelefsky 2019[23], SpaceOAR decreased the risk of both acute and late GI/rectal and GU toxicity.

Nine other reviews were identified during the search, which reported similar findings on the dosimetric and clinical outcomes associated with the use of a perirectal hydrogel spacer.[5,36-43] Afkhami Ardekani 2019[5] reported on brachytherapy only, including 3 comparative studies, both in EBRT plus BT (2 in HDR-BT[26,27] and 1 in LDR-BT[29]), and concluded that the hydrogel spacer significantly reduces rectal dose and toxicity without influencing prostate immobilization. The most recent systematic literature review that included a meta-analysis, was reported by Miller 2020.[6] The review included 7 studies, 1 RCT and 6 cohort studies involving 1011 men, with a median follow-up of 26 months. The success rate of spacer placement was 97.0% (95%CI, 94.4%-98.8%) and the weighted mean perirectal separation distance was 11.2mm (95%CI, 10.1-12.3mm). v70 rectal dose was 66% lower in the spacer group compared with control (3.5% vs 10.4%; mean difference, −6.5%; 95%CI, −10.5% to −2.5%; P = .001), and mild and transient complications occurred in 0% to 10% of patients. The risk of grade 2 or higher rectal

Table 2. Dosimetry - rectal, comparative non—RCT

Study ID	Dosing metric	Units	Arm name	Mean	Median	SD or Range	*P*-value
			EBRT				
Pinkawa 2017[10]	V70	%	SpaceOAR	20	NR	NR	<.01
IMRT			No spacer	32			
	V90		SpaceOAR	4			<.01
			No spacer	13			
Te Velde 2019[14]	V40		SpaceOAR	25.9			<.0001
IMRT			No spacer	33.3			
	V75		SpaceOAR	2.1			<.0001
			No spacer	7.4			
	V65		SpaceOAR	5.2			<.0001
			No spacer	12.6			
Whalley 2016[15]	V40		SpaceOAR	22.9			<.01
IMRT			No spacer	32			
	V65		SpaceOAR	5.3			<.01
			No spacer	13.5			
Navaratnam 2020[6]	V70	%	SpaceOAR	NR			<.001
PBT			No spacer				
	V75		SpaceOAR				<.001
			No spacer				
Fried 2017[3]	D10	Gy	SpaceOAR	26.66			.0000
SBRT			No spacer	30.44			
	D50		SpaceOAR	10.9			.47
			No spacer	11.4			
			Brachytherapy				
Baghwala 2019[1]	V75	cc	SpaceOAR	0.02			<.05
HDR BT			No spacer	0.7			
	V90		SpaceOAR	>92			<.05
			No spacer				
			High-dose brachytherapy in combination with EBRT				
Chao 2019[2]	V40	%	SpaceOAR		4.6	0.8-17.7	<.001
HDR BT+IG-IMRT**			No spacer		10.7	3.2-21.8	
		cc	SpaceOAR		3.6	0.9-9.9	<.001
			No spacer		8.6	3.2-21.8	
	V75	%	SpaceOAR		0	0-0.25	<.001
			No spacer		0.55	0-1.4	
		cc	SpaceOAR		0	0-0.22	<.001
			No spacer		0.45	0-1.46	
	V80	%	SpaceOAR		0	0-0.09	<.001
			No spacer		0.21	0-0.66	
		cc	SpaceOAR		0	0-0.08	<.001
			No spacer		0.2	0-0.56	
Wu 2018[17]	V40		SpaceOAR		8.11	NR	.16
HDR BT +/- EBRT*			No spacer		9.38		
	V75		SpaceOAR		<0.005		<.0005
			No spacer		0.12		
	V80		SpaceOAR		<0.005		.007
			No spacer		0.01		
	V90		SpaceOAR		NR		.1
			No spacer		<0.005		
Saigal 2019[12]	D1	Gy	SpaceOAR		35.3		<.05
HDR BT + EBRT			No spacer		54.6		
	D90		SpaceOAR		100.1		.354
			No spacer		101.3		
			Low-dose brachytherapy in combination with EBRT				
Morita 2020[5]	V100	cc	SpaceOAR	0.026		0.14	<.001
LDR BT+IMRT			No spacer	0.318		0.34	
	V150		SpaceOAR	0.001		0	
			No spacer	0.025		0.04	
Patel 2018[7]	V50		SpaceOAR	0.53			<.001
LDR BT + EBRT			No spacer	4.21			
	V100		SpaceOAR	0.0001			<.001
			No spacer	0.25			
Taggar 2018[13]	V100		SpaceOAR	0.01		0.05	.000
LDR BT+EBRT			No spacer	0.07		0.19	
Liu 2020[4]	D2	Gy	SpaceOAR	-25.1†		14.1	<.0001
LDR BT +/- EBRT			No spacer	5†		19.2	
	D0.1		SpaceOAR	-65.7†		27.4	<.0001
			No spacer	-13†		27.2	

* V50, V60 and V70 also reported and $P < .01$.
† Post- minus intra-operative dose.

Table 3. Toxicity outcomes*, comparative non–RCT

Study ID	Type of AE	Grade of AE	Follow-up (mo)	Arm name	N	% having AE	*P*-value	OR (95% CI)
				EBRT				
Te Velde 2019[14] IMRT	Diarrhea	1	During RT	SpaceOAR	65	13.8	.02	0.34 (0.14,0.84)
				No spacer	60	31.7		
			3	SpaceOAR	65	4.6	1	0.92 (0.18,4.72)
				No spacer	60	5		
			36, baseline corrected	SpaceOAR	65	1.7	.192	0.22 (0.03,1.86)
				No spacer	56	7.3		
		2	During RT	SpaceOAR	65	0	1	NE
				No spacer	60			
			3	SpaceOAR	65			
				No spacer	60			
			36, baseline corrected	SpaceOAR	65			
				No spacer	56			
	Proctitis	1	During RT	SpaceOAR	65	9.2	.6	0.66 (0.22,2.03)
				No spacer	60	13.3		
			3	SpaceOAR	65	1.5	.3	0.29 (0.03,2.86)
				No spacer	60	5		
			36, baseline corrected	SpaceOAR	65	1.7	.606	0.46 (0.04,4.88)
				No spacer	56	3.6		
		2	During RT	SpaceOAR	65	4.6	0.6	2.79 (0.28,27.56)
				No spacer	60	1.7		
			3	SpaceOAR	65	0	1	NE
				No spacer	60			
			36, baseline corrected	SpaceOAR	65		.227	
				No spacer	56	3.6		
	Faecal incontinence	1	During RT	SpaceOAR	65	3.1	1	0.94 (0.13,6.87)
				No spacer	60	3.3		
			3	SpaceOAR	65	0	.5	NE
				No spacer	60	1.7		
			36, baseline corrected	SpaceOAR	65	0	1	
				No spacer	56			
		2	During RT	SpaceOAR	65			
				No spacer	60			
			3	SpaceOAR	65			
				No spacer	60			
			36, baseline corrected	SpaceOAR	65			
				No spacer	56			
	Haemorrhoids	1	During RT	SpaceOAR	65	23.1	.8	1.2 (0.51,2.83)
				No spacer	60	20		
			3	SpaceOAR	65	3.1	.09	0.24 (0.05,1.21)
				No spacer	60	11.7		
			36, baseline corrected	SpaceOAR	65	5	.708	0.67 (0.15,2.98)
				No spacer	56	7.3		

Continued

Table 3. Continued

Study ID	Type of AE	Grade of AE	Follow-up (mo)	Arm name	N	% having AE	*P*-value	
		2	During RT	SpaceOAR	65	4.6	1	1.41
				No spacer	60	3.3		(0.23,8.76)
			3					SpaceOAR
				65	0	1	NE	OR (95% CI)
			No spacer	60				
			36, baseline	SpaceOAR	65	1.7	1	0.94
No spacer	56	1.8	corrected					(0.06,14.5)
Whalley 2016[15]	Rectal toxicity_late	1	Median 28 (range 24-38)	SpaceOAR	30	16.6	.04	0.28 (0.1,0.78)
IMRT			Median 26 (range 18-40)	No spacer	110	41.8		
		2	Median 28 (range 24-38)	SpaceOAR	30	3.3	NR	0.91 (0.1,8.49)
			Median 26 (range 18-40)	No spacer	110	3.6		
	Rectal toxicity_acute	1	Median 28 (range 24-38)	SpaceOAR	30	43		0.74 (0.33,1.66)
			Median 26 (range 18-40)	No spacer	110	50.6		
		2	Median 28 (range 24-38)	SpaceOAR	30	0		NE
			Median 26 (range 18-40)	No spacer	110	4.5		
Wolf 2015[16]	Rectal	1	NR	SpaceOAR	NR	16.6	NR	NE
IMRT	toxicity_acute			No spacer		9		
		2		SpaceOAR		0		
				No spacer		0		
	Genitourinary toxicity_acute	1		SpaceOAR		12.5		
				No spacer		21		
		2		SpaceOAR		36.6		
				No spacer		28.5		
	Any toxicity_acute	3		SpaceOAR		0		
				No spacer		0		
Navaratnam 2020[6]	Rectal toxicity_any	1	During RT	SpaceOAR	51	35.3	.061	5.2
				No spacer	21	9.5		(1.09,24.89)
PBT			Median (IQR):10.3 (9.02-11.7)	SpaceOAR	39	7.7	NR	NE
			Median (IQR):8.7 (7.5-9)	No spacer	14	0		
		2	During RT	SpaceOAR	51	2		
				No spacer	21	0		

Continued

Table 3. Continued

Study ID	Type of AE	Grade of AE	Follow-up (mo)	Arm name	N	% having AE	*P*-value	OR (95% CI)
			Median (IQR):10.3 (9.02-11.7)	SpaceOAR	39			
			Median (IQR):8.7 (7.5-9)	No spacer	14	7.1		
Zelefsky 2019[18] SBRT								

GI_toxicity_acute2+NRSpaceOAR2691.090.33 (0.07,1.55)No spacer2823GI_toxicity_lateSpaceOAR2691.010.16 (0.05,0.48)No spacer2826GU_toxicity_acuteSpaceOAR269 2829.190.73 (0.42,1.26)No spacer12GU_toxicity_lateSpaceOAR26915<.0010.38 (0.25,0.57)No spacer28232High-dose brachytherapy in combination with EBRTChao 2019[2] HDR BT+IG-IMRTGI_toxicity_acute23SpaceOAR320.480 (NE)No spacer651.51+SpaceOAR3213.3.050.34 (0.11,1.11)No spacer6530.8GI_toxicity_late1SpaceOAR320.110 (NE)No spacer657.7GU_toxicity_acute2SpaceOAR320.48No spacer651.51+SpaceOAR3283.3.220.42 (0.11,1.56)No spacer6592.3GU_toxicity_late3SpaceOAR323.3.570.52 (0.06,4.82)No spacer656.21+SpaceOAR3246.7.741.16 (0.49,2.71)No spacer6543.12+SpaceOAR323.3.40.41 (0.05,3.66)No spacer657.7Low-dose brachytherapy alone or in combination with EBRTTaggar 2018[13] LDR BT/LDR BT+/- EBRTAny rectal/GI toxicityNRNRSpaceOAR7420.3.950.79 (0.4,1.58)No spacer13624.3Taggar 2018[13] LDR BT monotherapyDiarrheaSpaceOAR267.7NR0.44 (0.08,2.31)No spacer4415.9ProctitisSpaceOAR260NENo spacer440Rectal bleedingSpaceOAR2600 (NE)No spacer446.8Rectal discomfortSpaceOAR2615.7NENo spacer440Taggar 2018[13] LDR BT monotherapy (salvage for recurrent PC)DiarrheaSpaceOAR1112.52.55 (0.14,45.36)No spacer195.3ProctitisSpaceOAR110NENo spacer190Rectal bleedingSpaceOAR1100 (NE)No spacer195.3Rectal discomfortSpaceOAR110NENo spacer190Taggar 2018[13] LDR BT + EBRT combination therapyDiarrheaSpaceOAR4212.53.34 (0.76,14.76)No spacer734.1ProctitisSpaceOAR4200 (NE)No spacer735.5Rectal bleedingSpaceOAR4250.22 (0.05,1.03)No spacer7319.2Rectal discomfortSpaceOAR425NENo spacer730

OR, odds ratio; calculated using N and number experiencing event; NE, not estimable due to either presence of zeros or N not reported (NR).

* According to Common Terminology Criteria for Adverse Events scoring of adverse events attributed to radiation.

toxicity was comparable between groups in early follow-up (4.5% in hydrogel spacer group vs 4.1% in control group; risk ratio, 0.82; 95%CI, 0.52-1.28; P = .38). In late follow-up the risk was 77% lower in the spacer group compared with control (1.5%vs 5.7%; risk ratio, 0.23; 95%CI, 0.06-0.99; P = .05). Changes in EPIC score measure for bowel quality of life were comparable between groups in the early follow up but improvements were again greater in late follow up (mean difference, 5.4; 95%CI, 2.8-8.0; P < .001) for the spacer cohort.

Our review adds to the existing body of evidence on perirectal spacers. To date, our review provides the most comprehensive report on hydrogel spacers, as this includes a wider range of comparative studies than previously reported. In addition, we included studies that reported on perirectal spacers using different types of RT, such as SBRT, proton therapy and BT plus EBRT combination therapy. One of the main limitations of the only RCT is that the method of delivering RT varies considerably in clinical practice and is rapidly evolving. Therefore, there could be a concern that the results may not be generalizable across different and evolving RT types, particularly hypofractionation. Our results support the findings from the latest systematic review and meta-analysis from Miller 2020, that suggests that the dosimetric and clinical effects of a hydrogel spacer was achieved regardless of RT type in real world trials.

The review was carried out to the highest standards, including adherence to PRISMA guidelines, the Cochrane Handbook and the Centre for Reviews and Dissemination.[7-9] To avoid bias the review protocol was also registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/inclusion_criteria.asp). Some of the limitations of our review were that the non−RCT comparative studies were of relatively low quality, therefore the conclusion must be interpreted with caution. Also, despite some toxicity outcomes not being statistically significant, no meta-analysis was conducted. There were also very few studies that reported on examined HRQOL in different RT modalities, only 1 study in HDR-BT monotherapy[25] and 1 study that reported on LDR-BT monotherapy.[29] Our review did not consider any resource or cost implications. However, economic evaluations, based on data from the RCT included in our review have shown that hydrogel spacers can be cost-effective.[44-46] Future research should focus on the development of better designed comparative studies, ideally RCT, of SpaceOAR in populations that include BT and hypofractionation. It should also include the whole range of outcomes, including HRQoL.

CONCLUSION

Injecting SpaceOAR hydrogel prior to prostate RT has been clinically proven to reduce radiation dose to the rectum during prostate RT in a single RCT, with long term follow-up demonstrating significant reductions in late gastrointestinal and genitourinary toxicities, and improvements in urinary, bowel, and sexual quality of life. This SLR supports the results of the only RCT for patients with prostate cancer in a wide body of observational studies across a range of RT types. However, there were no hypofractionation studies and only 1 of LDR monotherapy, which used Pd-103 instead of the more usual I-125 isotope.

There is a growing interest in spacing devices which would allow the use of hypofractionation and dose escalation as RT toxicity is still a significant problem: For these to be broadly adopted into clinical practice, strategies to protect OAR should be recommended as a research priority.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2021.05.013.

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