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Basic Original Report

Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall



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Abstract

Purpose: Hydrogel prostate-rectum spacers, biomaterials placed between the prostate and rectum, continue to gain interest as a method to reduce or limit rectal dose during dose escalated prostate cancer radiation therapy. Because the spacer is initially injected into the perirectal space as a liquid, the final distribution can vary. The purpose of this study was to evaluate hydrogel spacer (SpaceOAR system) implantation and distribution from a recent prospective randomized control trial and correlate spacer symmetry with rectal dose reduction as well as rectal wall infiltration (RWI) to acute and late toxicity.

Methods and materials: T2-weighted magnetic resonance imaging sets of 149 patients enrolled in a prospective clinical trial who received transperineal spacer injection were assessed for hydrogel spacer midline symmetry and RWI using a semiquantitative scoring system. Symmetry was then correlated to rectal dose reduction using a Student *t* test (1-tailed, paired), whereas a Fisher exact test was used to correlate RWI with acute and late rectal toxicity. All patients had control treatment plans created before spacer injection.

Results: Hydrogel spacer was symmetrically placed at midline for 71 (47.7%) patients at the prostate midgland as well as 1 cm superior and inferior to midgland. The remaining 78 (50.9%) patients had some level of asymmetry, with only 2 (1.3%) having far lateral distribution (ie, >2 cm) of hydrogel spacer. As the hydrogel spacer became more asymmetric, the level of rectal dose reduction relative to their control

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plans decreased. However, all but the most asymmetrical 1.3% had significant rectal dose reduction ($P < .05$). Rectal wall hydrogel spacer infiltration was seen in 9 (6.0%) patients. There was no correlation between RWI and procedure-related adverse events or acute/late rectal toxicity.

Conclusions: Significant reduction of rectal dose can still be achieved even in the setting of asymmetric hydrogel spacer placement. RWI does not correlate with patient complications.

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Introduction

Multiple randomized controlled trials have demonstrated that dose escalated radiation therapy (RT) for prostate cancer results in improved clinical outcomes, including local control, progression-free survival, and distant metastases-free survival.¹⁻⁴ However, despite improved outcomes, dose escalation is associated with increased gastrointestinal and rectal toxicity.¹ Although recent advances in radiation technology and/or delivery, including image guided radiation therapy (IGRT) and intensity modulated RT (IMRT), have reduced toxicity, it remains difficult to spare the anterior wall of the rectum. Interest has grown in biomaterials that can be injected between the prostate and rectum to allow for a separation that can ultimately reduce rectal dose for patients receiving external beam RT.⁵ As previously described in the literature, these biomaterial prostate-rectum spacers can include hyaluronic acid, collagen, absorbable balloons, and polyethylene glycol (PEG) hydrogels.⁶⁻¹¹

PEG hydrogels, specifically, have been the most widely studied and used biomaterial for perirectal spacing. They are primarily composed of water and cross-linked PEG and are injected into the anterior perirectal space/fat as a thin liquid. Once within the perirectal space, they then immediately polymerize into a soft hydrogel that is tissue-dense on computed tomography (CT) and hyperintense on T2-weighted magnetic resonance imaging (MRI). After approximately 3 months, the hydrogel begins to hydrolyze and eventually is cleared via renal filtration.

A recent multicenter randomized controlled trial studying a PEG hydrogel demonstrated a 98.7% hydrogel placement success rate, an average of 1.26 cm of perirectal spacing, a 73.3% relative reduction in the rectal volume receiving at least 70 Gy (rV70), and significant improvements in late rectal toxicity and bowel quality of life.¹² Although prior publications have evaluated application technique, patient safety and tolerance, dosimetric effects, and clinical outcomes for participants of the US Pivotal Trial as described previously, neither the distribution of the hydrogel nor hydrogel rectal wall infiltration (RWI) has been analyzed. The purpose of this secondary analysis of the SpaceOAR US Pivotal trial was to assess hydrogel distribution and its impact on rectal dose reduction as well as the rate of rectal wall infiltration and its impact on rectal toxicity.

Methods and materials

Setting and patients

All patients provided written informed consent and were enrolled in a multicenter randomized controlled trial of hydrogel spacer placement that was approved by the institutional review boards of all 20 participating centers under the US Food and Drug Administration–approved investigational device exemption. Inclusion and exclusion criteria were described previously.¹⁰ Men with stage T1 or T2 prostate cancer, Gleason score ≤ 7 , a prostate-specific antigen concentration ≤ 20 ng/mL, and Zubrod performance status 0 to 1 who were planning to receive IG-IMRT were potential study candidates.

In total, 149 patients included in the study were randomized to receive the hydrogel spacer (SpaceOAR System, Augmenix, Inc., Waltham, MA) before IG-IMRT. Patients received a preimplantation CT scan and T2-weighted MRI simulation for baseline treatment planning purposes. They were then placed in the dorsal lithotomy position. Using an aseptic, transperineal technique, 3 gold intraprostate fiducial markers were placed followed by transperineal injection of the spacer into the anterior perirectal space between Denonvilliers' fascia and the anterior rectal wall. Markers and hydrogel spacer were injected under transrectal ultrasound guidance with general anesthesia, local anesthesia, or monitored anesthesia care. Within 5 to 10 days of hydrogel spacer placement, patients received a repeat postprocedural CT scan and T2-weighted MRI simulation for treatment planning.

Each patient had plans created on both the baseline and postprocedural simulations to determine rectal dose reduction resulting from the hydrogel spacer. The clinical target volume (CTV) included the entire prostate with or without the inclusion of the seminal vesicles, at the discretion of the treating physician.¹⁰ Planning target volumes (PTV) were a 5- to 10-mm expansion of the CTV, also at the discretion of the treatment physician. The CTV and PTV margins did not vary between control and postinjection plans. The prescription dose was 79.2 Gy at 1.8 Gy fractions delivered to $\geq 98\%$ of the PTV and 100% of the CTV. Normal rectal dose constraint objectives were per the Quantitative Analysis of Normal Tissue Effects in

Table 1 Hydrogel scoring methodology

(A) Axial slice hydrogel symmetry scoring method	
Score	Description
0	No hydrogel in slice
1	Hydrogel centered on prostate midline
2L, 2R	1 cm hydrogel asymmetry from midline, left, or right
3L, 3R	>2 cm hydrogel asymmetry from midline, left, or right
(B) Patient-level symmetry scoring method	
Score	Description
Sym 1	All 3 slices with symmetrical distribution
Sym 2	1 of 3 slices with 1 cm lateral distribution
Sym 3	2 of 3 slices with 1 cm lateral distribution
Sym 4	All 3 slices 1 cm lateral or $\leq 2/3$ slices 2 cm lateral distribution
Sym 5	All 3 slices with 2 cm lateral distribution
(C) RWI scoring method	
RWI	Description
0	No RWI
1	Minimal RWI (ie, small discrete areas of gel in wall)
2	Moderate RWI (ie, <25% rectal wall circumference)
3	Significant RWI (ie, $\geq 25\%$ rectal wall circumference)

RWI, rectal wall infiltration.

the Clinic guidelines.¹³ The planning methodology for baseline and postprocedural plans was the same. All plans were reviewed by a blinded, independent core laboratory for verification of the target volume contours, critical normal structure contours, dosimetric data, measurement of the perirectal space, and success of hydrogel placement.

Patients were evaluated at baseline, weekly during IG-IMRT, and at 3-, 6-, 12-, and 15-month follow-up visits for adverse events as well as for changes in medications for both urinary and rectal symptoms. An independent Clinical Events Committee, blinded to treatment randomization, evaluated all adverse events, and related them to device, procedure, radiation, or other causes. All adverse events attributed to radiation by the Clinical Events Committee were included for toxicity analysis per the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Distribution analysis

The posthydrogel implanted T2-weighted MRI for all treated patients were used to evaluate hydrogel spacer distribution. The hydrogel spacer is approximately 90% water, resulting in a hyperintense T2-weighted MRI signal. A team of 3 radiation oncologists evaluated the postimplant T2-weighted MRI for all 149 patients and determined hydrogel symmetry using a semiquantitative scoring system, as seen in Table 1. As shown in Figure 1, three axial slices were evaluated in every patient (the

midgland axial slice, 1 cm superior to midgland, and 1 cm inferior to midgland). Table 1A contains the semiquantitative scoring method used to score hydrogel symmetry on every slice. Axial slices without hydrogel spacer received a score of 0, slices with midline spacer symmetry received a score of 1, and asymmetric lateral hydrogel distributions, based on the medial aspect of the spacer, of 1 or 2 cm received scores of 2 or 3, respectively. Figure 2 shows representative images of symmetrical and asymmetrical gel distribution. To obtain a single symmetry score per patient, the scoring method outlined in Table 1B was used, with a score of 1 being gel symmetry in all 3 slices and scores 2 through 5 representing increasing hydrogel asymmetry. The patient level symmetry score was then compared with the pre and post hydrogel treatment plans to determine the impact of spacer asymmetry on rectal dose reduction. In addition to evaluation 1 cm above and below midgland, the presence of hydrogel at the apex and base of the prostate was also quantitatively evaluated.

The extent of hydrogel RWI was assessed for each patient by the same radiation oncologists. Evaluating every axial slice, the most extensive hydrogel RWI in each patient was scored using the qualitative method outlined in Table 1C. Scoring ranged from no rectal wall infiltration (0) to minimal (1, small discrete areas), moderate (2, <25% of rectum circumference), and significant (3, $\geq 25\%$ of rectum circumference) infiltration. Correlations of patient RWI score with procedure-related adverse events and with acute and late rectal toxicity (per CTCAE 4.0) were then determined.

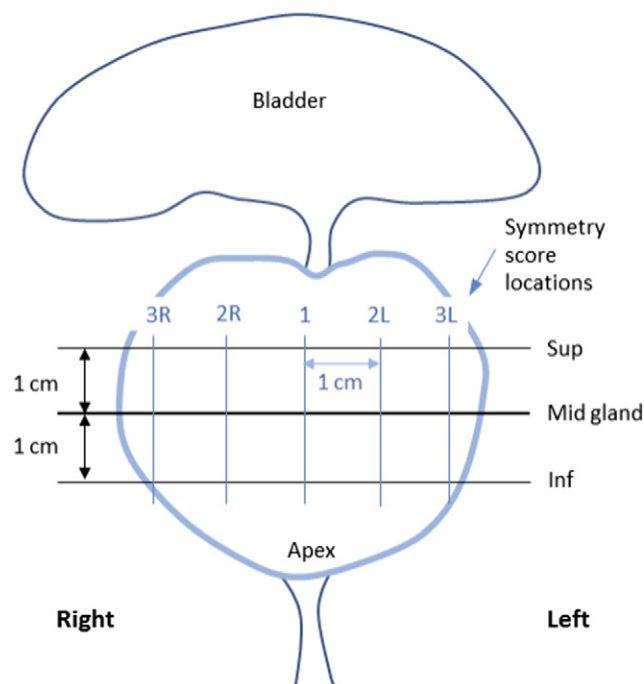


Figure 1 Coronal view of the prostate with location of the midgland, superior (Sup), and inferior (Inf) axial slices evaluated. Also shown are symmetry locations, with 1 representing midline, 2L/2R representing 1 cm left and right, and 3L/3R 2 cm left and right, respectively.

Statistical analysis

Student *t* test was used to evaluate the statistical significance between the Sym 1 and other Sym groups regarding rectal dose reduction and the difference between pre- and postspacer rectal dose for each Sym group. The Fisher exact test was used to determine the statistical significance between hydrogel RWI and procedural adverse events and with acute and late rectal toxicity. A *P* value of $<.05$ was considered statistically significant, and data analysis was performed using Excel 2013 (Microsoft Corporation, Redmond, WA) and SPSS Statistics v.23 (IBM Corporation, Armonk, NY).

Results

Spacer symmetry analysis

PEG hydrogel was found in every axial MRI slice while scoring hydrogel symmetry. Overall, a symmetrical spacer application was found in 92 (62%) of the midgland and superior axial slices, and in 108 (72%) of the inferior slices, as shown in Figure 3A. On average, 24 (16%) and 26 (17%) of the axial slices had 1 cm lateral distribution (left and right, respectively), with 2 (1.3%) and 1 (0.7%) with ≥ 2 cm lateral distribution. There was no apparent trend for left or right asymmetry. Regarding overall

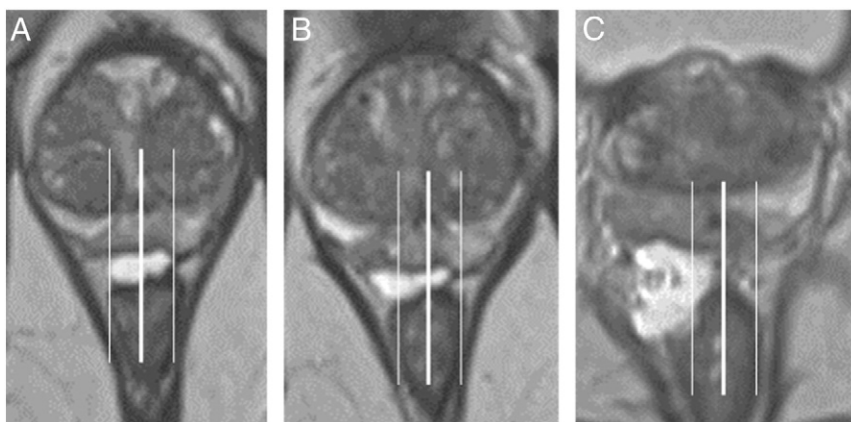


Figure 2 T2-weighted magnetic resonance images of symmetrical hydrogel distribution (A, score = 1), 1 cm lateral distribution (B, score = 2), and >2 cm lateral distribution (C, score = 3).

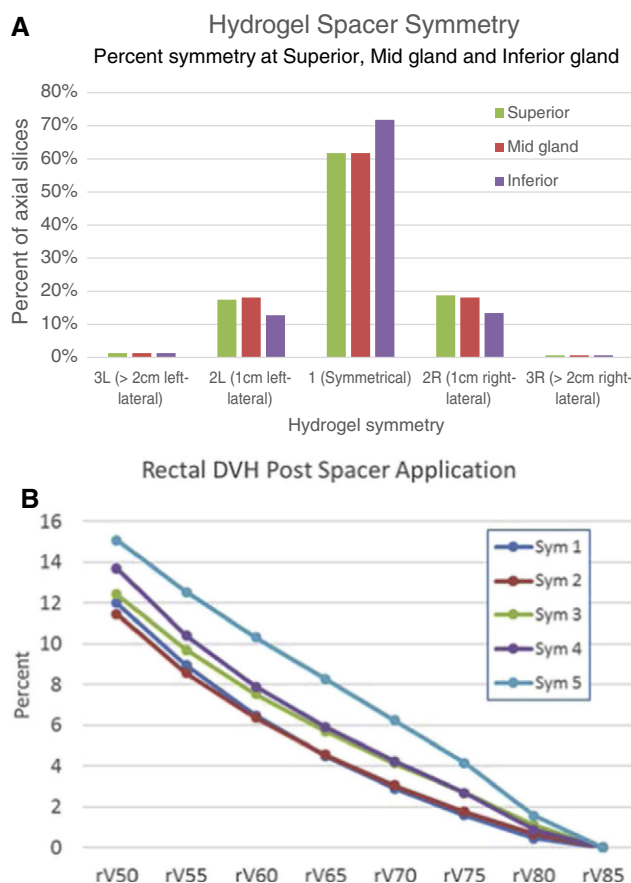


Figure 3 (A) Axial slice symmetry scores, per Table 1: Hydrogel symmetry was observed in 61.7% of midgland and superior axial slices and in 71.8% of inferior slices. (B) Absolute rectal dose-volume histogram (DVH) for each Sym score group following spacer application.

symmetry per patient, 73 (49.0%) patients had spacer symmetry in all 3 (midgland, 1 cm above and below) axial slices (Sym score 1), with 26 (17.4%), 20 (13.4%), 28 (18.8%), and 2 (1.3%) patients with scores of Sym 2 through Sym 5, respectively. Hydrogel was present at both the apex and base of the prostate in 48 (32%) of patients, and was absent at either the apex and/or base in 101 (68%) of patients.

When subtracting the postspacer from the prespacer rectal dose-volume histograms (DVHs), a rectal dosimetric benefit was observed in all groups. The rectal dose

reduction (prespacer to postspacer) for groups Sym score 1 through Sym score 4 was statistically significant for rV50 through rV80 ($P < .0001$). Figure 3B depicts the rectal DVH and percentage of rectal volume that could be anticipated to receive a specific dose as a function of Sym score. The percent absolute dose reduction at rV50, rV60, rV70, and rV80 for all Sym groups was 13.4%, 11.6%, 9.1%, and 3.9%, respectively. Sym scores 1/2 had lowest percentage of rectal volume receiving each high dose metric (i.e. rV50-85) followed by Sym scores 3/4. Sym group 5 had the least reduction in rectal dose, which was statistically inferior when compared with Sym scores 1-4 ($P < .001$). For all Sym groups, the mean relative dose reduction at rV50, rV60, rV70, and rV80 was 52.4%, 63.5%, 73.5%, and 71.6%, respectively. The percent mean relative dose reduction for each Sym group is depicted in e-Figure 1 (available as supplementary material online only at www.practicalradonc.org).

In total, 4 patients (2.7%) did not meet a $\geq 25\%$ reduction in rV70Gy based on post- to prespacer DVH. This included 1 patient with Sym score 3 (absolute rV70Gy reduction = 5.1%), 2 patients with Sym score 4 (absolute rV70Gy reduction = -27.6% and -3.2%), and 1 patient with Sym score 5 (absolute rV70Gy reduction = -37.7%). The 2

Table 2 Rates of hydrogel RWI and average rectal wall gel volume

RWI score	No. of patients (%)	Average RW gel volume (mL)
0	140 (94.0)	0.0
1	5 (3.4)	0.1
2	3 (2.0)	0.9
3	1 (0.7)	2.4

RWI, rectal wall infiltration.

Table 3 RWI impact on procedure-related AEs, acute, and late toxicity

(A) Procedural AEs			
RWI	No. of patients (%)	<i>P</i> value ^a	Maximum CTCAE grade
0	14/140 (9.3)	NA	3 ^b
1	1/5 (20) ^c	.43	2
2	0/3 (0.0)	1.00	0
3	0/1 (0.0)	1.00	0
(B) Acute rectal toxicity (0-3 months)			
RWI	Number of patients (%)	<i>P</i> value ^a	Maximum CTCAE grade
0	36/140 (25.7)	NA	2
1	3/5 (60.0)	.12	1
2	1/3 (33.3)	1.00	1
3	0/1 (0.0)	1.00	0
(C) Late rectal toxicity (3-15 mo)			
RWI	No. of patients (%)	<i>P</i> value ^a	Maximum CTCAE grade
0	2/140 (1.4)	NA	1
1	1/5 (20.0)	.10	1
2	0/3 (0.0)	1.00	0
3	0/1 (0.0)	1.00	0

AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; NA, not available; RWI, rectal wall infiltration.

^a Relative to RWI = 0.

^b AE description: urinary track obstruction.

^c Hospitalization resulting from postanesthesia tachycardia.

(1.34%) patients with marked lateral (≥ 2 cm) distribution in all 3 axial slices (Sym score 5) on average still had some rectal dosimetric benefit relative to the prespacer rectal DVH, although the difference between pre- and postspacer plans was not significant ($P > .05$).

Spacer rectal wall infiltration analysis

As shown in Table 2, of the 149 spacer patients evaluated, 140 (94.0%) had no gel within the rectal wall, whereas 5 (3.4%), 3 (2.0%), and 1 (0.7%) had RWI scores of 1, 2, and 3, respectively. The average hydrogel volumes delineated in rectal walls was 0.1, 0.9, and 2.4 mL, for RWI scores of 1, 2, and 3, respectively. Of the 149 spacer treated patients, 15 (10%) had transient adverse events (eg, anorectal pressure, perineal pain) following the spacer application procedure.¹² As seen in Table 3, 14 of those events occurred in patients with no RWI, whereas 1 patient with a urinary tract obstruction was in the RWI 1 group. A total of 36 of the 140 patients with no rectal wall infiltration had acute rectal toxicity (26%, maximum grade 2), compared with 3 of 5 (60%, maximum grade 1), and 1 of 3 (33%, maximum grade 1) of the RWI 1 and RWI 2 patients, respectively. In the entire study, there were only 3 (2.0%) patients with late rectal toxicity through 15 months (all grade 1), 2 of which were in the RWI 0 group and 1 in the RWI 1 group. There were no significant differences between RWI rating and procedure-related events or acute/

late toxicity rates. The only patient with RWI 3 (gel in $\geq 25\%$ rectal wall circumference) experienced no procedure-related event and no acute or late rectal toxicity. For those patients who did not meet a $\geq 25\%$ reduction in rV70Gy (4 patients), only 1 had RWI with a score of 1. Figure 4 shows representative images of patients with the different RWI scores.

Discussion

For patients receiving external beam RT for prostate cancer, the volume of rectum receiving a high dose (ie, ≥ 60 Gy) is consistently associated with the risk of \geq grade 2 rectal toxicity or rectal bleeding, based on CTCAE.¹³ There has been significant interest in methods to reduce the high dose to the anterior rectum, including modern delivery techniques of RT (ie, IMRT or proton therapy) as well as advanced imaging and target localization. One option receiving growing interest has been the use of absorbable balloons and biomaterials placed between the prostate and rectum with the goal of separating these structures and ultimately reducing rectal dose and toxicity.⁵ Some of these biomaterials have included hyaluronic acid, collagen, absorbable balloons, and PEG hydrogels.⁶⁻¹¹ PEG hydrogel is of particular interest given its stability during the course of fractionated RT and its easy visualization on imaging. The recent hydrogel spacer prospective, multicenter, randomized,

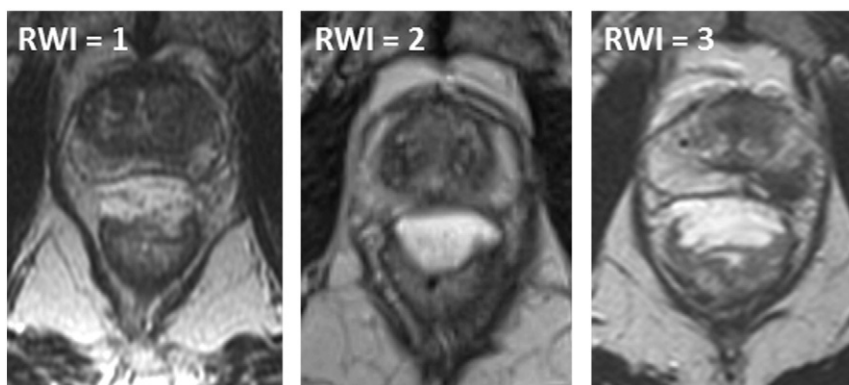


Figure 4 T2-weighted magnetic resonance imaging scans of patients with varying amounts of hydrogel rectal wall infiltration.

controlled trial also showed that physicians placing hydrogels found the procedure to be straightforward and achieved a very high placement success rate.¹⁰ This prior study, however, did not discuss how often the hydrogel was placed asymmetrically or if rectal wall infiltration had occurred. Because PEG hydrogels are injected as liquids that polymerize in situ, there is potential for dosimetrically suboptimal positioning or hydrogel infiltration into the anterior rectal wall; therefore, the rates of suboptimal distribution and RWI, and their effects on rectal dose reduction and clinical outcomes, were investigated in this study.

Although some spacer asymmetry occurs in approximately one-half of all treated patients, all but the most severe asymmetry results in a significant rectal dose reduction. In this analysis, only 2 of 149 (1.3%) patients with ≥ 2 cm lateral distribution at the apex, midglad, and base did not have a statistically significant rectal dose reduction relative to the prespacer plans. Conversely, 98.6% (147 of 149) of treated patients were in the Sym 1 through 4 groups, all of whom had significant rectal dose reductions from rV50 to rV80. There was significant absolute dose reduction in the rV50 and rV60, whereas the higher dose areas had less absolute rectal dose reduction given the lower prespacer high-dose value and therefore less potential for reduction. However, when comparing the mean relative dose reduction, the rV70 and rV80 volumes have superior reduction than the lower doses. This relative reduction in the high-dose region is likely responsible for the decreased patient-reported rectal toxicity, which is consistent with the literature that associates rectal toxicity with the volume of high dose.¹³ In this study, we also found that hydrogel was absent at either the apex and/or base in 68% of patients; however, relative rectal dose reduction of $>25\%$ in both the low- and high-dose volumes was still appreciated in $>95\%$ of cases and is not likely associated with incomplete spacing at these locations.

In the US Pivotal Trial, 2 primary endpoints were defined as¹ a primary effectiveness endpoint investigating the proportion of patients achieving $\geq 25\%$ reduction in the rectal volume receiving at least 70 Gy because of spacer placement and² a primary safety endpoint to determine the

proportion of spacer and control patients experiencing grade 1 or greater or procedural events in the first 6 months following treatment.¹⁰ The study concluded that more than 97.3% of spacer patients experienced a $\geq 25\%$ reduction in rV70 Gy, resulting in attainment of the primary effectiveness endpoint.^{7,10} When correlated with spacer symmetry, the 2.7% (4 patients) that did not achieve a 25% reduction of rV70Gy had Sym scores ranging from 3 to 5 and all patients with Sym scores 1/2 met the primary effectiveness endpoint. This may indicate that, in the scenario of asymmetrical spacer placement (ie, Sym groups 3-5), the likelihood of rV70 reduction of 25% may be less common; however, the greater majority ($>95\%$) of patients with asymmetrical placement still achieved this reduction.

Additionally, some amount of hydrogel RWI occurred in 9 (6.0%) patients, although no correlations were observed between RWI and procedure-related adverse events or with acute or late rectal toxicity. Regarding mechanisms of imperfect distribution, asymmetric hydrogel positioning could be related to anatomical factors such as fibrosis, or more frequently because of the spacer placement learning curve. Pinkawa et al performed 64 consecutive hydrogel spacer applications and demonstrated significantly improved dosimetric benefit in the last 32 patients relative to the first 32; the rectum volume was entirely excluded from the PTV volume in 31% of the first 32 patients compared with 56% of the second 32 patients ($P = .04$).¹⁴ Furthermore, spacer symmetry was improved after the first 15 patients; the latter 49 patients had mean differences between right and left placement at the midglad of 0.6 cm versus 0.3 cm ($P = .03$). Spacer thickness was also improved between the first 15 patients and the following 49 patients.¹⁴

Hydrogel RWI may also be related to the application technique, although this has not been studied to date. Potential mechanisms for hydrogel RWI include direct injection into the rectal wall, as was observed in the hydrogel spacer prospective, nonrandomized, multicenter, single-arm, open-label European clinical trial.¹⁵ Procedural improvements since that time included the use of a side fire transrectal ultrasound probe, stabilizer/stepper,

and hydrodissection in the midgland perirectal fat layer, which have improved hydrogel distribution. Additionally, excess hydrodissection volumes could in theory disrupt the outer rectal wall layers allowing entry of the PEG hydrogel liquid precursors before they polymerize. Reducing the volume of injected spacer could also potentially decrease RWI by minimizing rectal wall stress; the use of stool softeners could also possibly reduce stool-induced stress from bowel contents. One limitation of this study is that spacer placement was supervised by trained professionals and might be more accurate than real-world placement by unsupervised physicians. As with any technical procedure, however, the placement of hydrogels is likely to improve with experience. This study depicts results from physicians in the initial training phase of placing the hydrogels. Additional studies will be needed to better understand the effects of technique for optimal hydrogel symmetry and avoidance of RWI.

Conclusion

As previously demonstrated in the SpaceOAR System pivotal study, hydrogel placement is a safe method to displace the rectal wall away from the prostate in men undergoing IG-IMRT for low- to intermediate-risk prostate cancer.¹⁰ The additional separation between these structures significantly reduced rectal dose, which likely correlates with decreased rectal toxicity. In this study, asymmetry of hydrogel was found to be common; however, all but the most extreme asymmetry still resulted in significant rectal dose reductions. Additionally, rare RWI was observed but was not correlated with patient complications.

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