Update

Absorbable Hydrogel Spacer Use in Prostate Radiotherapy: A Comprehensive Review of Phase 3 Clinical Trial Published Data

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OBJECTIVE

To provide an update on SpaceOAR System, a Food and Drug Administration–approved hydrogel indicated to create distance between the prostate and the rectum which has been studied in phase 2 and 3 clinical trials. Here, we review and summarize these clinical results including the safety of prostate-rectum spacer application technique, the implant quality and resulting rectal dose reduction, acute and long-term rectal, urinary, and sexual toxicity, as well as patient-reported outcomes.

MATERIALS AND METHODS

A prospective, randomized patient-blinded clinical study was performed comparing image-guided intensity modulated prostate radiotherapy (79.2 Gy in 44 fractions) in men with or without prostate-rectum hydrogel spacer. Patients were followed up for 3 years, allowing assessment of long-term safety and efficacy.

RESULTS

Spacer application was well tolerated with a 99% technical success rate. The mean additional space created between the prostate and the rectum was just over 1 cm, which allowed significant rectum and penile bulb radiation dose reduction, resulting in less acute pain, lower rates of late rectal toxicity, and improved bowel and urinary quality of life (QOL) scores from 6 months onward. Improvements in sexual QOL were also observed at 37 months in baseline-potent men, with 37.5% of control and 66.7% of spacer men capable of “erections sufficient for intercourse.”

CONCLUSION

Prostate-rectum hydrogel spacer application is a relatively safe technical procedure that is well tolerated and has a high technical success rate. Spacer application significantly reduces rectal radiation dose and results in long-term reductions in rectal toxicity, as well as improvements in bowel, urinary, and sexual QOL.

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Recent technical improvements such as image-guided intensity modulated radiotherapy (IG-IMRT) have improved prostate radiation delivery accuracy and outcomes. Despite these technological advances, sexual, urinary, and bowel side effects may still occur after IG-IMRT. The rectum, because of its anatomical adjacency to the prostate and function, is considered an organ at risk in prostate radiation therapy and is commonly referred to as a dose-limiting structure.

This anatomic proximity may render compromises between adequate prostate dosing and acceptable radiation side effects. The ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) study demonstrated that, compared with men receiving 78 Gy external beam radiotherapy, men that received a brachytherapy boost (allowing significant further prostate dose escalation) were twice as likely to be free from biochemical failure at 6.5-year median follow-up.¹ However, this prostate dose escalation also increased the cumulative grade 3 rectal toxicity rate from 3.2% to 8.1%.²

The prostate-rectum proximity may also serve as contraindication for prostate radiation therapy in men with...
certain comorbidities such as inflammatory bowel disease, vascular disease, or diabetes. Because radiation dose is cumulative, prostate-rectum proximity typically precludes re-irradiation in men with localized recurrence after previous radiation therapy.

To address the rectum proximity issue, biomedical spacers have been developed to displace the rectum away from the prostate to minimize rectal radiation injury (Fig. 1). Prada et al published the first prostate-rectum spacer results in 2006, in which hyaluronic acid was used to spare the rectum during low-dose rate brachytherapy. Other materials, including autologous blood, absorbable balloons, collagen, and polyethylene glycol (PEG) hydrogels, have also been evaluated. PEG hydrogel (SpaceOAR System, Augmenix, Inc., Bedford, MA) is the only material systematically studied in a randomized, controlled, multicenter clinical trial. We herein review the publications stemming from this study, including the spacer application technique, patient tolerance, dosimetric impact, and the 3-year patient-reported outcomes after dose-escalated prostate radiotherapy.

**MATERIALS AND METHODS**

**Spacer Application Technique**
After bowel and perineal skin prep, patients were placed in lithotomy position and anesthetized with either general anesthesia, conscious sedation, or local anesthesia. For local anesthesia, buffered lidocaine (1%-2%) was injected into the perineal skin, and along the needle track to the prostate and to the potential perirectal space. Using transrectal ultrasound guidance, a 15 cm × 18 G needle was advanced through the perineum into Denonvilliers space (fat tissue posterior to Denonvilliers fascia). Saline was then injected to expand the perirectal space under direct visualization with ultrasound. After confirmation of proper needle location, the PEG hydrogel liquid precursors are injected through the applicator, effectively separating the rectum from the prostate. The injected precursors polymerize within 10 seconds to form a soft hydrogel (Fig. 2). The resulting hydrogel spacer is tissue compatible, impervious to radiation damage, maintains its shape for 3 months during radiotherapy, and then undergoes hydrolysis, liquefaction, and absorption into the bloodstream where it is cleared via renal filtration.

**Phase 3 Clinical Trial**
The protocol and results of this randomized phase 3 trial have been previously reported. However, in brief, after informed consent, 222 men with low-intermediate risk prostate cancer were randomized 2:1 to spacer hydrogel (n = 149):control (n = 73). The study was performed at 20 U.S. centers between 2012 and 2016. Men were blinded to randomization and not told of their allocation as long as they remained on study. At the same time as spacer placement, fiducial markers were placed for image guidance. Anesthesia was administered per investigator discretion with general anesthesia (36.4%), local (31.4%), monitored anesthesia care (25.4%), conscious sedation (5.5%), and other (10.5%).

Within 1 week of the procedure, spacer and control patients underwent computed tomography and magnetic resonance imaging (MRI) for IG-IMRT dose planning utilizing a prescription dose of 79.2 Gy in 44 fractions to the prostate ± seminal vesicles. An independent Core Laboratory ensured strict compliance to dose planning protocols, assessed procedure technical success (postimplant MRI visibility of hydrogel between the posterior prostatic capsule and the anterior rectal wall), and performed all dose and space measurements. All acute (0-3 months) and late (3-37 months) rectal and urinary adverse events were recorded and adjudicated by an independent clinical events committee blinded to treatment arm. Adverse events attributed to radiation were scored as toxicity in accordance with the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0. Additionally, patients completed the Expanded Prostate Cancer Index Composite (EPIC) health-related quality of life (QOL) questionnaire at baseline and at 3, 6, 12, 15, and 37 months. QOL summary scores were assessed in regard to mean changes and changes that met prespecified thresholds for a minimally important difference. For some domains, exploratory analysis of individual items was also undertaken using previously established thresholds.

![Figure 1](image.png)

**Figure 1.** T2-weighted magnetic resonance images of a spacer patient showing hydrogel persistence through completion of radiation therapy (left), and absorption 6 months after implantation (right).
RESULTS
Prophylactic antibiotics were administered in 95% of patients, and nearly equal proportions of patients received general anesthesia, conscious sedation, or local anesthesia. Typically, spacer-randomized patients experienced little or no spacer sensation immediately after placement. However, 10% of spacer patients reported transient grade 1 (n = 6.7%) application procedure-related adverse events (mild hematospermia, anorectal pressure, hematuria, discomfort while sitting, and so on) or grade 2 events (n = 3.3%) requiring medication (mild lower urinary tract symptoms, hypotension, and moderate perianal pain) as adjudicated by the clinical events committee. There were no adverse events attributed to the hydrogel spacer itself.

Two of the 149 spacer patients had no hydrogel present after application (hydrogel injected beyond the prostate in 1 patient, no hydrogel injected in the other due to inadvertent needle penetration of the rectal wall requiring study mandated termination of the procedure), resulting in a 99% technical success rate. The spacer group midgland prostate-rectum space increased from 1.6 ± 2.2 mm (±standard deviation) before implant to 12.6 ± 3.9 mm after implant.

Median rectal V70 dose (percent volume of rectum receiving 70 Gy radiation) was 2.3% vs 10.5% (78% relative reduction, P ≤ 0.0001) in the spacer and control groups, respectively. In addition, significantly less median penile bulb dose was noted in the spacer group (10.8 Gy vs 21.1 Gy, 49% relative reduction, P = .036). No difference in prostate or bladder dose was observed between groups. Importantly, 100% of the dose plans in the spacer group met all QUANTEC rectal planning minimal acceptable dose constraints (V50, V60, V65, V70, and V75) compared with 92% of the plans in the control group.11 The hydrogel spacer was shown to persist through radiation therapy, with complete spacer absorption confirmed at 12 months.

The quality and symmetry of the spacer placement was assessed on MRI.12 Overall, spacer left-right symmetry at base, midgland, and apex was noted in 47.7% of patients, with 50.9% of patients having some level of asymmetry. All but the most asymmetrical of spacer distributions (1.3% or patients) resulted in a statistically significant rectal dose reduction. Some hydrogel spacer infiltration into the rectal wall was noted in 9 patients (6.0%), although there was no correlation between rectal wall infiltration and adverse events or acute or late rectal toxicity.

There was no difference in the rates of acute rectal grade 2 or greater (G2+) toxicity (4.1% vs 4.2%, P = .5) or acute urinary G2+ toxicity (37.8% vs 44.4%, P = .5) in the spacer and control groups, respectively. However, there was a significant reduction in rectal pain adverse events during the acute phase favoring the spacer group (2.7% vs 11.1%, P = .022; Table 1).

Late G1+ rectal toxicity through 37 months favored the spacer arm (2% vs 9%, P < .03), with no spacer men experiencing rectal toxicity greater than G1. There was no difference between groups in regards to late G1+ urinary toxicity, although fewer spacer men experienced G1+ urinary incontinence (4% vs 15%, P = .046).

Radiation therapy–induced declines in bowel QOL were similar between both groups at 3 months; however, from 6 to 37 months, the SpaceOAR group mean bowel QOL returned to near or above baseline, whereas the control mean bowel QOL was significantly lower (P = .002). At 37 months, the mean control bowel QOL score was 5.8 points lower than spacer and was near the 3-month level immediately after radiotherapy. At 37 months, 41% of control and 14% of spacer men were experiencing bowel QOL declines beyond the established threshold for minimally important difference (MID, 5 points for bowel, P = .002).
Similarly, the radiotherapy-induced declines in urinary QOL were similar between both groups through 15 months. At 37 months, the control arm had a 3.9-point decline relative to spacer, which was near baseline. At study end, 30% of control and 17% of spacer men were experiencing MID (6+ points) declines in urinary QOL (P < .05).

Baseline sexual function in the study was low, with only 41% of patients having baseline EPIC sexual scores >60. Of those patients, there was a trend favoring spacer sexual QOL at 37 months (EPIC summary for spacer or 58 vs 45 for control, P = .07), with 53% and 75% (P = .064) of spacer and control patients experiencing a decline of 11 or more points (meeting the threshold of an MID). For those potent at baseline, at 37 months, 37.5% of control and 66.7% of spacer patients had retained “erections sufficient for intercourse” (P = .046).

Overall well-being after radiotherapy was assessed by reviewing the proportion of patients experiencing MID declines in all 3 QOL domains. At 37 months, 2.5% of men in the spacer arm (1 of 40) experienced MID declines in bowel, urinary, and sexual QOL compared with 20% (1 of 5) of men in the control arm.

**DISCUSSION**

The results of this trial indicate that the hydrogel spacer is a safe and efficacious adjunct that can improve QOL outcomes for patients electing radiation therapy for treatment of their prostate cancer. Placement of the spacer was relatively easy for physicians experienced with transrectal or transperineal prostate procedures, whereby the vast majority of implants achieved significant rectal radiation dose reduction.

Although a significant rectal dose reduction is the anticipated result of prostate-rectum spacer placement, reduction to the penile bulb was not. The mechanism behind penile bulb dose reduction is under investigation, but one theory suggests the spacer-facilitated rectum dose reduction allows the dose plan optimization algorithm to better reduce dose to secondary structures, such as the penile bulb. The significance is that the penile bulb dose reduction may explain the also unanticipated improvements in sexual QOL relative to the control group. While the mechanism for the urinary QOL findings is still under investigation, radiation sparing of the erectile or vascular structures around the bulb may account for the sexual QOL findings. Higher penile bulb doses have been found to increase the risk of erectile dysfunction, adding credibility to this theory. The ability to reduce dose in secondary structures when using prostate-rectum spacers is an area of ongoing investigation.

Although patients in the spacer arm demonstrated a lower rate of rectal pain adverse events in the acute phase (first 3 months), a significant reduction in overall rectal toxicity during that same time frame was not observed. One hypothesis is that any spacer acute rectal toxicity benefit may have been masked by toxicity secondary to unintended small bowel or sigmoid colon radiation. Recent evidence has suggested that acute patient reported bowel toxicity is associated with doses between 20 and 40 Gy to these structures.

These structures were not independently contoured on the radiation plans, as such further evaluation of potential differences (or lack thereof) between treatment arms is ongoing. Even though an acute rectal toxicity benefit was not measured, the significant long-term benefits (0% G2+ late rectal toxicity, improved rectal QOL) demonstrate that the spacer deceased injury to the rectum during radiation therapy.

To better appreciate the low toxicity rate related to SpaceOAR-treated patients, recently published 1G-IMRT studies report G2+ late rectal toxicity rates ranging from 14% to 25%. By comparison, none (0%) of the 149 spacer patients in the SpaceOAR randomized controlled clinical trial experienced G2+ late rectal toxicity at 37-month follow-up. This finding further suggests that the PEG hydrogel spacer technology may significantly reduce long-term rectal toxicity, resulting in durable QOL benefits.

**Table 1.** Statistically significant clinical differences resulting from polyethylene glycol (PEG) hydrogel spacer use during prostate radiotherapy: percent difference relative to nonspacer patients and number needed to treat (NNT) with PEG hydrogel spacer to prevent 1 event

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Spacer Arm (%)</th>
<th>Control Arm (%)</th>
<th>P-Value</th>
<th>Difference Relative to Control (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal pain adverse events (0-3 mo)</td>
<td>2.7</td>
<td>11.1</td>
<td>&lt;.022</td>
<td>76</td>
<td>11.9</td>
</tr>
<tr>
<td>Late G1+ rectal toxicity (3-37 mo)</td>
<td>2.0</td>
<td>9.2</td>
<td>&lt;.028</td>
<td>78</td>
<td>13.9</td>
</tr>
<tr>
<td>Late G2+ rectal toxicity (3-37 mo)</td>
<td>0.0</td>
<td>5.7</td>
<td>&lt;.015</td>
<td>100</td>
<td>17.5</td>
</tr>
<tr>
<td>Late G1+ urinary incontinence (3-37 mo)</td>
<td>4</td>
<td>15</td>
<td>&lt;.046</td>
<td>73</td>
<td>9.1</td>
</tr>
<tr>
<td>Percentage of patients experiencing MID declines in bowel QOL (at 37 mo)</td>
<td>14</td>
<td>30</td>
<td>&lt;.05</td>
<td>43</td>
<td>7.7</td>
</tr>
<tr>
<td>Percentage of patients experiencing MID declines in urinary QOL (at 37 mo)</td>
<td>17</td>
<td>30</td>
<td>&lt;.05</td>
<td>43</td>
<td>7.7</td>
</tr>
<tr>
<td>Potent men at baseline retaining erections sufficient for intercourse (at 37 mo)</td>
<td>66.7</td>
<td>37.5</td>
<td>&lt;.046</td>
<td>78</td>
<td>3.4</td>
</tr>
<tr>
<td>Men experiencing MID declines in all 3 QOL domains (bowel, urinary, and sexual) (at 37 mo)</td>
<td>2.5</td>
<td>20.0</td>
<td>&lt;.002</td>
<td>88</td>
<td>5.7</td>
</tr>
</tbody>
</table>

MID, minimally important difference; QOL, quality of life.
The hydrogel spacer used in this study was found to be effective in improving patient-reported outcomes at 37 months. For example, the number of spacer patients needed to treat to prevent 1 patient from experiencing significant MID declines in bowel QOL at 37 months was 3.7 (Table 1). Similarly, the number of spacer patients needed to treat to prevent MID declines in urinary QOL (7.7), erectile dysfunction (3.4), and MID declines in all 3 domains (bowel, urinary, and sexual) was 5.7. These results support the role for spacers which reduce rectal dose during prostate radiotherapy, leading to both short- and long-term patient benefits.

Although this is the first randomized trial, this hydrogel spacer has been evaluated in many other clinical trials. A multicenter pilot study evaluated the ability to safely apply the spacer, its ability to create and maintain space throughout IMRT, reduce radiation dose to the rectum, and its impact on toxicity for 12 months after radiotherapy. In this 52-patient study, the transperineal approach using a stepper-stabilizer mounted side-fire ultrasound probe resulted in safe and effective spacer placement. Prostate-rectum spacer separation was ≥7.5 mm in 95.8% of the patients, resulting in a significant 8.0 Gy reduction in mean rectal dose. The gel was stable during the course of radiotherapy, with absorption confirmed by imaging at 9–12 months. Through 12 months, the rate of late grade 1 GI toxicity was 4.3%, with no late grade 2 + GI toxicity in the study. Pinkawa et al followed 114 patients (54 with spacer, 60 control) for a median of 63 months after prostate IMRT and published 1.5- and 5-year QOL data changes relative to baseline. Increases in mean bowel bother QOL scores (>10 points from baseline) were reported over 5 times more often by control patients at the 1.5-year follow-up (32% vs 6%, P < .01), and hydrogel spacer–treated patients had significantly fewer moderate to big problems with bowel urgency at 1.5 years (0% vs 13%, P < .01) and at 5 years (0 vs 14%, P = .01), relative to control patients. In alignment with the unexpected sexual QOL findings in the randomized clinical trial, the researchers also found that hydrogel spacer patients were significantly more likely to have erections sufficient for intercourse at 5-years post-treatment (24% vs 3% P < .01). te Velde et al evaluated hydrogel spacer impact on prostate IMRT dosimetry and toxicity in a 125-patient trial (65 with spacer, 60 control) and found rectal dosimetry parameters were all significantly lower in the spacer group, with an associated reduction in acute diarrhea (13.8% vs 31.7%, P = .02). In a 140-patient study (30 spacer, 110 control), Whalley et al found that the spacer significantly lowered radiation dose to the rectum, and that at median 28-month follow-up late grade 1 rectal toxicity was significantly less frequent in the hydrogel spacer group (16.6% vs 41.8%, P = .04).

Researchers have also compared hydrogel spacers with other potential spacing concepts. Wolf et al compared the hydrogel spacer with a saline-inflated absorbable balloon. Both spacer products were found to significantly reduce rectum radiation dose immediately after implant, but the balloon exhibited >50% volume loss during EBRT, whereas the hydrogel volume remained fairly constant. This balloon volume loss was recently confirmed by other researchers, where an average volume loss of 70.4% was observed at the end of radiotherapy. Chapet et al evaluated hyaluronic acid as a spacer in a 36-patient phase 2 study. Although the product appeared to be well tolerated and significantly reduced rectum radiation dose, 1 patient developed a hematoma behind the bladder in the hours after spacer injection, requiring laparotomy removal. Hyaluronic acid has also been shown to be degraded by therapeutic levels of radiation, and there are reports of hypersensitivity reactions when used in other indications.

We believe urologists who treat newly diagnosed patients with prostate cancer should become knowledgeable with the potential use of this technology for patients considering prostate radiotherapy. Additionally, beyond mitigating side effects and improving QOL, prostate-rectum spacers may potentially enable the development of radiation protocols investigating hypofractionation or other conventional dose escalation studies, especially in the setting of high-risk prostate cancer. An area not yet fully studied is whether spacers may proffer the safe delivery of radiation therapy in patients with inflammatory bowel disease, vascular disease, diabetes, or those requiring potradiotherapy salvage with either brachytherapy or external beam radiation. Reducing the toxicity of salvage radiotherapy may allow patients with recurrent or residual localized cancer a salvage procedure. Further studies are required to fully investigate these specific high-risk patient populations. Similar hydrogels used as neurosurgical sealants and abdominal adhesion barriers have been shown to prevent fibrosis after surgical procedures. Although it is yet to be demonstrated, if prostate-rectum hydrogel spacers prevent radiotherapy-induced prostate-rectum fibrosis, the potential for salvage prostatectomy after localized cancer recurrence may potentially be optimized.

CONCLUSION

These clinical trial results demonstrate that the prostate-rectum spacer application technique is safe and well tolerated, and that the space created significantly reduces rectal injury during radiation therapy, leading to long-term clinical benefits. We believe that urologists treating newly diagnosed patients with prostate cancer appropriate for radiation therapy are well suited to perform this spacing procedure. A clinically significant reduction in radiation therapy complication rates should lead to improved patient outcomes, reduced toxicity concerns, and hopefully overall cost reductions.

References
