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Clinical Investigation

Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy

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Summary

Prostate radiation therapy rectal toxicity is largely due to the prostate-rectum proximity. A randomized, controlled, multicenter study of an absorbable polyethylene glycol hydrogel perirectal spacer (SpaceOAR System) used in men undergoing image guided prostate intensity modulated radiation therapy was performed. Spacer safety and effectiveness in consistent perirectal space creation and reduction of rectal irradiation was demonstrated. Spacer use was associated with low toxicity rates and a reduction in patients experiencing declines in bowel and urinary quality of life.

Purpose: Perirectal spacing, whereby biomaterials are placed between the prostate and rectum, shows promise in reducing rectal dose during prostate cancer radiation therapy. A prospective multicenter randomized controlled pivotal trial was performed to assess outcomes following absorbable spacer (SpaceOAR system) implantation.

Methods and Materials: Overall, 222 patients with clinical stage T1 or T2 prostate cancer underwent computed tomography (CT) and magnetic resonance imaging (MRI) scans for treatment planning, followed with fiducial marker placement, and were randomized to receive spacer injection or no injection (control). Patients received postprocedure CT and MRI planning scans and underwent image guided intensity modulated radiation therapy (79.2 Gy in 1.8-Gy fractions). Spacer safety and impact on rectal irradiation, toxicity, and quality of life were assessed throughout 15 months.

Results: Spacer application was rated as "easy" or "very easy" 98.7% of the time, with a 99% hydrogel placement success rate. Perirectal spaces were 12.6 ± 3.9 mm and 1.6 ± 2.0 mm in the spacer and control groups, respectively. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either group. Pre-to postspacer plans had a significant reduction in mean rectal V70 (12.4% to 3.3%, $P<.0001$). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain ($P=.02$). A significant reduction in late (3-15 months) rectal toxicity severity in the spacer group was observed ($P=.04$), with a 2.0% and 7.0% late rectal toxicity incidence in the spacer and control groups, respectively. There was no late rectal toxicity greater than grade 1 in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel quality of life. MRI scans at 12 months verified spacer absorption.

Conclusions: Spacer application was well tolerated. Increased perirectal space reduced rectal irradiation, reduced rectal toxicity severity, and decreased rates of patients experiencing declines in bowel quality of life. The spacer appears to be an effective tool, potentially enabling advanced prostate RT protocols.

Introduction

Radiation therapy (RT) is a well-established and widely used treatment modality for prostate cancer, endorsed by national guidelines (1), but implementation of hypofractionation, dose escalation, and salvage RT protocols is limited by the risk of rectal toxicity (2-4). As prostate-rectum proximity contributes to this toxicity, there is growing interest in perirectal spacing, whereby biomaterials are used to push the rectum away from the prostate to reduce rectal radiation exposure (5). A safe, well-tolerated, and effective means of perirectal spacing may enable dose escalation or hypofractionation protocols.

Several injectable agents including hyaluronic acid, collagen, and polyethylene glycol hydrogels, along with an implantable absorbable balloon have been evaluated as spacing materials with encouraging results (6). Pilot studies have demonstrated ease of spacer application, patient tolerance, consistent rectal dose reduction, and good clinical outcomes (7-10).

The most widely studied of these materials is a novel polyethylene glycol hydrogel that expands the perirectal space as an injected liquid and then polymerizes (solidifies) into a soft, absorbable spacer (SpaceOAR system; Augmenix, Waltham, MA). The hydrogel spacer has been shown to be stable throughout the typical course of radiation therapy (11), resulting in a significant decrease in rectal irradiation (12) and encouraging acute and late outcomes (11).

This report describes the first prospective randomized pivotal trial of a prostate-rectum spacer, investigating the safety and effectiveness of this hydrogel in men undergoing prostate image guided intensity modulated RT (IG-IMRT).

Methods and Materials

Setting and patients

A multicenter randomized, controlled pivotal trial of the hydrogel spacer was approved by the Institutional Review Boards of each of the 20 participating centers under US Food and Drug Administration-approved investigational device exemption. All patients provided written informed consent.

Men with stage T1 or T2 prostate cancer, a Gleason score of $\leq$7, a prostate-specific antigen (PSA) concentration of $\leq$20 ng/mL, and a Zubrod performance status 0 to 1, who were planning to undergo IG-IMRT were potential study candidates. Exclusion criteria included a prostate volume of $>$80 cm^3, extracapsular extension of disease or $>$50% positive biopsy cores, metastatic disease, indicated or recent androgen deprivation therapy, and prior prostate surgery or RT.

Study design

Two primary endpoints were defined. The primary effectiveness endpoint was the proportion of patients achieving $>$25% reduction in rectal volume receiving at least 70 Gy (rV70) due to spacer placement. The 25% reduction was deemed clinically relevant as it approximates the reduction achieved when progressing from 3-dimensional conformal RT to IMRT (13), and rV70 was selected due to published correlations with the risk of late gastrointestinal toxicity (14,15). The primary safety endpoint was the proportion of spacer and control patients experiencing grade 1 or greater rectal or procedural adverse events (AEs) in the first 6 months.

Patients underwent a physical examination, including collection of medical and surgical history, baseline concomitant medications, and a computed tomography (CT) scan and magnetic resonance imaging (MRI) for baseline IG-IMRT treatment planning. Using an aseptic transperineal technique, we placed at least 3 gold intraprostate fiducial markers, and patients were immediately randomized (envelope opened) to receive transperineal injection of spacer (16) or no injection as a control. Patients were blinded to randomization. Five to 10 days later, patients underwent a second CT and MRI for postprocedural IG-IMRT treatment planning.

Clinical target volumes (CTVs) included prostate with or without inclusion of the proximal seminal vesicles (physician's discretion). The planning methodology for baseline and postprocedural plans was the same. The prescription dose was 79.2 Gy at 1.8 Gy per fraction, delivered to $\geq$98% of the planning target volume (PTV) and 100% of the CTV, with the CTV maximum of $\leq$110% of the prescription dose. PTV margins were institutionally determined within protocol-defined limits of 5 to 10 mm, and normal rectal dose constraint objectives for 15%, 20%, 25%, 35%, and 50% of the rectal volume were $<$75 Gy, $<$70 Gy, $<$65 Gy, $<$60 Gy, and $<$50 Gy, respectively, per quantitative analysis of normal tissue effects in the clinic (QUANTEC) guidelines (17). All IG-IMRT planning documentation and CT and MRI scans were forwarded to a blinded, independent core laboratory (JM, HG, WB) for verification of GTV, CTV, PTV, and critical normal structures (rectum, bladder, penile bulb) contours and dose-volume histograms. The core laboratory verified all dosimetric study data, measured the perirectal spaces (distance between the posterior prostatic capsule and anterior rectal wall on axial mid-gland T2-weighted MRIs) at baseline and at 3 months, evaluated patients for hydrogel placement success (hydrogel present in the perirectal space), and assessed gel absorption using the 12-month MRI (Fig. 1).

Patients were evaluated at baseline, weekly during IG-IMRT, and at 3-, 6-, 12-, and 15-month follow-up visits for rectal and other AEs and for changes in medications used to treat urinary or rectal symptoms. All AEs were recorded, and adjudication of event type, severity, event cascading, and relatedness to device, procedure, radiation or other was performed by an independent Clinical Events Committee (CEC), blinded to treatment randomization. Rectal and urinary AEs attributed by the CEC to radiation were included for toxicity analysis according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, when not attributed to diet, medication, or medical history.

At baseline and 3, 6, 12, and 15 months, patients completed the Expanded Prostate Cancer Index Composite health-related quality of life (QOL) questionnaire. QOL data were analyzed to determine the mean change in QOL score from baseline to 15 months. In addition, the proportion of patients experiencing declines in bowel and urinary QOL from baseline was evaluated using previously determined 5- and 10-point thresholds for minimal clinically detectable QOL changes (18).

Statistical analysis

The accrual goal for this study was 222 patients (randomized spacer-to-control ratio of 2:1). For these sample sizes, the power of the test for the primary effectiveness endpoint, that at least 70% of the spacer patients would achieve a $\geq$25% reduction in rV70 was 99.4%. The power of the test for the primary safety endpoint, assuming endpoint event rates of 60% and 40% for the control and spacer groups, respectively, was 80.8%. The overall probability that both null hypotheses would be rejected was at least 80.2%.

Group demographic and cancer differences were determined using the two-sample t test for continuous variables and the Fisher exact test for categorical data. The exact binomial test was used to compare the proportion of spacer patients experiencing a $\geq$25% rV70 dose reduction, whereas the Cochran-Mantel-Haenszel test was used to

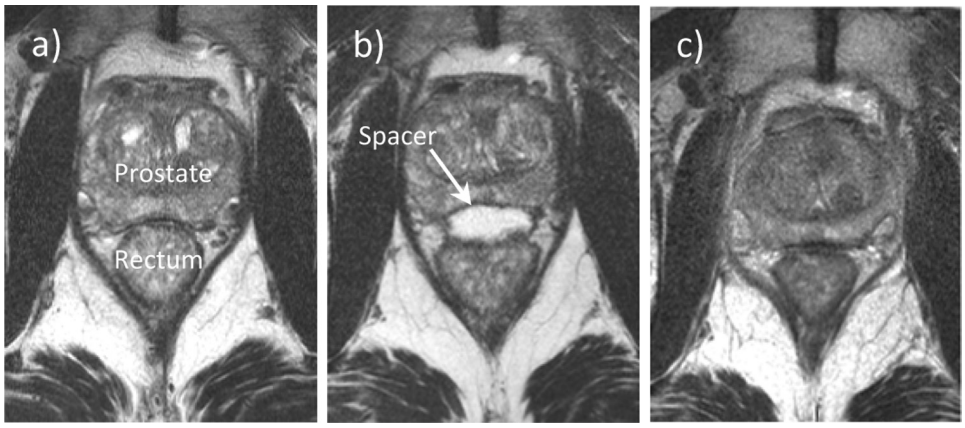

Fig. 1. T2-weighted magnetic resonance images of a spacer patient at baseline (a), post-application (b), and 12 months after spacer application (c).

compare toxicity severity. Differences in spacer and control patients experiencing declines in QOL were determined using the χ^2 test. Statistical analysis was performed using SAS version 9.1.3 software. All statistical tests were performed at a significance level of .05.

Results

Between January 2012 and April 2013, 149 and 73 patients were randomized to the spacer and control groups, respectively. Strict protocol adherence resulted in 219 of 222 (98.5%) patient follow-up through completion of study at 15 months. There were no differences between groups in regard to medical comorbidities, demographics, or baseline tumor characteristics, as detailed in Table 1.

In the study, antibiotic prophylaxis was administered prior to fiducial or fiducial and spacer procedure 95% of the time, whereas forms of anesthesia and sedation included general (36.4%), local (31.4%), monitored anesthesia care (25.5%), conscious sedation (5.5%), and other (10.5%). Both the radiation oncologists and urologists who applied the spacer rated the device's ease of use as "easy" or "very easy" 98.7% of the time. The hydrogel placement success in the spacer group was 98.7%.

The mean perirectal distance in the spacer group was 1.6 ± 2.2 mm, 12.6 ± 3.9 mm, and 9.0 ± 5.9 mm at baseline, postspacer application, and at 3 months (±1 week), respectively. Hydrogel absorption was evident during the 3-month imaging, with the mean space in patients imaged the week prior to their 3-month date being 10.9 ± 5.8 mm, compared to 6.8 ± 5.4 mm for those imaged the week after. T2-weighted MRI at 12 months confirmed spacer absorption, with 3 (2%) of the spacer patients exhibiting small, simple water density remnant cysts in otherwise unremarkable perirectal tissues.

The core laboratory-measured spacer group rectal dose reduction (Table 2), calculated by comparing the baseline to postprocedure rectal DVH, was statistically significant ($P<.0001$) from rV50 through rV80. The mean spacer and control group rV70s at baseline were 12.4% and 12.4% ($P=.95$), respectively, and in the postprocedure treatment plans were 3.3% and 11.7% ($P<.0001$), respectively. Overall, 97.3% of spacer patients experienced a ≥25% reduction in rV70, resulting in attainment of the primary effectiveness endpoint. Additionally, 100% and 92% of spacer and control patient plans met all rectal dose constraints, respectively.

Table 1 Mean data for demographics and pretreatment prostate cancer history

Attribute	Spacer group	Control group	*P* value
Age (y)	66.4	67.7	.217
% racial distribution			
White	85.2	83.6	.843
African American	10.7	11.0	1.000
Asian	1.3	2.7	.600
Other	2.8	2.7	1.000
Weight (kg)	88.8	90.1	.551
Height (cm)	176.1	176.3	.817
BMI (kg/m^2)	28.6	29.0	.608
% with smoking history			.931
Current smoker	8.1	9.6	
Past smoker	51.7	50.7	
Never smoked	40.3	39.7	
Prostate volume (mL)	47.3	49.6	.286
Number of biopsy cores	12.6	12.3	.369
% of positive biopsy cores	23.1	23.0	.942
% with combined Gleason score of:			.059
6	64.4	50.7	
7	35.6	49.3	
% with T stages shown			.549
T1 (T1, T1a, T1b, T1c)	63.8	68.5	
T2 (T2, T2a, T2b, T2c)	36.2	31.5	
Pretreatment PSA (ng/mL)	5.6	5.7	.813
Palpable tumor (%)	23.0	24.7	.537

Abbreviations: BMI = body mass index; PSA = prostate-specific antigen.

Table 2 Mean ± SD spacer group rectal dose volume histogram data comparing baseline to post-spacer dose plans*

Parameter	rV50	rV60	rV70	rV80
% before spacer	25.7 ± 11.1	18.4 ± 7.7	12.4 ± 5.4	4.6 ± 3.1
% after spacer	12.2 ± 8.7	6.8 ± 5.5	3.3 ± 3.2	0.6 ± 0.9
% of absolute reduction	13.442	11.563	9.078	3.933
% of relative reduction	52.3	62.9	73.3	86.3
P value	<.0001	<.0001	<.0001	<.0001

Abbreviation: rV = reduction in rectal volume dose of, eg, 50 Gy.
* Also listed are absolute percentage of reductions and relative reductions of dose volume histogram means.

Spacer application did not increase the dose in neighboring tissues, with the mean pre- and postapplication spacer group bladder V70 being 11.3% and 11.0%. The mean penile bulb dose was less in the spacer group (18.0 Gy) than in the control group (22.8 Gy, $P=.036$).

Regarding the primary safety endpoint, the rates of grade 1 or greater rectal or procedure AEs in the first 6 months were 34.2% and 31.5% in the spacer and control groups ($P=.7$), respectively. Mild transient procedural AEs (perineal discomfort and others) were noted in 10% of the spacer patients, contributing to this overall rate. Aside from a reduction in the rate of patients with acute rectal pain AEs during RT (spacer: 2.7%; control: 11.1%, $P=.022$), differences in all other rectal or urinary acute AEs were not statistically significant.

As with AEs in the first 6 months, no differences in acute rectal or urinary toxicity in the first 3 months were observed (Table 3). Late rectal toxicity (3-15 months) was observed in 2.0% of the spacer patients (1 grade 1 rectal bleeding, 1 grade 1 rectal urgency, and 1 grade 1 proctitis) and 7.0% of the control patients (3 grade 1 rectal bleeding, 1 grade 1 rectal urgency, and 1 grade 3 proctitis). The spacer group reduction in late rectal toxicity severity was statistically significant ($P=.044$), with no spacer patients experiencing grade >1 late rectal toxicity.

Mean changes in bowel and urinary QOL domains for both the spacer (−7.5 and −11.5) and the control groups (−6.2 and −11.2), respectively, at 3 months were small relative to those cited in published reports, with no statistical significance between groups and a return to near baseline QOL at 6 months. However, an appreciable percentage of patients experienced persistent declines in bowel QOL from baseline after 3 months. At 3 months, a similar percentage of spacer and control patients experienced 5- and 10-point declines in bowel QOL (Fig. 2). At 6, 12, and 15 months, a lower proportion of spacer patients reported declines in bowel QOL relative to those of control, with 11.6% and 21.4% of spacer and control patients, respectively, experiencing 10-point declines at 15 months ($P=.087$). Additionally, at 6 months, 8.8% and 22.2% of spacer and control patients, respectively, had 10-point urinary declines ($P=.003$). At 12 and 15 months, the declines in urinary QOL were similar for both groups.

Overall, the rates of AEs and serious AEs for the spacer (96.6% and 13.4%, respectively) and control (100% and 15.1%, respectively) groups were not significantly different. The CEC blinded adjudication of all recorded AEs found no spacer-related AEs. The proportion of patients requiring at least 1 medication change for mitigation of rectal or urinary symptoms in the first 6 months was 56.4% and 63.9% for spacer and control groups, respectively ($P=.3102$). There were no differences in PSA values of the spacer and control groups at 12 months (1.257 ng/mL and 1.309 ng/mL, $P=.968$, respectively) and 15 months (1.135 ng/mL and 1.073 ng/mL, respectively, $P=.787$). No subjects experienced a delay in RT associated with a procedure or device-related AE. There were no rectal perforations, serious rectal bleeding, or rectal infections in either group.

Table 3 Acute and Late rectal and urinary toxicity*

	Acute toxicity (from procedure through 3-month visit)					
	Rectal toxicity scores (%)			Urinary toxicity scores (%)		
Grade	Spacer (n=148)	Control (n=72)	*P* value	Spacer (n=148)	Control (n=72)	*P* value
0	108 (73.0%)	49 (68.0%)	.525	14 (9.5%)	7 (9.7%)	.488
1	34 (23.0%)	20 (27.8%)		78 (52.7%)	33 (45.8%)	
>2	6 (4.1%)†	3 (4.2%)‡		56 (37.8%)†	32 (44.4%)†	
Grade	Late toxicity (between the third and 15th month visits)					
	Spacer (n=148)	Control (n=71)	*P* value	Spacer (n=148)	Control (n=71)	*P* value
0	145 (98.0%)	66 (93.0%)	.044	134 (90.5%)	65 (91.5%)	.622
1	3 (2.0%)	4 (5.6%)		4 (2.7%)	3 (4.2%)	
>2	0 (0.0%)	1 (1.4%)‡		10 (6.8%)†	3 (4.2%)†	

* According to Common Terminology Criteria for Adverse Events scoring of adverse events attributed to radiation.
† No grade 3 or 4 toxicity reported.
‡ One grade 3 case; no grade 4 reported.

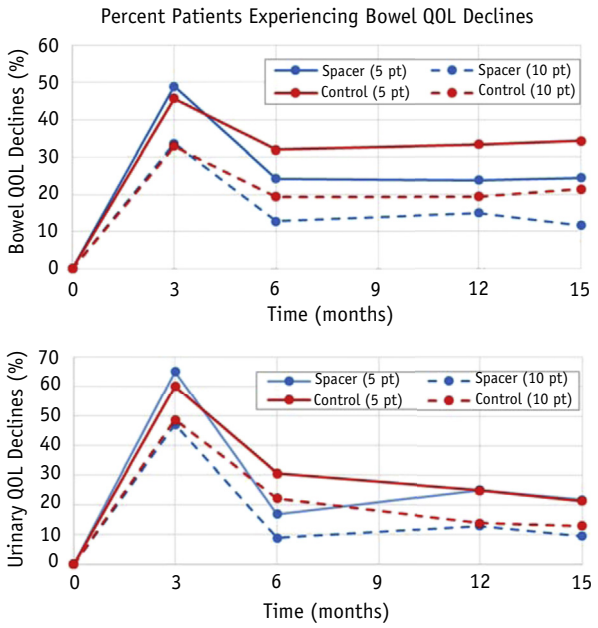

Fig. 2. Percentage of patients with 5- and 10-point declines in bowel (top) and urinary (bottom) quality of life (QOL).

Discussion

Spacer appliers found the procedure to be straightforward, with a high hydrogel placement success rate. Application resulted in an average of 12.6 mm of perirectal space. Hydrogel remained in place for 3 months, with absorption confirmed at 12 months.

Hydrogel application significantly reduced rectal irradiation from rV50 to rV80 relative to both the control and prespacer plans. Additionally, dose reduction was consistent, with 97.3% of spacer patients achieving ≥25% reduction in rV70. Spacer application did not result in higher dose elsewhere, as seen in bladder dosimetry. Finally, achievement of rectal dose constraints appeared easier in the spacer group, with 100% of patients meeting all constraints.

Even though the spacer group did not have fewer rectal or procedural AEs than the control group in the first 6 months, the similar AE rate demonstrates that spacer use does not create new safety issues. The statistically significant reduction in acute rectal pain AEs in spacer patients is supported by a bowel domain QOL question on rectal pain (painful stools half or more of the time) at 6 months (0% and 5.6%, $P<.05$) and 12 months (0% and 4.2%, $P<.05$) for the spacer and control groups, respectively.

Late rectal toxicity in the spacer group was significantly less severe than in the control group ($P=.044$), with no spacer patients experiencing grade >1 late rectal toxicity. Of note, this is the second clinical evaluation of this spacer product showing no late rectal toxicity grade >1. Also of interest is the low control group toxicity rate (11). The most likely explanations for the low control toxicity rate include uniform IGRT use and core laboratory review and approval of treatment plans. Arguably, this study-mandated forced precision planning led to low toxicity in the control group relative to that in standard practice.

Compared to previous studies, the decline in bowel and urinary QOL in both groups was very modest. Although the time points are not the same, the PROSTQA study (external beam RT, 75-79.2 Gy in 1.8- to 2.0-Gy fractions) comparison is most relevant (19). At 2 and 24 months, the PROSTQA study reported QOL changes (bowel: −16.0%, −7.0%; urinary: −12.2%, 0.2%), compared to declines at 3 and 15 months for the spacer group (bowel: −7.5% and 0.02%; urinary: −11.5% and −1.9%) and control (bowel: −6.2%, −2.1%; urinary: −11.2%, −2.5%), respectively.

Similar proportions of spacer and control group patients experienced 5- and 10-point declines from baseline in bowel and urinary QOL at 3 months. At 6, 12, and 15 months, the spacer group had a lower percentage of patients with declines in bowel QOL, in agreement with the decreased late rectal toxicity data. The reason why fewer spacer patients had declines in urinary QOL at 6 months is unknown.

Conclusions

Overall safety of the spacer seemed to be excellent, with no device-related AEs and no rectal infections, rectal complications, and other AEs. Creation of perirectal space was consistent in spacer randomized patients, with a high hydrogel placement success rate and resulting in a clinically significant reduction in rectal irradiation in almost all patients. The low spacer group late toxicity and favorable bowel QOL results are expected outcomes from reduced rectal irradiation.

The short follow-up period is a study limitation, as researchers have published the median time to late gastrointestinal grade >2 toxicity onset was 17 months (20). The study was also limited by the exclusion of patients with prostate volumes >80 mL, patients with extracapsular extension, and those with prior radiation or surgery. Patients with extracapsular extension have the theoretical risk of pushing posterior extracapsular disease farther from the prostate during RT, whereas patients with prior radiation or surgery may have perirectal scar formation, limiting space creation. Use of spacers in these populations should proceed cautiously in separate clinical trials.

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