

Clinical Investigation

Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial



Daniel A. Hamstra, MD, PhD,^{*} Neil Mariados, MD,[†] John Sylvester, MD,[‡] Dhiren Shah, MD,[§] Lawrence Karsh, MD,^{||} Richard Hudes, MD,[¶] David Beyer, MD,[#] Steven Kurtzman, MD,^{**} Jeffrey Bogart, MD,^{††} R. Alex Hsi, MD,^{‡‡} Michael Kos, MD,^{§§} Rodney Ellis, MD,^{|||} Mark Logsdon, MD,^{¶¶} Shawn Zimberg, MD,^{##} Kevin Forsythe, MD,^{***} Hong Zhang, MD, PhD,^{†††} Edward Soffen, MD,^{‡‡‡} Patrick Francke, MD,^{§§§} Constantine Mantz, MD,^{||||} Peter Rossi, MD,^{¶¶¶} Theodore DeWeese, MD,^{###} Stephanie Daignault-Newton, MS,^{****} Benjamin W. Fischer-Valuck, MD,^{††††} Anupama Chundury, MD,^{††††} Hiram Gay, MD,^{††††} Walter Bosch, DSc,^{††††} and Jeff Michalski, MD, MBA^{††††}

Texas Oncology, Texas Center for Proton Therapy, Irving, Texas; †Associated Medical Professionals of NY, PLLC, Syracuse, New York; ‡21st Century Oncology, Inc, Lakewood Ranch, East Bradenton, Florida; §Western New York Urology Associates, LLC, Doing Business as Cancer Care of WNY, Cheektowaga, New York; ||The Urology Center of Colorado, Denver, Colorado; ¶Chesapeake Urology Associates, Doing Business as Chesapeake Urology Research Associates (The Prostate Center), Owings Mills, Maryland; #Arizona Oncology Services Foundation, Phoenix, Arizona; **Urological Surgeons of Northern California Inc, Campbell, California; ††The Research Foundation of State University of New York/State University of New York Upstate Medical University, Syracuse, New York; ‡‡Peninsula Cancer Center, Poughkeepsie, New York; §§Urology Nevada, Reno, Nevada; |||University Hospitals Case Medical Center, Cleveland, Ohio; ¶¶Sutter Health Sacramento Sierra Region, Doing Business as Sutter Institute for Medical Research, Sacramento, California; ##Advanced Radiation Centers of New York, Lake Success, New York; *Oregon Urology Institute, Springfield, Oregon; †††University of Rochester, Rochester, New York; ‡‡‡CentraState Medical Center, Freehold, New Jersey; §§§Carolina Regional Cancer Center, LLC, 21st Century Oncology, Inc, Myrtle Beach, South Carolina; |||| 21st Century Oncology, Inc, Fort Meyers, Florida; ¶¶¶Emory University, Atlanta, Georgia; ###The Johns Hopkins University, Baltimore, Maryland; ****Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; and ††††Washington University School of Medicine, St Louis, Missouri*

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Reprint requests to: Daniel A. Hamstra, MD, PhD, Texas Oncology, Texas Center for Proton Therapy, 1501 W Royal Ln, Irving, TX 75063. Tel: (469) 513-5595; E-mail: Daniel.Hamstra@gmail.com

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and Ms Daignault-Newton have provided consulting services for Augmenix.

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Summary

A phase III trial was performed using an absorbable hydrogel (SpaceOAR System) to provide space between the prostate and rectum for men undergoing dose-escalated prostate radiation therapy. At 3 years, the men in the spacer arm had decreased bowel toxicity and fewer declines in both urinary and bowel quality of life compared with the control group.

Purpose: SpaceOAR, a Food and Drug Administration–approved hydrogel intended to create a rectal–prostate space, was evaluated in a single-blind phase III trial of image guided intensity modulated radiation therapy. A total of 222 men were randomized 2:1 to the spacer or control group and received 79.2 Gy in 1.8-Gy fractions to the prostate with or without the seminal vesicles. The present study reports the final results with a median follow-up period of 3 years.

Methods and Materials: Cumulative (Common Terminology Criteria for Adverse Events, version 4.0) toxicity was evaluated using the log-rank test. Quality of life (QOL) was examined using the Expanded Prostate Cancer Index Composite (EPIC), and the mean changes from baseline in the EPIC domains were tested using repeated measures models. The proportions of men with minimally important differences (MIDs) in each domain were tested using repeated measures logistic models with pre-specified thresholds.

Results: The 3-year incidence of grade ≥ 1 (9.2% vs 2.0%; $P = .028$) and grade ≥ 2 (5.7% vs 0%; $P = .012$) rectal toxicity favored the spacer arm. Grade ≥ 1 urinary incontinence was also lower in the spacer arm (15% vs 4%; $P = .046$), with no difference in grade ≥ 2 urinary toxicity (7% vs 7%; $P = 0.7$). From 6 months onward, bowel QOL consistently favored the spacer group ($P = .002$), with the difference at 3 years (5.8 points; $P < .05$) meeting the threshold for a MID. The control group had a 3.9-point greater decline in urinary QOL compared with the spacer group at 3 years ($P < .05$), but the difference did not meet the MID threshold. At 3 years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; $P = .002$) and urinary QOL (30% vs 17%; $P = .04$). Furthermore, the control group were also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; $P = .02$) and urinary QOL (23% vs 8%; $P = .02$).

Conclusions: The benefit of a hydrogel spacer in reducing the rectal dose, toxicity, and QOL declines after image guided intensity modulated radiation therapy for prostate cancer was maintained or increased with a longer follow-up period, providing stronger evidence for the benefit of hydrogel spacer use in prostate radiation therapy. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

External beam radiation therapy (RT) is used to treat men with prostate cancer and results in outcomes similar to those with surgery for patients with low- or intermediate-risk disease (1) and improved survival when added to androgen deprivation therapy (ADT) for high-risk disease (2, 3). Dose escalation improves the outcomes but increases the risk of urinary and bowel toxicity (4). Both image guided RT (IGRT) (5-7) and intensity modulated RT (IMRT) (8) have been used to limit margins and conform the high-dose radiation volume to limit toxicity. Nevertheless, because the rectum and prostate are often in physical contact, the ability of IGRT and IMRT to spare the rectum has been limited.

The SpaceOAR System (Augmenix, Inc, Waltham, MA) is the only Food and Drug Administration–approved absorbable hydrogel that can be introduced between the prostate and rectum to decrease toxicity and minimize the changes in quality of life (QOL) after prostate RT. The 15-month follow-up data from the SpaceOAR phase III trial were previously reported. The results showed that >97% of men had a clinically significant 25% relative reduction in the rectal V70, with a reduction

in rectal toxicity and improvements in bowel QOL (9). The present study reports the updated results with a median follow-up period of 37 months.

Methods and Materials

Patient population and treatment

The details of the phase III study were previously reported (10, 11). Men with National Comprehensive Cancer Network–determined low- or intermediate-risk prostate cancer and a Zubrod performance status of 0 to 1 were enrolled in a multi-institutional institutional review board–approved single-blind phase III trial (ClinicalTrials.gov identifier NCT01538628). The exclusion criteria included prostate volume ≥ 80 cm³, extraprostatic extension, >50% positive biopsy cores, previous or planned use of ADT, and/or previous treatment of prostate cancer. The patients were randomized 2:1 to the spacer or control group, with all men receiving fiducial markers for IGRT. The patients were unaware of the treatment allocation and had the fiducial

markers or markers plus the hydrogel spacer placed without knowing to which treatment they had been randomized.

Magnetic resonance imaging–based planning was used, with the postfiducial marker computed tomography scan fused with the magnetic resonance imaging scan. The use of intravenous, oral, or bladder/urethral contrast were at the discretion of the investigators. The radiation plans were evaluated by an independent core laboratory before treatment for compliance to the protocol guidelines and determination of the dosimetric endpoints (H.G., W.B., J.M.).

The clinical target volume was the prostate with or without the seminal vesicles at the physician's discretion. A planning target volume (PTV) margin of 5 to 10 mm was used. The radiation dose was 79.2 Gy in 1.8-Gy daily fractions, delivered 5 days weekly.

Data collection and follow-up protocol

The men were followed up weekly during treatment and at 3, 6, 12, and 15 months after enrollment. The primary endpoint was reported at 15 months (10). Extended follow-up data at 3 years were recorded, with local institutional review board approval to gather Expanded Prostate Cancer Index (EPIC) data, prostate-specific antigen, medical and surgical history, rectal and urinary adverse events, and medication changes since the 15-month visit. Participation in this extended follow-up protocol was voluntary, with each institution choosing whether they would participate. Rectal and urinary adverse events were adjudicated by an independent clinical events committee that was unaware of the treatment arm according to the event type, severity, and relatedness to radiation or other factors. Adverse events attributed to radiation were included for toxicity analysis in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The toxicity events from enrollment through 3 months of follow-up were classified as acute, and those occurring after 3 months were classified as late. The cumulative incidence of late toxicity was evaluated using the log-rank test and Kaplan-Meier analysis by randomization arm.

For the QOL analysis, the mean changes in the EPIC summary scores from baseline were evaluated in linear mixed models with the fixed effects of randomized treatment, questionnaire completion date, and baseline score. The interaction of randomized treatment and questionnaire completion date and repeated measures within patient groups were accounted for using an autoregressive correlation structure. Pairwise testing was done within the modeling framework. Minimally important differences (MIDs) in the EPIC summary scores were evaluated according to previously published thresholds: bowel (5 points), urinary (6 points), sexual (11 points), and vitality/hormonal (5 points) (12). In addition, a second preplanned cutpoint was

evaluated twice at each of these thresholds. Each binary MID variable was modeled using a General Estimating Equation model with a logit link to account for the repeated surveys for each patient over time and the independent effects of randomized treatment, questionnaire completion date, baseline domain score, and the interaction of randomized treatment and questionnaire completion date. Analysis was performed in SAS, version 9.4 (SAS Institute, Cary, NC).

Biochemical failure was defined using the Phoenix definition (nadir plus 2 ng/mL) (13).

Results

From January 2012 to April 2013, 222 eligible men from 20 participating institutions were enrolled and randomized to the control ($n=73$) or spacer ($n=149$) arm. No differences were found in the demographic data between the 2 arms (Table E1; available online at www.redjournal.org). The primary endpoints were reported at a minimum follow-up point of 15 months, when 97% of the control group and 99% of the spacer group were evaluable. Extended follow-up was continued through April 2016, when 63% of both control ($n=46$) and spacer ($n=94$) patients were evaluable. No difference was found in the median follow-up period between the 2 treatment arms in the extended study (control: median 37.0 months, range 26–46; spacer: median 37.1 months, range 32–47; $P>.5$; Fig. E1; available online at www.redjournal.org).

Dosimetry

Compared with the control arm, those with the hydrogel (spacer arm) had a smaller volume of rectum treated to all volumes from V50 to V80 ($P<.0001$ for all; Fig. 1A). For V50, a 54% relative reduction was found (21% vs 10% for control vs spacer), with increasing relative reductions at higher doses. These included a 79% relative reduction in V70 (10% vs 2% for control vs spacer) and a 96% reduction in the V80 (4% vs 0.1% for control vs spacer). No differences were found in the dosimetry values for the bladder, bladder wall, or bladder/bladder wall within 1 or 2 cm of the prostate ($P>.1$ for all). In addition, no differences were found in the hot spots in the PTV (>79.2 Gy; $P>.1$). The dose to the penile bulb was significantly reduced in the spacer arm for the mean, median, maximum dose, and doses from V10 to V30 (Fig. 1B).

Toxicity

Grade ≥ 1 rectal toxicity at 3 years of follow-up was decreased by 75% in the spacer arm (control: 9%, 95% confidence interval [CI] 4%–20%; spacer: 2%, 95% CI 1%–6%; $P<.03$; hazard ratio 0.24, 95% CI 0.06–0.97), and no grade ≥ 2 rectal toxicity was observed in the spacer arm (3-year rate: control, 6%, 95% CI 2%–17%; spacer 0%; $P<.015$; Figs. 2A and 2B). One case of grade 3 rectal toxicity developed in the control arm. A reduction was also seen in cumulative grade ≥ 1 urinary

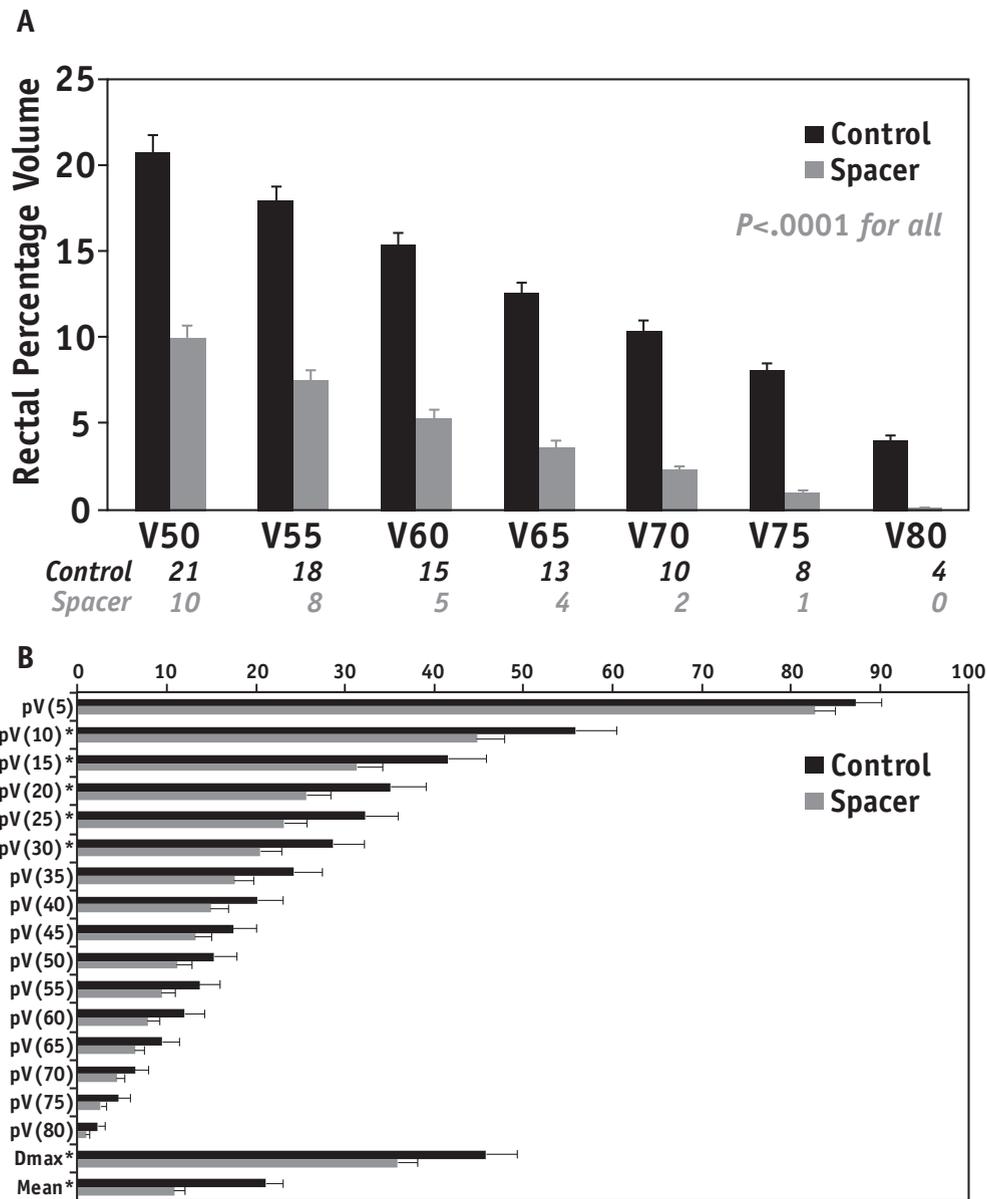


Fig. 1. Radiation dosimetry to rectum (A) and penile bulb (B) as a function of treatment arm. Doses presented as the mean ± standard error of the mean. *Abbreviations:* Dmax = maximum dose; pV(x) = the percentage of penile bulb at or above “x” Gy.

incontinence at 3 years (control: 15%, 95% CI 8%-29%; spacer: 4%, 95% CI 2%-10%; *P* = .046; hazard ratio 0.36, 95% CI 0.12-1.1), without a difference in other grade ≥1 urinary toxicities (*P* > .5) or grade ≥2 urinary toxicity (*P* > .5; **Figs. 2C** and **2D**; **Fig. E2**; available online at www.redjournal.org).

Quality of life

Bowel QOL

Both arms had similar acute declines in bowel QOL between enrollment and 3 months after treatment, with return toward baseline at 6 months (**Fig. 3A**). Numerically, from 6 months through 3 years, the spacer arm bowel QOL score was near or greater than the baseline score but had declined in the control arm (*P* = .002). The mean difference of 5.8 points in

the bowel summary score at 3 years between the control (−5.3 points) and spacer (+0.5 points) groups met the previously established threshold for a MID of 4 to 6 points (**12**).

The proportion of patients with measurable changes in bowel QOL meeting the MID threshold (5 points; **Fig. 3B**) or twice that threshold (10 points; **Fig. 3C**) was also evaluated. From 6 months through 3 years, more men in the control arm had a MID in bowel QOL meeting the threshold of 5 points (*P* = .009), but no difference was found for a 10-point decline (*P* = .14). Both differences increased with a longer follow-up duration, such that at 3 years, men treated with the spacer were less likely to have a detectable change in bowel QOL for both thresholds (5-point: 41% vs 14%, *P* = .002, odds ratio [OR] 0.28, 95% CI 0.13-0.63; 10-point: 21% vs 5%, *P* = .02, OR 0.30, 95% CI 0.11-0.83).

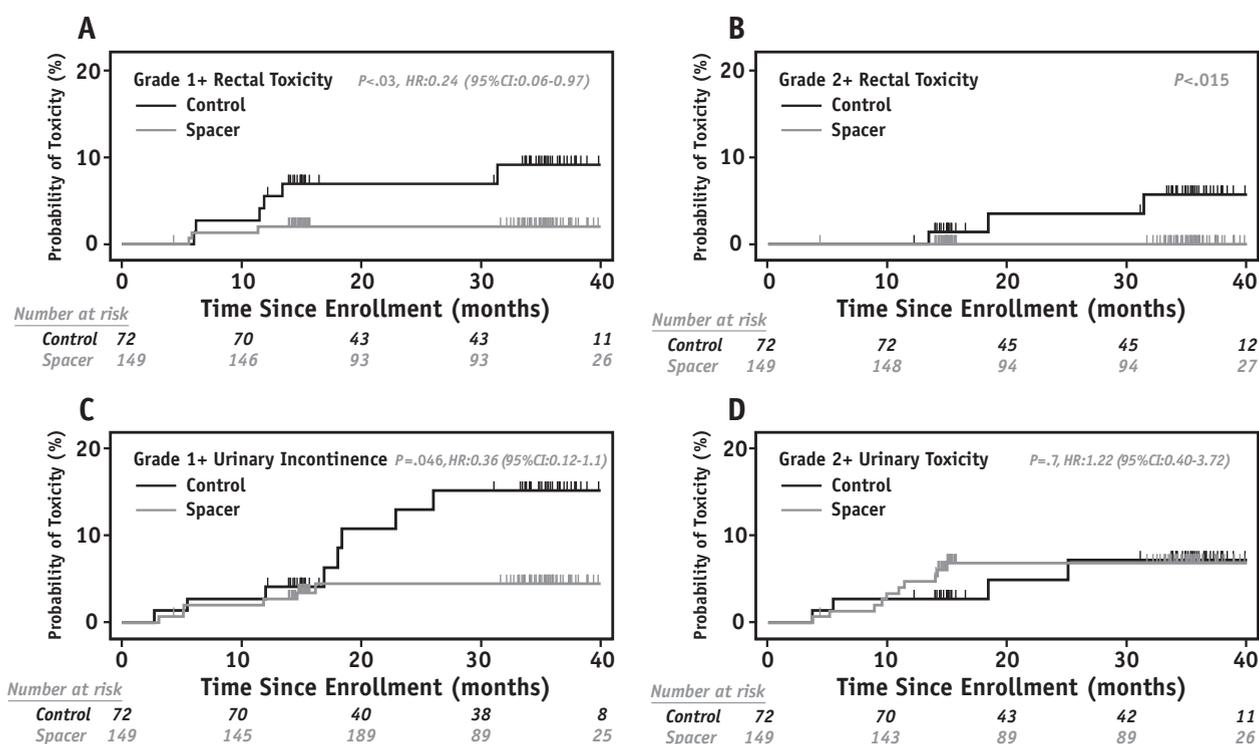


Fig. 2. The cumulative incidence of grade ≥ 1 (A) and ≥ 2 (B) bowel toxicity and grade ≥ 1 urinary incontinence (C) and grade ≥ 2 urinary toxicity (D). *Abbreviations:* CI = confidence interval; HR = hazard ratio.

Dosimetric analysis revealed a correlation between an increasing rectal V50 to V80 and a decline in bowel QOL ($P<.03$ for all; [Table E2](#); available online at www.redjournal.org). In addition, those treated to the prostate and seminal vesicles were more likely to have a decline in bowel QOL compared with those treated to the prostate only; however, the relative benefit of hydrogel spacer use was independent of seminal vesicle treatment ([Fig. E3](#); available online at www.redjournal.org).

Urinary QOL

For urinary QOL, a similar decline was seen at 3 months between the treatment arms, which again had approached baseline by 6 months ([Fig. 4A](#)). When averaged over the entire follow-up duration, no significant difference was found in the mean urinary QOL between the 2 arms ($P<.13$). At the 3-year point, a statistically significant difference was found in urinary QOL favoring the spacer arm (+0.6 points) compared with the control arm (-3.3 points; $P=.04$). However, the difference of 3.9 points did not meet the criteria for a MID (5-7 points). When assessing the proportion of men throughout the follow-up period with a MID in urinary QOL, no difference was found in those with a 6-point decline ($P=.13$; [Fig. 4B](#)). However, a smaller proportion of men had a 12-point decline in urinary QOL in the spacer arm ($P<.035$; [Fig. 4C](#)). Again, the differences increased over time, such that at 3 years, significantly fewer men had either a 6-point (30% vs 17%, $P<.05$, OR 0.41, 95% CI 0.18-0.95) or 12-point (23% vs 8%, $P<.03$, OR

0.31, 95% CI 0.11-0.85) decline. No dosimetric variables correlated with urinary QOL.

Other QOL analysis

As previously reported, no significant differences were found in sexual QOL or vitality/hormonal QOL between the randomized arms ([Fig. E4](#); available online at www.redjournal.org). Nor were significant differences found in the proportion of patients with MID changes between the treatment arms for either the vitality/hormonal or sexual domains ($P>.1$ for both; data not shown). The dose to the penile bulb, although different between the treatment arms ([Fig. 1B](#)), was low in both groups and did not correlate with the change in the EPIC sexual summary score for all patients or each randomized arm.

The proportion of patients with moderate or large problems in QOL according to each item on the EPIC questionnaire was also assessed ([Tables E3-E6](#); available online at www.redjournal.org). At 3 years, only 1 item showed a statistically significant difference at this threshold between the treatment arms (both secondary to urinary frequency: control 18% vs spacer 5%; $P<.05$). However, of all 50 items, 14 had differences of $\geq 5\%$ between treatment arms at 3 years. Of these items, 13 favored the spacer arm (3 bowel, 3 urinary, 5 sexual, and 2 vitality/hormonal) and only 1 (weight gain) favored the control arm.

For all patients in the study (spacer plus control), an overall decline in urinary QOL of 6 and 12 points at 3 years was seen in 21% and 13% of the patients, respectively. A strong association was found between the decline in bowel

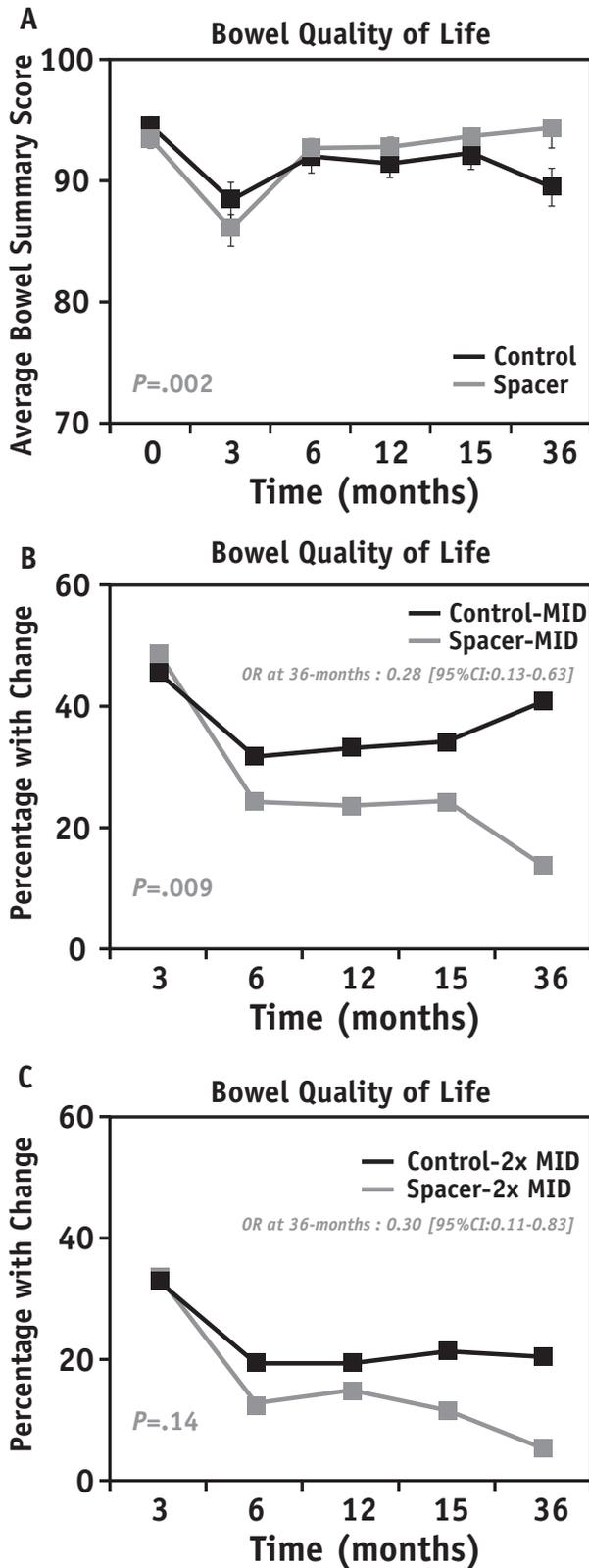


Fig. 3. Mean changes in bowel quality of life summary score (A) as a function of treatment arm. Data presented as mean ± standard error of the mean. The proportion of patients with detectable changes in bowel quality of life at the 5-point (B) or 10-point (C) threshold. *Abbreviations:* CI = confidence interval; MID = minimally important difference; OR = odds ratio.

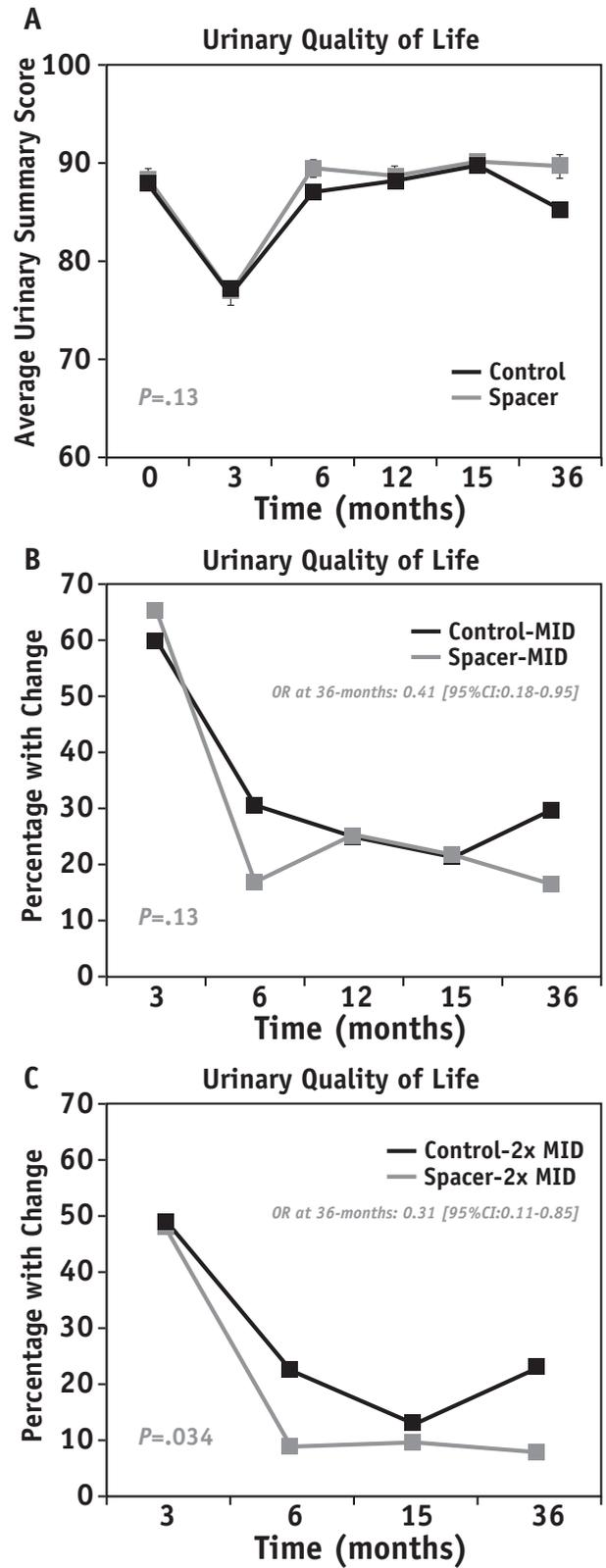


Fig. 4. Mean changes in urinary quality of life summary score (A) as a function of treatment arm. Data presented as mean ± standard error of the mean. The proportion of patients with detectable changes in bowel quality of life at the 6-point (B) or 12-point (C) threshold. *Abbreviations:* CI = confidence interval; MID = minimally important difference; OR = odds ratio.

QOL and concomitant decline in urinary QOL. The 6-point urinary decline was seen in 14% of the men who did not have a bowel change but in 45% of those with a detectable 5-point decline in bowel QOL ($P < .0001$, OR 4.3, 95% CI 3.3-5.8), with a similar correlation found for the 12-point decline in urinary QOL. A 12-point decline was observed in 7.5% of the men with stable bowel function but in 62% of the men with a detectable 10-point decrease in bowel QOL ($P < .0001$, OR 7.4, 95% CI 5.2-10.6).

Given the greater likelihood of experiencing urinary QOL changes in the face of bowel changes, we next assessed the overall burden of QOL changes at 3 years at the 1× and 2× MID thresholds for bowel, urinary, and sexual QOL (Fig. 5). At 3 years, 46% of men in the spacer arm had no detectable change in any of the 3 QOL domains compared with 35% in the control arm, and 67% of the spacer group had no changes meeting the 2× thresholds compared with 58% of the control group. Furthermore, in

the control arm, more men had a decline in all 3 domains (20% control vs 2.5% spacer for 1× MID and 12.5% control vs 0% spacer for 2× MID). The statistical significance of the differences in the patients with declines in ≥ 1 QOL domain were different between the 2 treatment arms (χ^2 , $P = .0017$ for 1× MID and $P = .0049$ for 2× MID).

Given the 63% response rate at 3 years, we also performed sensitivity analyses comparing potential differences between those with or without a response at the 3-year point (Table E7; available online at www.redjournal.org). No difference was found in the QOL at either baseline or 15 months between those with and without a response. For all QOL domains, a similar relationship was found between the treatment arm and the change in mean QOL for those with and without a response both during the follow-up period time and at 36 months (Table E8; available online at www.redjournal.org). For bowel QOL, similar differences were also observed in those achieving a 5- or 10-

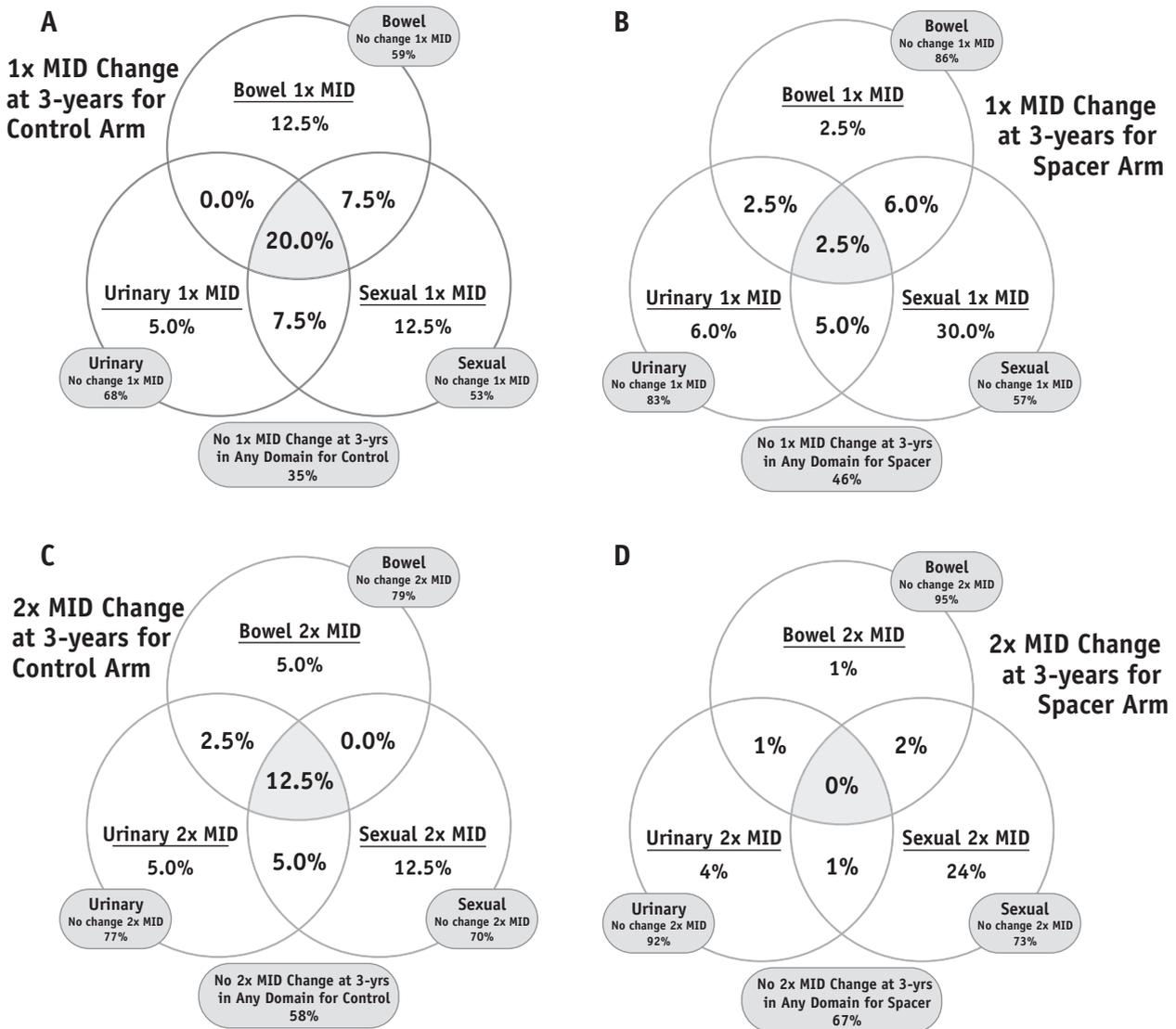


Fig. 5. The proportion of patients by treatment arm with changes across all 3 quality of life domains (bowel, urinary, and sexual) at the 1× (A, B) or 2× (C, D) thresholds. The overlaps between circles show patients with declines in 2 or 3 domains. *Abbreviation:* MID = minimally important difference.

point decline when limited to those with all data available compared with the initial analysis of all patients (Fig. E5; available online at www.redjournal.org).

Disease control

No biochemical failure developed in any patient during the follow-up period in either arm. Also, no difference was found in the nadir prostate-specific antigen level after RT in either arm (0.5 ng/mL; $P > .5$).

Discussion

The results of the present prospective single-blind randomized phase III trial have demonstrated that the hydrogel spacer was safe to apply and well tolerated and resulted in a significant rectal dose reduction. Furthermore, the benefit seen with the hydrogel spacer at 15 months for bowel toxicity and QOL was maintained or had increased at the 3-year median follow-up period.

The control arm had very low rates of rectal toxicity compared with previous reports (14-19). The cumulative rate of grade ≥ 2 bowel toxicity was 6% at 3 years in the control arm, with no cases of grade ≥ 2 toxicity in the spacer arm. These results compare favorably with those from recently published multi-institutional studies such as the Radiation Therapy Oncology Group 0126 trial (79.2 Gy in 1.8-Gy fractions, IMRT, unknown use of IGRT, grade ≥ 2 rectal toxicity rate of 15.1%) (14) or Radiation Therapy Oncology Group 0415 trial (73.8 Gy in 1.8-Gy fractions, all IGRT, 79% IMRT, grade ≥ 2 rectal toxicity rate of 11.4%) (17). The low toxicity in the control arm might have been related to a number of factors, including different toxicity scales, uniform use of both IMRT and IGRT, small PTV margins, magnetic resonance imaging planning, and strict dosimetric constraints with centralized pretreatment review of the plans. Nevertheless, despite the overall excellent results in the control arm, the addition of the hydrogel spacer still resulted in statistically significant and clinically meaningful reductions in toxicity and improvements in bowel QOL. This highlights 1 notable strength of the present study in that the outcomes using both physician-scored toxicity (Common Terminology Criteria for Adverse Events, version 4.0) and patient-reported outcomes (PROs; EPIC) resulted in similar and complementary conclusions, both favoring the spacer arm. The present study was also performed across 20 centers, reflecting broad applicability.

Despite the low rates of physician-scored toxicity, the analysis of PROs revealed greater rates of measurable declines in QOL. In the control arm at 3 years, 41% of patients exhibited a detectable decline in bowel QOL (5 points) using the PROs, which met the definition of a MID, and 21% experienced a more serious decline (10 points). These rates were both reduced by 70% in the spacer arm (14% and 5%, respectively). Additionally, for urinary QOL at 3 years, 30% of the men in the control arm reported detectable declines (6

points), with most (23%) reporting a decline in urinary QOL, which was ≥ 2 times the MID (12 points). Again, the use of the hydrogel spacer reduced the likelihood of either a MID or more serious changes in urinary QOL by $>60\%$ (with rates in the spacer arm of 17% and 8%, respectively). Thus, despite an overall favorable toxicity profile, a substantial portion of patients were still likely to obtain a benefit from the use of the absorbable hydrogel spacer, as measured by PROs. This difference was also evident when analyzing the proportion of patients with multidomain changes across all 3 domains (urinary, sexual, and bowel). In the spacer arm, 46% of the men had no clinically detectable change in any QOL domain at 3 years; the rate was 35% for the control arm. In addition, for the men in the control group, 20% had changes meeting the threshold for MID in all 3 arms compared with only 2.5% in the spacer group. Also, 12.5% of the control group had large changes ($2\times$ MID) in all 3 domains at 3 years compared with no men with $2\times$ MID across all 3 domains in the spacer group.

The number needed to treat (NNT) is a useful metric to estimate the proportion of patients expected to derive a benefit from the use of an intervention. The NNT to spare 1 cumulative grade ≥ 1 bowel toxicity at 3 years was 14.3 and for grade ≥ 2 bowel toxicity, was 16.7. The patient-reported QOL outcomes might provide a more sensitive metric, because it better reflects the patient's experience and priorities and is complementary to physician-scored toxicity. The NNT to prevent 1 detectable change in bowel QOL at 3 years (5-point threshold) was 3.7 compared with a NNT of 6.3 for the more severe change in bowel QOL (10-point threshold). Furthermore, the use of a hydrogel spacer also decreased the incidence of urinary incontinence and resulted in a statistically significant (albeit not clinically significant) improvement in the average urinary QOL at 3 years. Despite not causing, on average, a clinically meaningful benefit in urinary QOL, a substantial minority of patients did have detectable declines in urinary QOL, such that the NNT to prevent 1 patient with a MID decline in urinary QOL (6-point threshold) at 3 years was 7.7 and was 6.7 when the more severe threshold of twice the MID was used (12 points). When considering QOL more broadly, the NNT to prevent 1 man from experiencing a measurable decline in all 3 domains was 9.1 for the $1\times$ MID threshold and 8.0 for the $2\times$ MID threshold.

Unlike bowel QOL, for which previous studies have identified strong correlations between radiation dosimetry and declines in PROs, which we also noted (Fig. 1; Table E2; available online at www.redjournal.org) (19, 20), we were unable to identify dosimetric characteristics that correlated with the differences in urinary toxicity and QOL. The structures evaluated included the bladder, bladder wall, bladder neck, prostate, and penile bulb (as a surrogate for genitourinary diaphragm). Some, although not all, previous studies have reported a correlation between the dose to the urethra and the occurrence of urinary toxicity after high-dose RT. However, using the treatment plans available, we did not have a urethral structure for evaluation. Men

with a detectable change in bowel QOL were approximately five-fold more likely to exhibit detectable changes in urinary QOL. A number of possibilities exist to explain this association: different organs at risk with an association to urinary QOL that have not yet been identified (eg, intraprostatic urethra, distal urethra, or bladder trigone) (21, 22) but that might have been spared by the spacer treatment; potentially more intrinsic radiosensitivity in those exhibiting both bowel and urinary QOL declines (23); a greater likelihood of reporting urinary differences, even if not present, when bowel differences are present (24); and a greater likelihood of men reporting urinary issues owing to increased restroom usage secondary to bowel changes.

Since the initiation of the present clinical trial, the use of other dose-escalated RT modalities for the treatment of prostate cancer has increased, including moderately hypofractionated RT, stereotactic body RT, brachytherapy as monotherapy or a boost, and proton therapy (17, 18, 25-33). With each of these treatment modalities, bowel toxicity and changes in QOL have been associated with the dose to the rectum, which in some cases can be extreme. In 1 recent stereotactic body RT trial, nearly 10% of patients in the highest dose arm required a colostomy (33). Thus, the benefits obtained through prostate-rectal spacing using conventionally fractionated RT could also be evident using these other treatment techniques, such that with further dose intensification, the hydrogel spacer might have greater effects.

Conclusions

We have reported the first level 1 evidence from a randomized phase III trial of an RT technique for prostate cancer to demonstrate reductions in rectal dosimetry and improvements in both toxicity and QOL. Encouragingly, the differences identified at the 15-month minimum follow-up point (10) appear to have been maintained or increased at 3 years. For radiation technologies, only the use of 3-dimensional conformal RT had previously been tested in such a phase III trial (34). Nevertheless, both IGRT and IMRT have been routinely adopted despite lacking a similar level of evidence (35). Future work might be able to identify the clinical and dosimetric risk factors that can determine those at greatest risk of rectal toxicity and who might stand to benefit the most from the use of a spacer (36). It is also notable that the use of this hydrogel spacer provided a clinically meaningful improvement even in the best current standard of care for conventionally fractionated dose-escalated RT, with PROs identifying significant improvements in both urinary and bowel QOL.

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