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Basic Original Report

Who Benefits From a Prostate Rectal Spacer? Secondary Analysis of a Phase III Trial

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Abstract

Purpose: Previously a phase III trial of a hydrogel rectal spacer during prostate radiation therapy found decreased toxicity and a clinically significant improvement in bowel quality of life (QOL) at 3 years by the Expanded Prostate Cancer Index. We performed a secondary analysis to identify men less likely to benefit.

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Methods and Materials: Clinical and dosimetric data for the 222 patients enrolled on the SpaceOAR phase III trial were analyzed. The volume of rectum treated to 70 Gy (V70) and the quantitative analysis of normal tissue effects in the clinic (QUANTEC) rectal dose goals were used as surrogates for clinical benefit and plan quality. Mean bowel QOL was assessed at 15 and 36 months posttreatment and the likelihood of 1× (5 points) or 2× (10 points) minimally important difference changes were assessed.

Results: Rectal V70 was correlated with physician scored toxicity ($P = .033$) and was used as a surrogate for plan quality. There was no correlation between prostate volume and rectal V70 ($r = 0.077$). Rectal V70 pre- and post-hydrogel was 13% and 3% for the smallest prostates (<40 mL) and 12% and 2% for the largest (>80 mL). The relative reduction in rectal V70 of 78% did not vary by prespacer V70, but the absolute reduction was greater for a higher V70. All spacer plans met the 5 QUANTEC rectal dose constraints, although 92% of control plans met all constraints. At 3 years, those not meeting all QUANTEC goals had a 15.0-point (standard deviation 15.1) decline, control patients meeting QUANTEC goals had a 4.0-point (9.5) decline, and spacer had >0.5 (7.6; $P < .01$). Previous surgery was not correlated with QOL ($P = .8$). Across prognostic groups, including age, body mass index, previous surgery, target volume, or quality of radiation plans, there was no statistically significant heterogeneity in the relative benefit of spacer in decreasing the risk of 1× or 2× the minimally important difference declines.

Conclusions: There was little heterogeneity in the likelihood of spacer reducing the risk of declines in bowel QOL across clinical and dosimetric variables. Even for the >95% of plans meeting QUANTEC rectal criteria, hydrogel spacer provided potentially meaningful benefits.

Introduction

Prostate cancer is common, with an estimated 180,890 new cases and 26,120 deaths predicted in the United States in 2016.[1,2] Clinical outcomes after external beam radiation therapy have been improved with dose-escalation, but at a cost of increased urinary and bowel toxicity, despite improvements associated with image guided radiation therapy and intensity modulated radiation therapy. This persistent bowel toxicity is in part due to the proximity of the prostate gland to the rectum.

Therefore, a single-blinded, phase III randomized trial evaluating the benefits of SpaceOAR, an absorbable hydrogel spacer, to increase the separation between the rectum and prostate was conducted. This study analyzed 222 men randomized to hydrogel spacer or control. At a median follow-up of 37 months, spacer reduced rectal dose and toxicity while improving quality of life compared with control.[3] The present study is a secondary analysis of the phase III trial with the objective to identify, based on clinical, anatomic, and dosimetric factors, a subgroup of men who may not benefit from spacer placement.

Methods and Materials

Patients and treatment

The details and methods of the original phase III study are described previously.[3–5] Briefly, men with low- or intermediate-risk prostate cancer, as defined by the National Comprehensive Cancer Network, and Zubrod performance 0 to 1 were enrolled in a multi-institutional, institutional review board–approved, single-blinded, phase III trial. Men with prostate glands ≥80 cm^3, extraprostatic extension, >50% positive core biopsies, previous or planned use of androgen deprivation therapy, or prior treatment of prostate cancer were excluded. Randomization was 2:1 to the hydrogel spacer or control group, with all patients having fiducial markers for image guided radiation therapy. Clinical and dosimetric data for the 222 patients enrolled on the original trial were analyzed in the present study. Of these patients, 218 were assessed for bowel quality of life (QOL) at 15 months, and 140 with a minimum of 3 years of follow-up were assessed for more long-term changes in bowel QOL.

Pre- and postfiducial computed tomography (CT) simulation scans were fused to the magnetic resonance image for planning. The use of contrast agents was at the discretion of the investigators. Radiation plans were reviewed by an independent core laboratory before treatment to ensure compliance to protocol guidelines. The clinical target volume was defined as the prostate with or without the seminal vesicles, per physician's discretion. The planning target volume was generated as a 5- to 10-mm expansion on the clinical target volume. The prescription dose was 79.2 Gy in 1.8 Gy daily fractions, delivered once daily. The distance between the prostate and rectum was assessed based upon the midsagittal and midcoronal slice of the prostate gland measuring the distance between the posterior most point of the rectum and the anterior most point of the prostate, which was deemed zero if these were in contact at this level.

Data collection and patient follow-up

All patients were evaluated weekly during treatment and at 3, 6, 12, and 15 months after enrollment. After approval by the institutional review board, extended

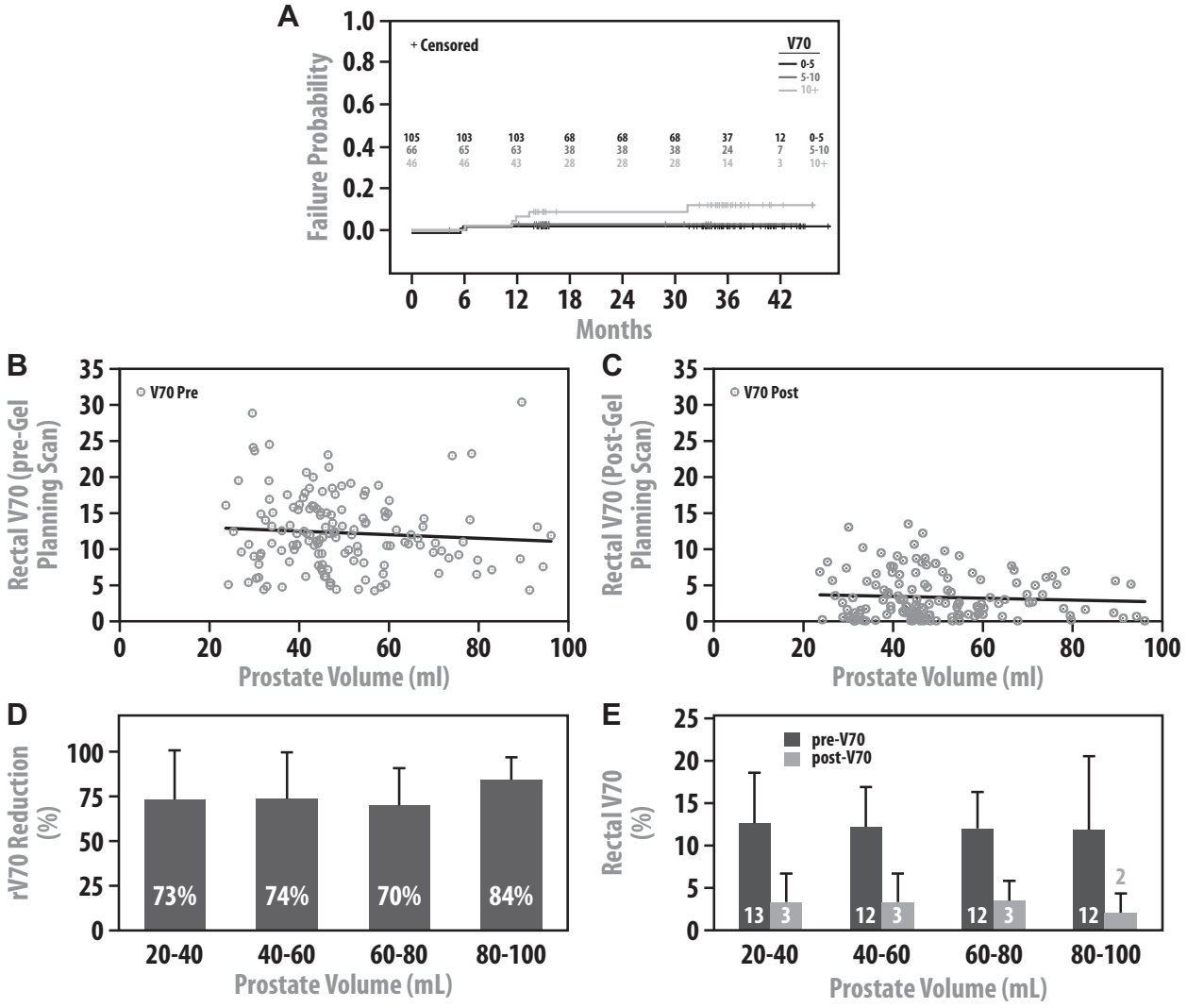

Figure 1 Correlation of rectal V70 with toxicity and prostatic volume. Grade 1 or greater rectal toxicity as a function of rectal V70 (A). Rectal V70 and prostatic volume are plotted pre-hydrogel (B) and post-hydrogel (C) placement. Relative (D) and absolute (E) reductions in rectal V70 for different prostatic volume groups are depicted. Values are represented as mean percentage + standard deviation.

follow-up data at 36 months were recorded with voluntary institutional participation.

Statistical analysis

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Pearson correlations (r) were used to assess correlation between prostate volume and midgland prostate/rectum distance with rectal dose volumes. Physician-scored toxicity was assessed via Common Terminology Criteria for Adverse Events, version 4.0. Analysis of QOL was performed using the changes in Expanded Prostate cancer Index Composite (EPIC) summary scores from baseline. These changes were evaluated with linear mixed models with fixed effects of randomized treatment, time to questionnaire completion, and baseline score. The minimally important difference (MID) in bowel EPIC summary score was defined as 5 points,[6] and twice MID (2xMID) as 10 points. Post hoc subgroup analyses of age (45-67 or 68-84 years), body mass index (<28 or >28), smoking status (current, never, or former), abdominal/pelvic surgery (no or yes), prostatic volume (≤ 55 mL or >55 mL), treatment (prostate only or with seminal vesicles), quantitative analysis of normal tissue effects in the clinic (QUANTEC) constraints (not met or met), and more stringent constraints (not met or met) were performed. The analyses used logistic regression models and reported odds ratios with 95% confidence intervals.

Results

The characteristics of the clinical trial and results have been reported previously.[3,4] For this analysis, clinical and dosimetric data were assessed for the 222 patients who

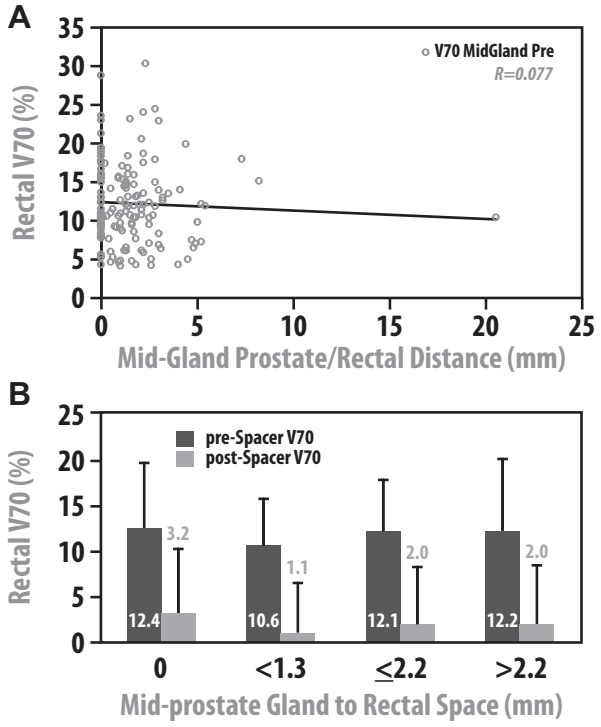

Figure 2 Correlation of rectal V70 and prostate/rectum distance. Rectal V70 and midprostate gland to rectum distance are plotted pre-hydrogel (A). The rectal V70 pre- and post-hydrogel placement for different midprostate gland to rectum distances are shown (B).

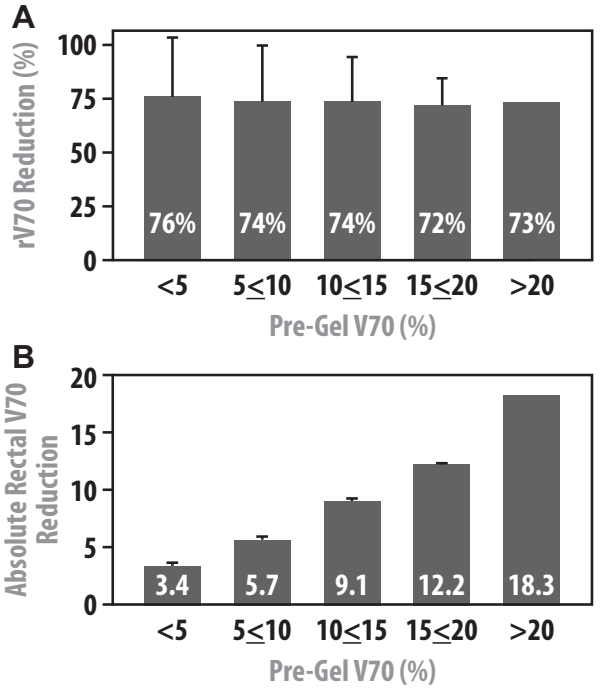

Figure 3 Relative and absolute reduction in V70 as a function of pre-hydrogel V70. The corresponding relative (A) and absolute (B) reduction in rectal V70 are reported. Values are represented as mean percentage + standard deviation.

enrolled on either arm, whereas analysis of changes in bowel QOL was limited to those with baseline and follow-up QOL assessments at 15 or 36 months. Hydrogel spacer has previously been demonstrated to reduce rectal volume exposed to radiation over the entire range of rectal dose-volume histogram (DVH) assessed. For this analysis we focused on rectal V70, as it has been most commonly used as a measure of radiation plan quality and has been correlated with both bowel toxicity and QOL. The cumulative incidence of grade ≥1 rectal toxicity at 3 years was directly dependent on V70 ($P = .033$) with higher toxicity in those with higher V70 (Fig 1A and Fig E1; available online at https://doi.org/10.1016/j.prro.2019.12.011). For those with grade ≥1 rectal toxicity, mean percentage of rectum at 70 Gy (median [standard deviation {SD}] interquartile ratio [IQR]) was 10.8 (12 [7.8], 6.4-18.1), although in those without grade ≥1 toxicity rectal V70 was mean 5.9 (median [SD], IQR; 5.0 [5.1], 1.2-9.0). Grade ≥2 rectal toxicity was observed in 3 patients (V70: mean 13.2; median 14.2, [5.5] 7.2-18.1), which was higher compared with those without grade 2 toxicity (V70: mean 6.0; median 5.1, [SD 5.4], IQR 1.2-9.1).

Given the association between V70 and both rectal toxicity and QOL we next assessed pretreatment metrics to predict V70. It had previously been suggested that only patients with a large prostate volume would benefit from spacer placement. There was no correlation between prostatic volume and rectal V70 before (Fig 1B, r = 0.077) or after placement (Fig 1C, r = 0.062), nor was there a correlation in the reduction in V70 after spacer placement (r = 0.051). Regardless of prostatic volume, there was a consistent relative reduction in rectal V70 after spacer placement between 70% and 84% (Fig 1D). Rectal V70 before and after was 13% and 3% for the smallest prostates (<40 mL) and 12% and 2% for the largest (>80 mL; Fig 1E, all $P < .01$).

Next the potential interaction between the distance between the midgland prostate and the anterior rectal wall was assessed for its effect on rectal V70 and dose reduction with spacer. There was no correlation between prostate or rectal border distance and V70 before spacer placement (Fig 2A, r = 0.047). This distance was broken into quartiles (0 mm, <1.3 mm, <2.2 mm, and ≥2.2 mm). Regardless of the distance between the anterior aspect of the midgland and the rectum in initial scans, there was a reduction in V70 (Fig 2B, all $P < .01$). For those where the prespacer prostate and rectum were in contact (0-mm separation) the V70 decreased to 3.2% compared with 12.4% before placement (a 74% reduction), although for those with the largest space between the prostate and rectum at baseline (≥2.2 mm) the post-spacer rectal V70 was 2.0% compared with 12.2% before spacer (an 84% reduction).

We also evaluated the radiation plan that was generated before spacer placement to assess whether plan quality could identify those not likely to benefit (Fig 3).

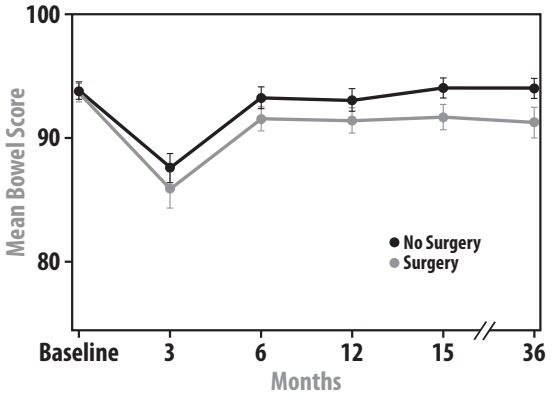

Figure 4 Effect of prior surgery on long-term rectal quality of life. Mean changes in bowel quality of life summary score for any previous pelvic or abdominal surgery. Data presented as mean ± standard error of the mean.

There was a consistent relative reduction in V70 of 72% to 76% across all plans, regardless if the V70 before spacer was <5% or >20% (Fig 3A, $P < .001$). However, the absolute reduction of V70 was different based on prespacer radiation plan quality (Fig 3B). For initial plans with a V70 <5%, there was a 3.4% absolute reduction in V70. This increased to 5.7%, 9.1%, 12.2%, and 18.3% for V70 of 5% to 9%, 10% to 14%, 15% to 19%, and ≥20%, respectively (all $P < .01$).

Given previous associations between prior abdominal, pelvic, and hemorrhoid surgery on rectal toxicity, the presence or absence of these procedures before radiation therapy and their affect on bowel QOL was assessed across all patients. Presence or absence of prior surgery was not correlated with baseline QOL ($P = .8$); although at 3 months, there was a small but clinically insignificant greater decline in bowel QOL in patients with prior surgery (−6.4 vs −8.1, $P = .35$). This small difference was not statistically significant but appeared to be maintained over time (Fig 4).

Finally, we evaluated the relative benefit of hydrogel spacer placement on the likelihood of patients having clinically significant declines in bowel QOL as assessed using pretreatment clinical characteristics and plan quality. Baseline bowel summary scores were compared with those at 3 years using thresholds of 5 points (equal to the minimal clinically important difference (MID) and 10 points (2xMID, Fig 5A and 5B). The QUANTEC dose constraints were assessed as a measure of plan quality. These were met in 100% of the spacer plans for all 5 constraints (V50 <50%, V60 <35%, V65 <25%, V70 <20%, and V75 <15%), whereas 91.7% of the control plans met all of these constraints. At 3 years, control patients not meeting all QUANTEC goals had on average a 15.0-point (SD 15.1) decline in EPIC bowel summary score, control patients meeting all QUANTEC goals had 4.0-point (9.5) decline, and spacer patients who all met QUANTEC constraints had stable bowel score (≥0.5 [7.6]; $P < .01$). As reported previously, the presence of spacer reduced the likelihood of declines in bowel QOL at both the smaller and larger thresholds (1×MID: 41% vs 14%, $P = .002$; odds ratio [OR], 0.28; 95% confidence interval [CI], 0.13-0.63; 2×MID: 21% vs 5%; $P = .02$; OR, 0.30; 95% CI, 0.11-0.83). Even for men who met all 5 QUANTEC rectal dose constraints, the odds of bowel MID (OR, 0.29; 95% CI, 0.12-0.70) and 2×MID (OR, 0.3; 95% CI, 0.09-1.09) continued to favor spacer placement. Given the small number of patients (n = 5) who did not achieve all dose constraints, the ability to assess the odds ratio in those with poor quality plans as defined by not meeting QUANTEC constraints is not evaluable. Therefore, more stringent rectal dose constraints were also assessed based on bivariate analyses to correlate rectal dosimetry with anticipated 5-point declines in EPIC bowel summary score (see supplemental material in Hamstra et al[3]) to ascertain if plans associated with very small average risk of bowel decline would still be associated with potential improvement in bowel QOL with spacer placement. Even with these much more stringent dosimetric constraints (V50 <26%, V60 <20%, V65 <17%, V70 <13%, and V75 <10%), 91.2% of the spacer plans met all 5 constraints, although 65.3% of control plans met all 5 constraints. Control patients who met these constraints (n = 28) had a mean decline in bowel summary score at 3 years of 4.3 points (SD 10.7), whereas control patients not meeting these more stringent constraints (n = 16) had a decline of 6.9 points (SD 10.6). For those with spacers, there was no significant decline in bowel summary whether all 5 more stringent constraints were met (n = 87, ≥0.4 points; SD 7.7) or not (n = 6, ≥1.8 points; SD 5.8). Finally, the effect of spacer placement was assessed in those who met all 5 of these more stringent rectal planning constraints where the presence of spacer still reduced the likelihood of decline in bowel function when compared to those without spacer that met the threshold for MID (OR, 0.34; 95% CI, 0.12-0.92) or 2×MID (OR, 0.28; (95% CI, 0.07-1.05). For all other subgroups (age, body mass index, smoking status, prior surgery, treatment volume), spacer placement was numerically favored for effect on bowel MID, although for some groups the 95% CI for the odds ratio did cross one. The only group in which the odds ratio did not favor spacer was among men with large (>55 cm^3) prostates where there was a greater decline in bowel QOL (2×MID; OR, 1.47; 95% CI, 0.13-17.1); however, in this subgroup, spacer did appear to be favored for the 1×MID smaller decline in QOL (OR, 0.30; 95% CI, 0.09-1.06). Similar dosimetric and clinical relationships were seen at 15 months (Fig E2A and EB; available online at https://doi.org/10.1016/j.prro.2019.12.011), for instance, 2×MID decline seen in 33.3% of control patients who did not meet all QUANTEC criteria, in 21.5% of control patients who met all QUANTEC dose criteria, and in 11.6% of hydrogel patients who met QUANTEC criteria.

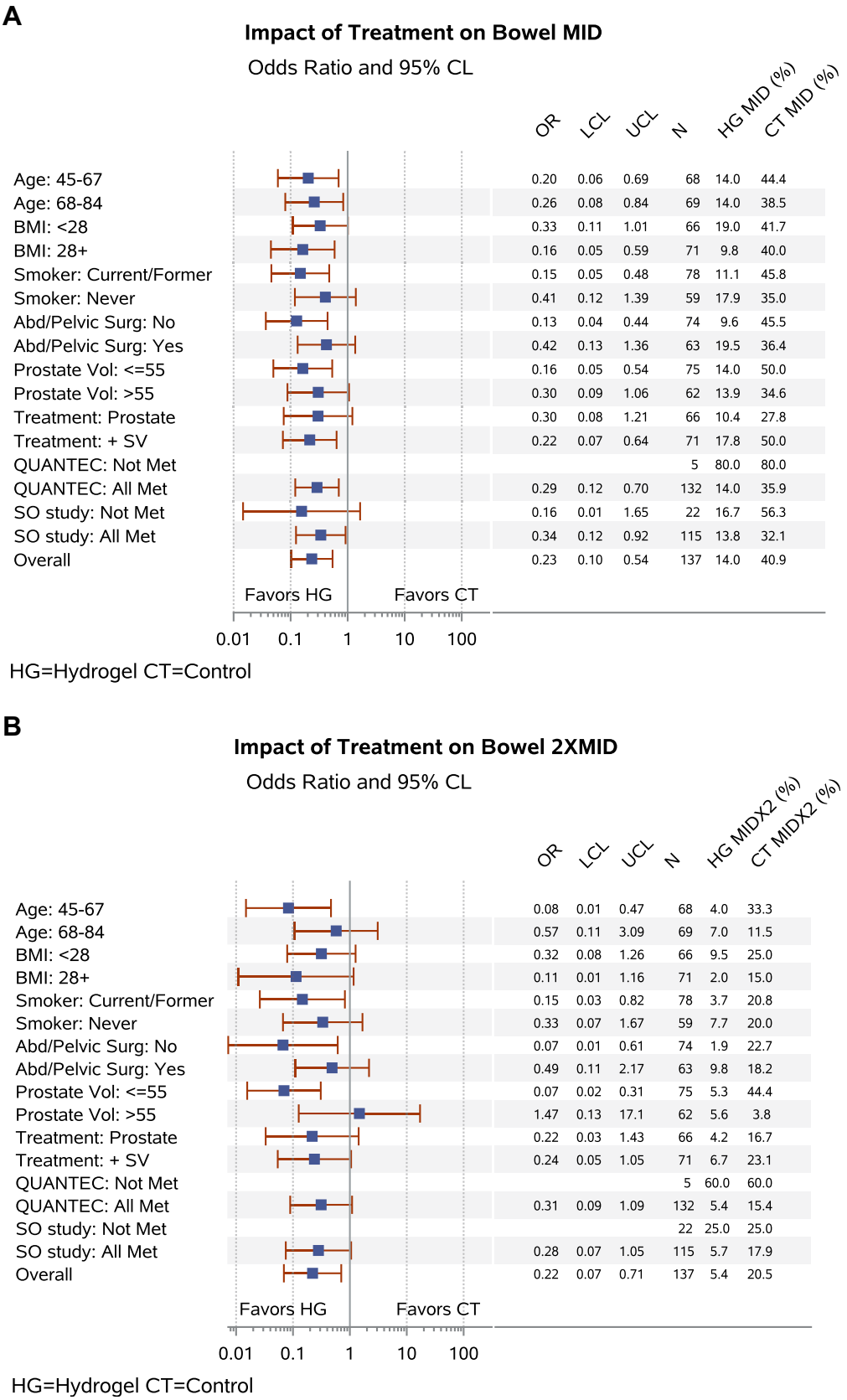

Figure 5 Relative benefit of hydrogel placement based on clinical subgroups. A subgroup analysis of various clinical and dosimetric parameters was performed to assess effect of treatment randomization on bowel quality of life scores for minimally important difference change (A) and 2× minimally important difference change (B).

Discussion

The results of this unplanned secondary analysis attempting to identify patients who would not benefit from spacer based on anatomic, clinical, and dosimetric parameters failed to identify any such subgroup, which clearly has a high likelihood of a substantially better clinical outcomes and, as such, would be significantly less likely to benefit from spacer placement. Namely, prostate size, rectal or prostate distance, prior surgical procedures, and preplan dosimetry all did not correlate with potential benefit. Rectal V70 did correlate with both physician scored toxicity ($P = .035$) and patient reported bowel QOL ($P = .006$), and as such, it is true that if a patient were to undergo a radiation plan and identify a plan with very low rectal V70 (and also other favorable rectal dosemetric characteristics) then the absolute benefit of spacer might be small. Nevertheless, even for patients whose plans met all QUANTEC dose criteria and would conventionally be viewed as acceptable, there still appeared to be benefit from hydrogel placement for 1×MID and 2×MID changes both at 15 and 36 months postrandomization. Although the QUANTEC dose constraints were not derived using bowel QOL assessments, they are a useful and validated starting point for correlating patient reported outcomes, especially given the correlations found previously between declines in bowel QOL and rectal dosimetry.[4,7] Indeed, even using present plan goals, as outlined by the QUANTEC, there was still a meaningful improvement in dosimetry and patient reported QOL expected with the use of spacer in patients in whom all QUANTEC dosimetric goals were met. For instance, in plans achieving all QUANTEC constraints, 36% of men had a measurable decline in bowel QOL (5 points) at 3 years in the control arm compared with 14% in the spacer arm (OR, 0.29; 95% CI, 0.12-0.70). Even with more stringent rectal dosimetric goals, which surpass that suggested by QUANTEC (V50 <26%, V60 <20%, V65 <17%, V70 <13%, and V75 <10%) 32% of control men had a measurable decline in bowel QOL compared with 13.8% of men treated with spacer (OR, 0.34; 95% CI, 0.12-0.92). For larger decline in bowel QOL with these very optimized plans, 17.9% of control men had a 10-point decline in EPIC bowel summary score compared with 5.7% of men with spacer (OR, 0.28; 95% CI, 0.07-1.05). As such it does not appear that in general the hydrogel spacer is making a "bad" plan acceptable because the vast majority of plans were already considered acceptable based on QUANTEC or even more stringent dosimetric goals. Instead, for the most part it appears the addition of spacer is taking what are otherwise acceptable or even "good" plans and still providing meaningful improvements in both dosimetry and in patient reported outcomes.

Traditionally, the primary dose-limiting toxicity for prostate cancer patients is gastrointestinal.[8] The incidence of chronic fecal incontinence is a relatively rare late side effect with conventionally fractionated radiation therapy, with an incidence at 3 years requiring pads of around 7% to 9% and with severe incontinence <1%.[9] However, as the field moves more toward hypofractionation, there is concern that grade 2 or higher fecal incontinence may become more prominent, with rates as high as 17.4% in a recent study that validated mean rectal dose and prior abdominal surgery as predictors for fecal incontinence.[10] As might be expected, fecal incontinence and rectal urgency have the most profound effect on quality of life.[11] Indeed, bowel side effects were shown to have the most effect on QOL outcomes compared with urinary and sexual side effects among patients treated with prostate cancer.[12] In the 3 year report of this phase III trial, bowel leakage >1× per week was reported in 3% of control patients at baseline and 13% at 3 years (a 10% absolute increase) with 6% reporting fecal leakage 1 or more times a day; in the spacer arm, bowel leakage >1× per week was reported in 6% at baseline and 5% at 3 years.[3] As such, the overall rate of bowel leakage was small, but it did appear that worsening of fecal leakage was decreased with spacer placement, and we were not able to identify subgroups of patients in whom this potential benefit was not observed (data not shown).

Prostatic volume is expected to have an effect on rectal toxicity owing to the increased radiation volume necessary to cover the whole gland. Indeed, several early studies evaluated the efficacy of neoadjuvant hormonal therapy (NHT) to reduce prostatic volume with corresponding rectal DVH analysis. One study demonstrated a median prostatic volume reduction of 25%, with NHT corresponding to a median of 25% reduction in rectal volume receiving 95% of the prescribed dose.[13] Another study noted that although NHT did reduce prostatic volume, this did not automatically translate into decreased rectal dose or improved therapeutic ratio because other anatomic variables may influence rectal toxicity.[14] In fact, randomized trials with and without NHT have not shown a difference in rectal toxicity,[15,16] reinforcing that prostate volume alone is not a direct surrogate for rectal DVH and the risk of bowel toxicity. We evaluated both prostatic size and midgland to rectal wall distance, expecting to find that patients with small prostates and greater distance would benefit less from hydrogel placement. Even for the smallest prostates (<40 cm^3) there was a significant reduction in rectal V70 of 73%, corresponding to an absolute reduction of 10%. Likewise, among patients with the largest distance from midgland to rectum (>2.2 mm), they had the largest numeric difference after spacer placement, with reduction in rectal V70 of 84%, corresponding to an absolute reduction of 10.2%. This observation may be related to the cost objective function used

in intensity-modulated radiation therapy optimization. For example, a greater distance in overall space may not necessarily result in a linear reduction in rectal V70.

Including clinical factors in rectal normal tissue complication probability modeling was previously shown to improve the predictive power over DVH analysis alone. In one such analysis prior abdominal surgery was found to be predictive of worse rates of rectal bleeding and fecal incontinence.[17] Likewise, prior abdominal surgery and history of gastrointestinal disease were found to be important clinical factors in normal tissue complication probability modeling.[18] In the present analysis, however, prior pelvic, abdominal, and hemorrhoid surgery did not substantially affect baseline bowel QOL or the likelihood or magnitude of decline in bowel QOL over time. The reason for differences in these findings and previous reports, which focus on physician reported bowel toxicity and not QOL, is unclear. It may be that surgery has a modest effect on baseline QOL but does not further increase the likelihood of declines in QOL over time after RT. Regardless, these prospective data suggest that the absence of prior pelvic surgery does not identify a more favorable group that would be less likely to benefit from spacer placement.

There is interest in identifying a cohort of patients who would benefit most from spacer placement. To that end, a multifactorial nomogram was previously proposed to predict toxicity scores and, therefore, identify patients who would benefit from placement. This nomogram identified clinical risk factors (anticoagulant use, hormonal therapy, antihypertensive use, DM, hemorrhoids, pelvic nodal RT, and prior abdominal surgery) to identify those patients who would benefit most from spacer. This approach seemed to identify patients appropriately; however, the system was designed from clinical data obtained between 2002 and 2004 when less conformal radiation therapy techniques were used. Furthermore, this nomogram was not externally validated and did not include dosimetric parameters.[19,20] In the present study no patients had pelvic RT or hormonal therapy and an association was not found between surgery and changes in bowel QOL. Nevertheless, the importance of dose-volume effects for normal tissue complication analysis is well established. For example, the QUANTEC review provides a summary of organ-specific dose-volume effect probabilities based on published toxicity outcomes as they pertain to dose-volume data. The most important rectal parameters looked at in DVH analysis and toxicity probability are the rectal V70 and V75, for which QUANTEC recommends $<20\%$ and $<15\%$, respectively.[7] Among the patients treated in this study, 100% of the spacer patients and over 90% of the control patients met all 5 QUANTEC constraints. Nevertheless, patients who met QUANTEC constraints still derived a relative benefit from spacer placement for both bowel MID and 2×MID. However, given that QUANTEC constraints were derived from the 3-dimensional conformal era, and in some sense represent a lower common denominator, it is not surprising to find that even better radiation plans may achieve a better QOL profile and as a result a smaller relative benefit with spacer. Therefore, more stringent rectal constraints were selected which were associated, on univariate analysis, with a mean 5-point decline (MID) in bowel summary score.[3] These included: V50 $<26\%$, V60 $<20\%$, V65 $<17\%$, V70 $<13\%$, and V75 $<10\%$. These constraints were achieved in 91% of spacer patients and 65% of control patients. Overall, the high prevalence of plans achieving QUANTEC dose goals (100% and 91%) and even better dosimetric thresholds (91% and 65%) for spacer and control, respectively, highlights the fact that these patients were treated with highly conformal plans, which overall meet criteria for good quality. Once again, even in those meeting these more stringent dosimetric constraints, the use of a hydrogel spacer was associated with a decreased likelihood of declines in bowel QOL meeting MID and 2×MID thresholds.

Conclusions

Within the confines of this centrally reviewed phase III clinical trial, overall radiation plans were of high quality based on pre-established DVH criteria, and there was little heterogeneity in the likelihood of hydrogel spacer placement reducing the risk of meaningful declines in bowel QOL across a variety of clinical and dosimetric parameters. Therefore, we were not able to identify a subgroup within this population that did not potentially benefit from spacer placement.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2019.12.011.

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