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Basic Original Report

Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: Secondary analysis of a phase 3 trial

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Abstract

Background: We previously reported the results of a phase 3 trial evaluating a prostate/rectal hydrogel spacer during prostate intensity modulated radiation therapy, which resulted in decreased rectal dose and toxicity and less decline in bowel quality of life (QOL). A secondary analysis was performed to correlate penile bulb dose and sexual QOL.

Methods and materials: Sexual QOL was measured with the Expanded Prostate Cancer Index Composite (EPIC) by mean scores, the proportion of patients with a minimal clinically important difference (MID), and analyses of the different items composing the sexual domain.

Results: A total of 222 men enrolled with median follow-up of 37 months. Hydrogel reduced penile bulb mean dose, maximum dose, and percentage of penile bulb receiving 10 to 30 Gy (all $P < .05$) with mean dose indirectly correlated with erections sufficient for intercourse at 15 months ($P = .03$). Baseline EPIC was low (53 [standard deviation ± 24]) with no difference between arms ($P > .1$). A total of 41% (88/222) of men had adequate baseline sexual QOL (EPIC >60 (mean, 77 [± 8.3]). This subgroup at 3 years had better sexual function ($P = .03$) with a spacer with a smaller difference in sexual bother ($P = .1$), which resulted in a higher EPIC summary on the spacer arm (58 [±24.1] vs control 45 [± 24.4]) meeting threshold for MID without statistical significance ($P = .07$). There were statistically nonsignificant differences favoring spacer for the proportion of men with MID and 2× MID declines in sexual QOL with 53% vs 75% having an 11-point decline ($P = .064$) and 41% vs 60% with a 22-point decline ($P = .11$). At 3 years, more men potent at baseline and treated with spacer had "erections sufficient for intercourse" (control 37.5% vs spacer 66.7%, $P = .046$) as well as statistically higher scores on 7 of 13 items in the sexual domain (all $P < .05$).

Conclusions: The use of a hydrogel spacer decreased dose to the penile bulb, which was associated with improved erectile function compared with the control group based on patient-reported sexual QOL.

Introduction

Intensity modulated radiation therapy (IMRT) is used to treat men with prostate cancer with common bowel, urinary, and sexual side effects. Sexual quality of life (QOL) after prostate treatment is important, with 1 study suggesting that 68% of men would risk a 10% greater chance of dying in the first 5 years to achieve a 50% improvement in the likelihood of maintaining good erectile function.[1]

Following prostate radiation therapy (RT), 45% to 70% of men retain potency at 2 years.[2-4] Decreased blood flow through the pudendal arteries posttreatment suggests that RT-associated erectile dysfunction (ED) is predominantly an arterial process.[5,6] Higher RT dose to the penile bulb (as a potential surrogate for other pelvic erectile/vascular structures) has been demonstrated to increase the risk of ED.[7] Supporting this vascular role, phosphodiesterase type 5 inhibitors can be effective in treating established ED after RT[8]; however, prophylactic use during RT did not clearly prevent new ED, with conflicting results from 2 randomized trials[9,10]; therefore, an approach to decrease the risk of ED following RT is needed.

The SpaceOAR System (Augmenix, Inc., Bedford, MA) is the only US Food and Drug Administration–approved absorbable hydrogel that can be introduced between the prostate and rectum to decrease rectal toxicity and minimize changes in bowel QOL. Prior analyses of the pivotal phase 3 trial noted lower penile bulb radiation dose with spacer, but there was no difference in average sexual QOL between arms; however, because nearly 60% of men who had moderate to severe sexual dysfunction at baseline, it is possible that an impact of the spacer on sexual function was masked. This post hoc analysis identified the subgroup of men with adequate baseline sexual QOL (41% of respondents) and found a correlation between reduced RT dose to penile bulb and better sexual QOL as well as quality of erections when comparing the spacer arm with control.

Methods and materials

Patient population and treatment

As previously reported, following institutional review board approval, men with National Comprehensive Cancer

Network low- or intermediate-risk prostate cancer were randomized 2:1 (spacer:control) with all receiving fiducial markers and IMRT (clinicaltrials.org; NCT01538628). Patients were blinded to treatment allocation.[11,12]

The postfiducial planning computed tomography and magnetic resonance imaging scans were fused, and structures were contoured on fused images. Clinical target volume was the prostate ± seminal vesicles. Planning target volume margins were 5 to 10 mm. Treatment was 79.2 Gy in daily fractions of 1.8 Gy. Radiation plans were evaluated by a core laboratory for protocol compliance (H.G., W.B., J.M.). The penile bulb dose was collected, but there were no planning goals for this structure.

Data collection and follow-up

For QOL, men were followed at enrollment, 3, 6, 12, 15, and 36 months. The primary endpoint was reported at 15 months.[11] Extended follow-up beyond 15 months was performed at those institutions electing to participate in this extended study.[12]

Statistical analysis

The EPIC sexual domain is provided in Appendix E1 (available as supplementary material online only at www.practicalradonc.org).[13] At baseline, 96% (212/222) of men answered all sexual QOL questions and were the study group. Based on a previously established threshold, men were dichotomized as having adequate sexual function (EPIC >60, n = 88, 41%) or moderate/poor sexual function (EPIC ≤60, n = 125, 59%).[14] Mean changes in EPIC sexual summary scores from baseline were evaluated in linear mixed models with fixed effects of randomized treatment, questionnaire time point, baseline domain score, and the interaction of randomized treatment and questionnaire time point and repeated measures within patient accounted for with an autoregressive correlation structure. Pairwise testing was done within the modeling framework. Minimal clinically important differences (MIDs) were evaluated based on a previously published threshold of 11 points (range, 10-12) and twice that threshold (22 points).[15]

The single question "How would you describe the usual QUALITY of your erections during the last 4 weeks?" was analyzed across the full scale or dichotomized with the favorable group reporting "Firm enough for intercourse",[4] whereas the unfavorable group reported all other responses ("None at all" (1), "Not firm enough for any sexual activity",[2] or "Firm enough for masturbation only".[3,16] Each of the other items in the EPIC sexual domain were analyzed in a similar fashion assessing the proportion with "moderate" to "severe" dysfunction or bother as indicated. The response was compared with baseline at each time point and then dichotomized into "worse" versus "the same or better." Binomial proportions and 95% confidence intervals (CIs) are reported by penile bulb dose constraint (percentage of penile bulb receiving doses ≥50 Gy [V50] and mean) with associated χ^2 test and odds ratios (ORs) between meeting the constraint or not.

Analysis was performed in SAS 9.4 (SAS Institute, Cary, NC). For all analyses P values <.05 were considered statistically significant. No corrections for multicomparisons were performed.

Results

Between January 2012 and April 2013, 222 eligible men enrolled at 20 US institutions and were randomized 2:1 (spacer:control). The primary endpoint was reported at 15 months[11]; extended follow-up continued through April 2016, when 63% of both control (n = 46) and spacer (n = 94) patients were evaluable.[12] There was no difference in median follow-up between arms (control: median, 37.0 months [range, 26-46] vs spacer 37.1 [32-47], $P > .5$).

Demographics

There were no differences between arms in age (control, 67.7 years; spacer, 66.4; $P = .2$), race (control, 84% white; spacer, 85%; $P = .8$), or body mass index (control, 29 kg/m^2; spacer, 29; $P = .6$). Baseline sexual QOL by EPIC was poor (mean 53 [±24 standard deviation]) with 59% having moderate/severe sexual dysfunction (defined as an EPIC score of ≤60) with no difference between arms (control, 58%; spacer, 61%; $P > .1$). Only 38% (80/213) of respondents had both adequate baseline sexual QOL and "erections firm enough for intercourse," which did not differ by arm (spacer, 39% [n = 56]; control, 34% [n = 24]; $P = .22$). Androgen deprivation was not allowed and no patients experienced biochemical failure or salvage therapy.

Dosimetry and sexual function

As previously reported, spacer use was associated with lower penile bulb dose for mean dose (21 vs 11 Gy), maximum dose (46 vs 36 Gy), and V10 to V30 (Fig 1A, all $P < .05$).To address the potential clinical significance of these differences, suggested cut-points for penile bulb dose were evaluated (Fig 1B).[17] Mean values were lower than suggested for all constraints for both arms; however, across all dose constraints, those on the spacer arm were more likely to achieve these constraints: 71% to 79% for spacer compared with 53% to 75% for control.

At enrollment, 38% (80/213) of men had erections firm enough for intercourse, which were maintained in 71% (55/77) at 3 months, 86% (69/80) at 6 months, 70% (56/80) at 12 months, 72% (57/79) at 15 months, and 57% (28/49) at 36 months. Given low baseline potency and the 63% response rate at 36 months, we focused dose-modeling on

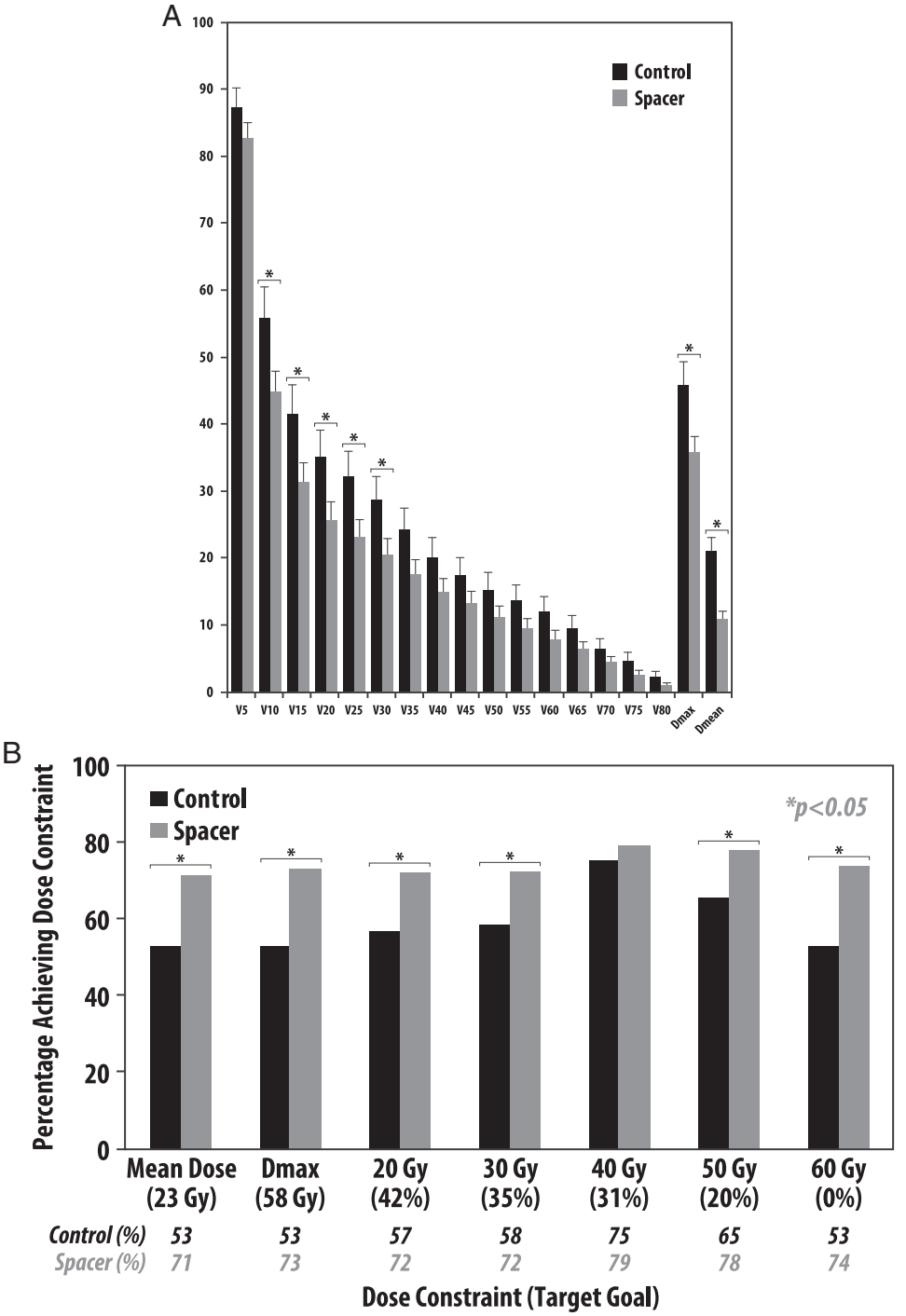

Figure 1 (A) Penile bulb dose in 5-Gy increments (5-80 Gy). Dose bins indicated with an asterisk (*) were statistically different ($P <$ .05). (B) The proportion of patients by treatment arm achieving the dose constraints recommended based upon the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer trial (goals are indicated in parentheses).

the 15-month time-point, where response rates were >96%. Mean penile bulb dose for all men was 14.3 Gy, which was broken into tertiles for analysis (Fig 2A). There was an inverse correlation between penile bulb dose and erections sufficient for intercourse ($P = .03$). Similarly, when looking at the predetermined dose constraints (Fig 2B) at 15 months, those achieving the specified dose constraints were more likely to have erections sufficient for intercourse than those not achieving the constraints. Those who did not meet the dosimetric goals had 29% to 35% potency as compared with 44% to 47% in those who did.

The question on "quality of erections" was also evaluated as a function of V50 (<20% vs ≥20%) and mean dose (<23 vs ≥23 Gy) over time (Fig 2C, Table E1). Baseline erectile

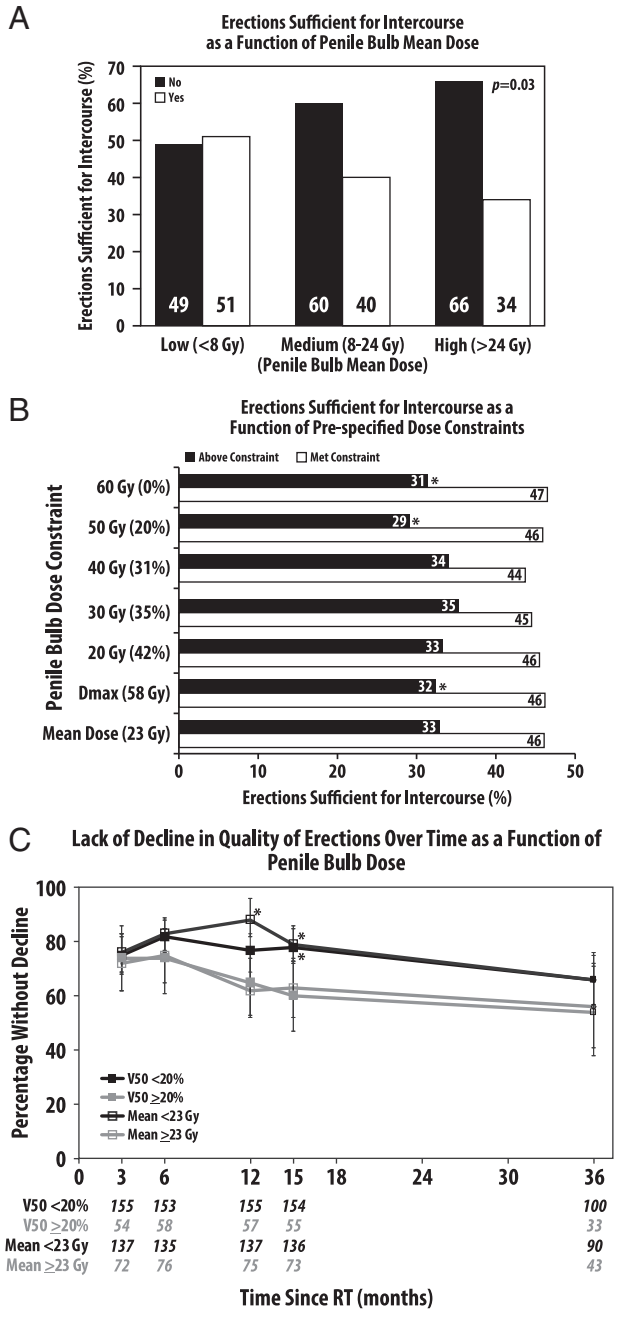

Figure 2 (A) Erections firm enough for intercourse at 15 months as a function of penile bulb dose broken down by tertiles. (B) Erectile function assessed by the dose constraints recommended based upon the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer trial. (C) Erectile function over time by V50 and mean dose. *$P < .05$. Dmax, maximum dose; RT, radiation therapy; V50, percentage of penile bulb receiving doses ≥50 Gy.

function ($P < .001$) and time since RT ($P < .001$) both correlated with erectile function, whereas higher penile bulb dose correlated with a greater likelihood of a decline in erectile function on the 4-step Likert scale. The curves began separating as early as 6 months posttreatment but were only statistically different for V50 at 15 months ($P = .007$; OR, 2.4 [95% CI, 1.3-4.7]) and for mean dose at 12 months ($P = .01$; OR, 2.2 [95% CI, 1.2-4.2]) and 15 months ($P = .01$; OR, 2.3 [95% CI, 1.2-4.3]).

EPIC sexual summary score as a function of treatment arm

As previously reported, there was no significant difference between EPIC summary score based upon randomization ($P = .6$, Figure E1).[11,12] Those with minimal to no sexual dysfunction at baseline (EPIC >60) had better sexual function at 36 months with the use of spacer (55.4; standard error of the mean [SEM], 3.9) compared with control (41.3 [SEM, 5.1], $P = .033$) with a smaller difference in sexual bother (57.7 [SEM, 4.1] vs 44.5 [SEM, 5.4], $P = .10$), which resulted in a borderline difference in overall sexual summary score ($P = .07$, Fig 3A). For those with better baseline QOL, the difference in EPIC summary score favoring spacer at 15 ($P = .069$) and 36 months ($P = .058$) of 10 and 13 points, respectively, crossed the threshold for an MID of 10 to 12 points.[15] There was no difference in function, bother, or sexual summary score in those with poor baseline QOL (EPIC ≤60, $P > .5$, Fig 3B).

For men with good baseline QOL (EPIC >60), we assessed the likelihood of having 11- or 22-point declines in QOL summary (where 11 points is a threshold established as an MID and 22 points is twice that threshold). A statistically nonsignificant difference was noted in the proportion having 1× MID declines on the control (75%) compared with the spacer arm (54%) at 36 months ($P = .06$, Fig 4A). There was a similar relationship for the 2× MID threshold, suggesting clinical significance even though statistical significance was not reached, with 60% of control men having a 22-point decline at 36 months compared with 41% of spacer men ($P = .11$, Fig 4B).

ED as a function of treatment arm

At baseline, 96% of men completed the sexual portion of the QOL survey; 41% had adequate sexual QOL (EPIC >60), 89% of this subset had erections sufficient for intercourse, and of these, response rate to the extended follow-up study was 63%. To measure erections sufficient for intercourse at baseline and 36 months, this yielded a usable sample of 22% (0.96 × 0.41 × 0.89 × 0.63 = 0.22) of those who enrolled (n = 49 [spacer, n = 33; control, n = 16]). In this group of men, the use of a spacer resulted in a greater likelihood of having erections firm enough for intercourse in the preceding 4 weeks ($P = .049$), which was apparent from 6 months onward and reached a difference of 67% versus 38% at 36 months (adjusted OR, 1.34 [95% CI, 1.02-1.76], Fig 5A).

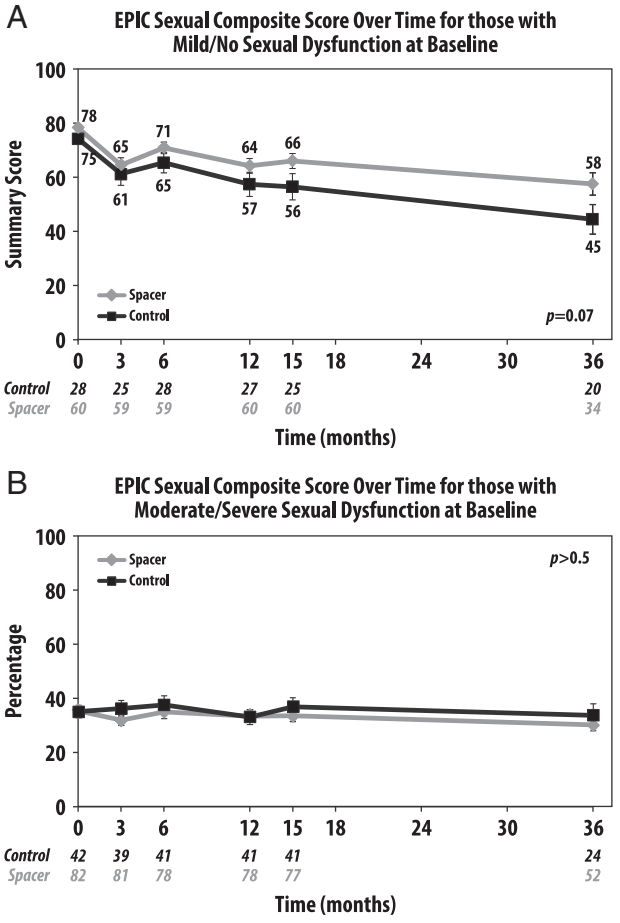

Figure 3 Expanded Prostate Cancer Index Composite (EPIC) sexual summary score over time (and standard deviation) as a function of treatment arm for those with better sexual quality of life (EPIC >60) at baseline (A) or for those with moderate-severe sexual dysfunction (EPIC ≤60) at baseline (B).

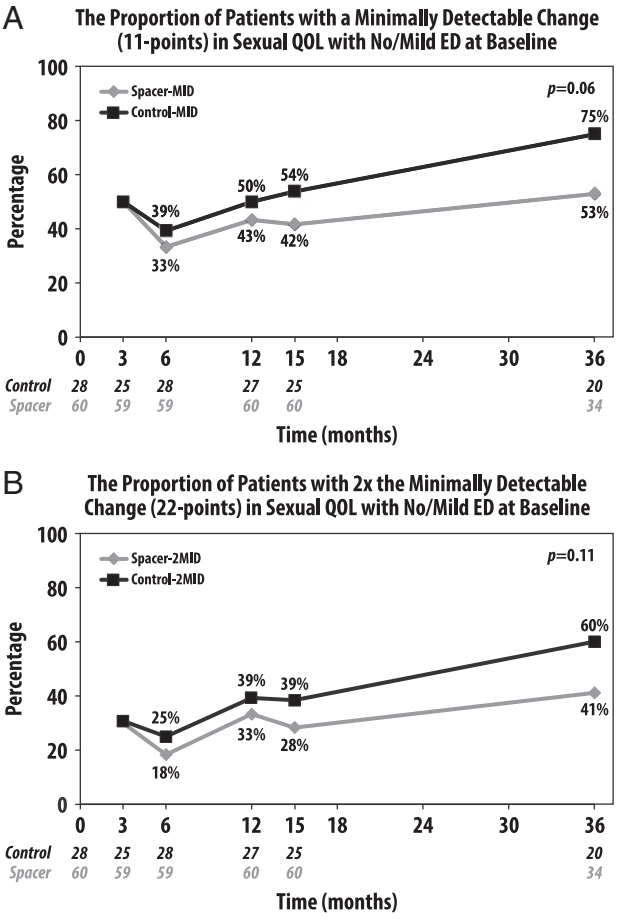

Figure 4 For men with better baseline sexual function (EPIC >60), the percentage of patients over time by treatment arm having a decline in sexual function meeting threshold for MID (11 points) (A) or 2× MID (22 points) (B). ED, erectile dysfunction; QOL, quality of life; MID, minimal clinically important difference. See Fig 3 for other abbreviations.

Individual EPIC items

To gain a robust understanding of differences between arms, the responses to the individual EPIC items were analyzed when stratified by those with better (Table 1) or worse (Table E2) sexual QOL at baseline. All responses were included (regardless of whether men answered at each time point) and were dichotomized as noted. For those with worse baseline sexual QOL upon enrollment, there were no differences with a spacer for any items.

In the men with better QOL at baseline, although there were no differences between control or spacer at randomization, at 3 years there were statistically significant differences for 6 of 9 functional items and 1 of 4 bother all favoring spacer (Table 1, Fig 5B). For example, no men reported erection ability as "very poor" or "poor" at baseline, but at 3 years this was 47% in the control arm compared with 19% in the spacer arm ($P < .05$). Similarly, "moderate" to "severe" sexual bother increased by 41% in the control arm versus 18% in the spacer arm ($P < .05$).

Discussion

The results for changes in sexual QOL reported here after IMRT are similar to those previously published.[18] Despite differences in penile bulb dose, we did not detect an overall difference in QOL with the prostate/rectal spacer.[12] Nevertheless, given the many men with poor baseline function, we hypothesized a substantial "floor effect" by which QOL would not worsen due to incident ED. This was clearly demonstrated when limited to the 59% of men with poorer baseline sexual QOL because there was no discernible difference between arms at 3 years and only a 4-point decline (on a 0-100 scale) in average sexual summary score. When limited to the 41% of men with better baseline EPIC scores, however, there was a 23-point decline with an apparent meaningful 13-point difference between arms ($P = .07$) that manifested as greater differences in sexual function ($P = .03$) than sexual bother ($P = .1$). These results suggest that in

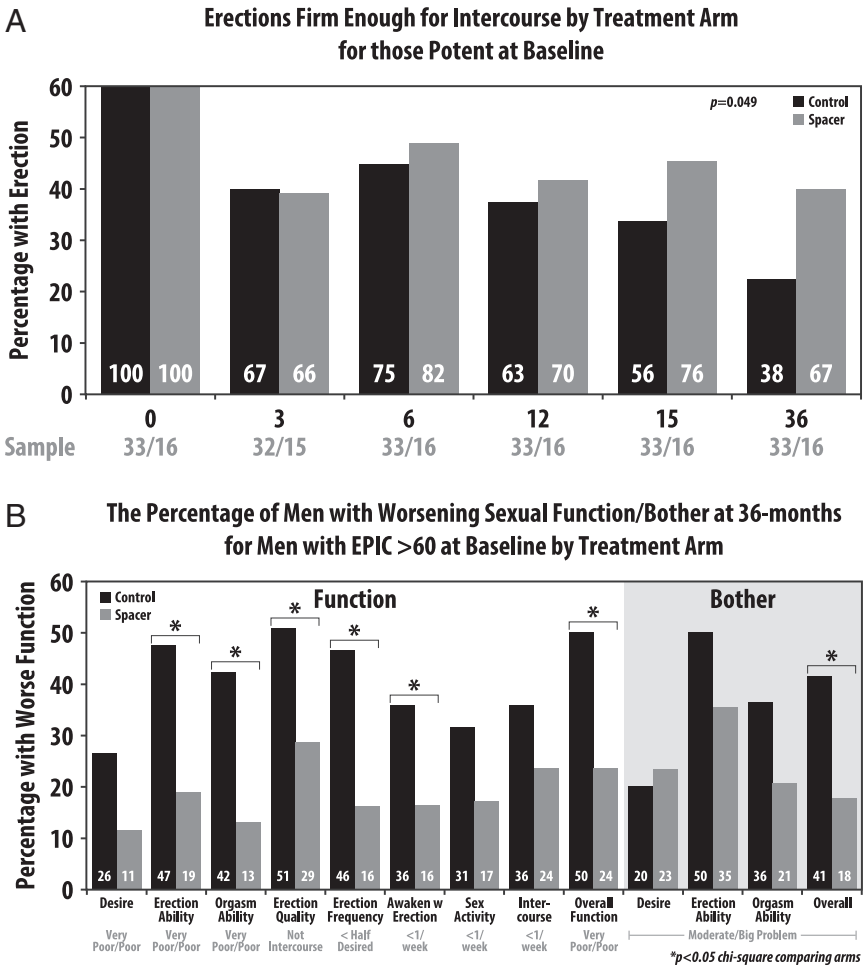

Figure 5 (A) Erections firm enough for intercourse as a function of treatment arm for men with EPIC >60, who had erections sufficient for intercourse at baseline, and responded at baseline and 3 years. (B) The difference in the percentage of men with good baseline function reporting "moderate" to "severe" problems for each of the EPIC sexual domain items between baseline and 3 years as a function of treatment arm. *$P < .05$. Abbreviation as in Fig 3.

appropriately selected men the spacer may lead to an improvement in sexual QOL after IMRT.

Based upon previous analyses, those with an EPIC summary score >75 are defined as having no sexual dysfunction, whereas those patients with scores of 61 to 75 have mild sexual dysfunction and those with lower scores have moderate to severe sexual dysfunction.[14] We used a subset analysis based upon this previously established stratification (≤60 vs >60). The MID for this instrument has been documented as 10 to 12 points.[16] In those patients with better baseline summary, we found a 10-point difference between randomized arms at 15 months and a 13-point difference at 36 months, although neither was statistically significant. In addition, consistent with other analyses, we also assessed potency using the single question on erections firm enough for intercourse where there were more effective erections at 3 years for spacer (67%) compared with control (38%, $P = .049$) groups.[16] As such, the number needed to treat to preserve erectile function in 1 man at 3 years was 3.4. In addition, for all 13 questions in the sexual domain, there were numeric differences favoring spacer for 12 of 13 questions, which were statistically different for 7 (6 in the functional domain and 1 in the bother domain).

We observed that 70% of men maintained erectile function at 1 year and 57% at 3 years in both arms of the study. Recently a population-based analysis using EPIC found erections sufficient for intercourse of 53% at 3 years following external beam RT.[18] Others have reported rates of potency preservation between 41% and 70% at 2 years.[3,4,19-21] However, differences in radiation technique, dose, and the QOL instruments make these comparisons difficult. Recently, the use of magnetic resonance imaging scans planned "vessel sparing" IMRT (most delivered with combined IMRT and brachytherapy) reported erections suitable for intercourse of 87% at 2 years for men potent at baseline, which was substantially better than predicted.[22]

Several studies have looked at the association between penile bulb radiation dose and ED following external beam

Table 1 Individual sexual items in those with better baseline sexual function

		Control (n = 28)						Spacer (n = 60)					
		BL	3 mo	6 mo	12 mo	15 mo	36 mo	BL	3 mo	6 mo	12 mo	15 mo	36 mo
Sexual function (%)	Desire (very poor/poor)	3.6	15.4	14.3	21.4	19.2	30.0	3.3	22.0	13.3	15.0	15.0	14.7
	Erection ability (very poor/poor)	0.0	12.0	17.9	20.0	28.0	47.4[a]	0.0	12.1	8.5	20.3	17.0	18.8[a]
	Orgasm ability (very poor/poor)	0.0	24.0	14.3	20.0	24.0	42.1[a]	0.0	13.8	6.8	11.9	11.9	12.9[a]
	Erection quality (<intercourse)	14.3	30.8	25.0	39.3	42.3	65.0[a]	6.7	30.5	15.0	30.0	26.7	35.3[a]
	Erection Frequency (<half desired)	3.6	23.1	14.3	17.9	23.1	50.0[a]	1.7	15.3	8.5	11.7	15.0	17.7[a]
	Awaken erection (<1/wk)	39.3	53.9	50.0[a]	60.7[a]	72.0[a]	75.0[a]	25.0	37.3	28.3[a]	31.7[a]	33.3	41.2[a]
	Sex activity (<1/wk)	28.6	46.2	35.7	53.6	42.3	60.0	30.0	39.0	36.7	45.0	38.3	47.1
	Intercourse (<1/wk)	39.3	50.0	57.1	64.3	57.7	75.0	38.3	49.2	41.7	56.7	51.7	61.8
	Overall function (very poor/poor)	0.0	19.2	17.9	25.0	19.2	50.0[a]	0.0	17.2	10.0	18.6	16.7	23.5[a]
Sexual bother (%)	Desire	0.0	11.5	7.1	18.5	32.0[a]	20.0	3.3	15.3	15.3	18.3	13.3[a]	26.5
	Erection ability	0.0	16.0	17.9	25.9	33.3	50.0	0.0	15.3	10.2	21.7	16.7	35.3
	Orgasm ability	3.6	12.0	17.9	26.9	20.8	40.0	0.0	17.0	8.5	18.6	10.0	20.6
	Overall	3.6	7.7	10.7	21.4	19.2	45.0[a]	0.0	17.0	10.2	15.0	15.0	17.7[a]

Responses to individual items on sexual domain dichotomized based upon sexual function as indicated and for sexual bother dichotomized based upon the percentage of patients reporting "moderate or big" bother for each item. [a]Items statistically different between the control and spacer groups (χ^2 $P < .05$).

RT.[23] In the Radiation Therapy Oncology Group 9406 trial, there was higher ED for those with penile bulb dose greater than the median (52.5 Gy).[4] Others noted correlations between ED and doses to the penile bulb at 30, 45, 60, and 75 Gy.[24] Analysis of the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial from Great Britain established a broad range of dosimetric goals, and we identified a higher likelihood of achieving these goals with the use of the prostate/rectal spacer as well as a correlation between meeting these goals and maintaining erectile function. Not all studies support the association between penile bulb dose and ED; however, a meta-analysis of 8 such studies scored the reliability of reports and found a higher quality of studies in those supporting the association between penile bulb dose and ED than those unable to find such an association.[25]

Despite the associations noted between penile bulb dosimetry and the use of the prostate rectal spacer, it is unclear why the use of a spacer resulted in a reduction in penile bulb dose. One possibility is that, with the use of inverse optimization, the treatment planning algorithms will favor solutions that attempt to spare the rectum with less priority placed on structures with lower priority such as the penile bulb. If the planning system has difficulty achieving rectal goals, it is unlikely that the planning process will routinely lead to favorable penile bulb doses; however, if the use of a rectal/prostate spacer substantially decreases the dose to the rectum, this may increase the ability of the optimization algorithm to address secondary planning goals such as the penile bulb. The average doses achieved for the penile bulb were favorable compared with many previous studies (mean dose: control, 21; spacer, 11 Gy). Nevertheless, a dose-dependent relationship between dose and erectile function was observed even with these lower doses, which was 51% for <8 Gy, 40% for 8 to 24 Gy, and 34% for >24 Gy ($P = .03$). This is consistent with a recent report from the UK CHHiP trial that advocated a mean penile bulb goal of <20 Gy and is thus suggestive that it may be appropriate to target even lower penile bulb doses than have been previously recommended.[17,26] Given that a penile bulb dose of 21 Gy is already considered acceptable by most standards, it is likely that no further effort was placed to reduce doses. We postulate that if there was more emphasis to reduce doses, lower doses could have been obtained in the control arm, which could have partially mitigated the effect seen with a spacer.

There are a number of limitations to such post hoc sub set analysis. The small sample size of patients with adequate sexual function at baseline limited the ability to detect differences. Within this small defined subset, differences in overall EPIC summary score (average and the proportion with MID) were suggestive of a difference but did not achieve statistical significance ($P = .06$-$.07$). Furthermore, analysis of the single question on erectile function did suggest a difference in quality of erections firm enough for intercourse over time ($P = .049$). For all questions in the sexual domain, statistical differences were identified in 7 of 13 items, each favoring the spacer arm. Nevertheless, there are also several strengths in the current analysis, including that the results were from a blinded phase 3 trial in which sexual QOL was prospectively

collected as part of planned analyses; in addition, there were no differences between arms in baseline QOL, age, race, body mass index, treatment, follow-up, or response. Although these conclusions are based on an unplanned analysis, the cut-points both for subset analysis and determination of MID were selected based on previously established thresholds. In addition, the analysis of penile bulb dose was preplanned, and we did see dosimetric differences that were statistically significant and fit within the context of multiple previous studies associating penile bulb dosimetry and ED. It is also worth noting that no previous prospective randomized trials of other radiation treatment modalities (such as IMRT, image guidance, proton therapy, or stereotactic therapy) have identified such an improvement in ED and sexual QOL. These reported results, although provocative, have a number of limitations and must be viewed as hypothesis generating with further studies needed to validate the observations.

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