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Clinical Investigation

Rectal Hydrogel Spacer Improves Late Gastrointestinal Toxicity Compared to Rectal Balloon Immobilization After Proton Beam Radiation Therapy for Localized Prostate Cancer: A Retrospective Observational Study

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Purpose: Our purpose was to compare dosimetric parameters and late gastrointestinal outcomes between patients treated with proton beam therapy (PBT) for localized prostate cancer with rectal balloon immobilization versus a hydrogel rectal spacer.
Methods and Materials: Patients with localized, clinical stage T1-4 prostate adenocarcinoma were treated at a single institution using conventionally fractionated, dose-escalated PBT from 2013 to 2018. Patient-reported gastrointestinal toxicity was prospectively collected, and the incidence of rectal bleeding was retrospectively reviewed from patient records.
Results: One hundred ninety-two patients were treated with rectal balloon immobilization, and 75 were treated with a rectal spacer. Rectal hydrogel spacer significantly improved rectal dosimetry while maintaining excellent target coverage. The 2-year actuarial rate of grade 2+ late rectal bleeding was 19% and 3% in the rectal balloon and hydrogel spacer groups, respectively ($P = .003$). In univariable analysis, the probability of grade 2+ rectal bleeding was significantly correlated with increasing rectal dose. In multivariable analysis, only receipt of spacer hydrogel (hazard ratio, 0.145; $P = .010$) and anticoagulation use (hazard ratio, 5.019; $P < .001$) were significantly associated with grade 2+ bleeding. At 2-year follow-up, patient-reported Expanded Prostate Cancer Index Composite bowel quality of life composite scores were less diminished in the hydrogel spacer group (absolute mean difference, 5.5; $P = .030$).

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Conclusions: Use of rectal hydrogel spacer for prostate PBT is associated with a significantly lower incidence of clinically relevant, late rectal bleeding and lower decrement in long-term, patient-reported bowel quality of life compared with rectal balloon immobilization. Our results suggest that hydrogel spacer may improve rectal sparing compared with rectal balloon immobilization during PBT for prostate cancer.

Introduction

External beam radiation therapy (EBRT) is a well-established standard of care for the primary treatment of localized prostate cancer.[1] The majority of patients undergo photon-based intensity modulated radiation therapy (IMRT), and a minority receive proton beam therapy (PBT).[2,3] The utilization of PBT ranges from 2% to 6%, depending on insurance type, although this figure is expected to increase as the number of proton facilities grows.[4]

Although PBT can dramatically reduce integral dose to organs at risk, normal tissues immediately adjacent to the target volume may still receive high dose exposure.[5] Rectal toxicity, specifically bleeding, remains a concern for EBRT with either IMRT or PBT.[6-9] To decrease the risk of late rectal toxicity, our institution adopted placement of a commercially available Food and Drug Administration−approved perirectal hydrogel spacer (SpaceOAR; Augmenix, Waltham, MA) for PBT. This replaced the routine use of a rectal balloon for treatment. In brief, a bioabsorbable hydrogel is inserted between the rectum and prostate before radiation therapy to create a temporary anatomic separation.[10] In a prospective randomized trial, this device decreased the rate of late rectal toxicity after IMRT for prostate cancer.[11] Although dosimetric analyses suggest improved rectal sparing with the use of a rectal spacer during PBT, clinical outcomes after this approach are lacking.[12-16] We report the first large, retrospective experience with clinical endpoints of using a hydrogel rectal spacer for PBT for localized prostate cancer. We hypothesized that using rectal hydrogel spacer would decrease the incidence of late gastrointestinal (GI) toxicity, particularly rectal bleeding, compared with using rectal balloon immobilization during PBT for localized prostate cancer.

Methods and Materials

Patients

The records of 313 men treated with PBT at a single institution between 2013 and 2018 were reviewed from a prospective, institutional review board−approved registry. Patients were excluded if they received prostatectomy, had prior radiation to the pelvis, underwent combined EBRT with a proton boost, or had less than 6 months of follow-up after completion of radiation therapy. Baseline patient characteristics are summarized in Table 1. All biopsy pathology results were reviewed at our institution. All patients underwent guideline-concordant staging including: digital rectal examination, pretreatment prostate-specific antigen measurement, pelvic computed tomography (CT) and/or multiparametric magnetic resonance imaging (MRI) for intermediate- or high-risk patients, and technectium-99 bone scans in high-risk patients.[1] Patients in the spacer cohort uniformly received pretreatment MRI scans, whereas those in the balloon cohort had MRI scans according to the treating physician's discretion.

Radiation therapy treatments and procedures

Before radiation therapy, all patients underwent intraprostatic, transperineal placement of 3 Visicoil fiducial markers (IBA Dosimetry GmbH, Schwarzenbruck, Germany) under the care of a board-certified urologist. Patients in the spacer cohort concurrently had the SpaceOAR hydrogel spacer placed between the anterior rectum and Denonvillier's fascia, via a previously described transperineal approach under rectal ultrasound guidance.[10] Patients were ineligible for rectal hydrogel spacer if they had radiographically overt extracapsular extension ([ECE]; T3a), seminal vesicle invasion ([SVI]; T3b), or T4 disease owing to concern for undercovering microscopic disease. Most patients with high-risk cancer did not receive the spacer.

All patients underwent bowel preparation before CT-based simulation with lower extremity immobilization using a vacuum-locked mold. Patients in the nonspacer cohort underwent insertion of a rectal balloon, filled with 90 mL of water, at time of simulation and for each daily treatment. Patients in both cohorts were instructed to follow a low-residue diet during treatment and were given stool softeners/laxatives as needed to maintain consistent interfraction rectal volume. Nearly all patients received 79.2 cobalt Gray equivalent ([CGE]; relative biological effectiveness = 1.1) in 44 fractions via the IBA Proteus Plus system (Louvain-la-Neuve, Belgium). Two lateral beams delivered radiation, with 1 or 2 fields daily. Patients treated before 2015 were mostly treated with uniform scanning (US) beams, whereas those after 2015 were treated exclusively with pencil beam scanning (PBS). Patients with unfavorable intermediate or high-risk disease typically received 6 to 24 months of concurrent and adjuvant androgen deprivation therapy.

Treatment planning, dose verification, and image guided radiation therapy were previously detailed in a prior report.[9] In brief, target structures and organs at risk were

Table 1 Baseline and treatment characteristics between cohorts

Patient characteristics	Rectal balloon (n = 192)	Hydrogel spacer (n = 75)	*P* value
Mean age (± SD), Y	68.7 (±6.3)	67.9 (±6.9)	.329
D'Amico risk group			
Low	38 (20%)	8 (11%)	.005
Intermediate	104 (54%)	57 (76%)	
High	50 (26%)	10 (13%)	
T-stage			
T1C	103 (54%)	49 (65%)	.108
T2	78 (41%)	26 (35%)	
T3/4	10 (5%)	0 (0%)	
Mean PSA, ng/mL	9.9	10	.944
WHO grade group			
1	42 (22%)	14 (19%)	.004
2-3	116 (61%)	57 (76%)	
4	14 (7%)	3 (4%)	
5	20 (10%)	1 (1%)	
Mean prostate volume (±SD), cm^3	42.2 (±19)	42.1 (±23)	.984
No aspirin use	118 (61%)	48 (64%)	.700
No anticoagulation	170 (89%)	69 (92%)	.407
No smoking history	103 (58%)	52 (69%)	.104
No hemorrhoids	166 (86%)	63 (84%)	.605
No IBD	188 (98%)	73 (97%)	.773
No hypertension	96 (50%)	37 (49%)	.922
Median follow-up, mo	19 (IQR:13.4)	22 (IQR:11.2)	.060
Mean prostate/SV PTV Rx dose (±SEM)	78.8 CGE (±0.13)	79.0 CGE (±1.1)	.374
Pencil beam scanning	143 (75%)	75 (100%)	<.001
No pelvic nodal irradiation	173 (90%)	57 (92%)	.668
No ADT	121 (63%)	43 (68%)	.4519

Abbreviations: ADT = androgen deprivation therapy; CGE = cobalt Gray equivalent; IBD = inflammatory bowel disease; IQR = interquartile range; PSA = prostate-specific antigen; PTV = planning target volume; SD = standard deviation; SEM = standard error of the mean; SV = seminal vesicle; WHO = World Health Organization.

delineated on planning CT (and pelvic MRI, when available) per the Radiation Therapy Oncology Group contouring guidelines. For low- to intermediate-risk disease, the clinical target volume (CTV) generally included the prostate and proximal 1 to 2 cm of the seminal vesicles depending on physician discretion. For high-risk disease, the CTV was prostate and entire seminal vesicles for high-risk disease. A uniform 5 mm CTV to planning target volume (PTV) was used except for a 4 mm posterior margin. At physician discretion, in high-risk patients, pelvic lymph nodes were treated to 45 to 50 CGE, with a sequential cone down to the prostate only to the total dose. The rectum was delineated based on planning CT and extended between the ischial tuberosities inferiorly and the sigmoid flexure superiorly. For dosimetric analyses in this study, the segment of rectum 1 cm superior and inferior to the PTV was used as the evaluation rectal volume. At our institution, this rectal volume is used—alongside the full rectal volume and rectal wall volume—as a conservative measure of dose to organs at risk. Treatment planning was performed using Xio (Impac Medical Systems, Maryland Heights, MO) or Raystation (RaySearch Laboratories AB, Stockholm, Sweden) for US and PBS, respectively. Patient-specific quality assurance (QA) and daily image guidance with orthogonal kilovoltage films were used. QA simulation scans were undertaken midcourse at the discretion of the treating physician.

Follow-up evaluation and endpoints

Patients were evaluated weekly during treatments and typically followed up at 3 to 6 month intervals until year 4 and annually thereafter. The majority of patients had an in-person follow-up visit, including prostate-specific antigen and physical examination, with digital rectal examination at the discretion of the physician. The coprimary endpoints of this study are incidence of late rectal bleeding and bowel quality of life (QOL). Late events were considered to be those that occurrent 3 months posttreatment. Rectal bleeding was retrospectively graded per the Common Terminology Criteria for Adverse Events version 4.0 using follow-up data (Table E1, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026).

Patients with a history of hemorrhoidal bleeding or inflammatory bowel disease were excluded from the grade 1 bleeding outcome group. Grade 2 bleeding events included medical interventions (steroid suppositories or enemas) or minor, outpatient procedures (laser photocoagulation, argon plasma coagulation, or electrocautery). Hospital admission and/or blood transfusions were considered grade 3 bleeding events. No patients in the entire study cohort experienced grade 4 bleeding. Bowel symptoms were evaluated at baseline and follow-up using the Expanded Prostate Cancer Index Composite (EPIC) bowel domain, which is a validated tool for measuring QOL in patients with prostate cancer.[17] Scores were recorded from 0 (worse) to 100 (best) at baseline, 6 months, 1 year, 1.5 year, and 2.0 year time points.

Statistical analysis

Statistical analyses were performed using R version 4.6 (R Foundation for Statistical Computing, Vienna, Austria). A P value of .05 was the threshold for statistical significance throughout this analysis. For baseline patient and treatment parameters, differences between groups were evaluated using Welch's T test and the χ^2 test for continuous and categorical variables, respectively. Differences in dose-volume histogram (DVH) parameters between groups were measured using 1-way analysis of variance (ANOVA). The cumulative incidence of events was estimated using the Kaplan-Meier method, with differences between groups measured via the log-rank test. Sensitivity analyses on time-to-event data excluded subgroups that were imbalanced between cohorts. For EPIC bowel outcomes, repeated measures 2-way ANOVA was used to compare differences between groups at different time points.

Univariable logistic regression was used to model rectal DVH parameters and incidence of rectal bleeding. The predicted probability of rectal bleeding was generated by applying the regression model over an interpolated rectal volume range. The performance of various DVH parameters in predicting rectal bleeding was compared using receiver operating characteristic curves. A multivariable Cox proportional hazards model was used to explore the association between baseline patient characteristics, treatment group, and the rates of rectal bleeding. Scaled Schoenfeld and Martingale residuals were calculated to validate the assumption of proportional hazards and linearity, respectively.

Results

A total of 267 patients, 192 treated with rectal balloon immobilization and 75 treated with rectal spacer, were included in the final analysis. The median follow-up was 19 and 22 months, respectively. Baseline patient characteristics and treatment parameters are summarized in Table 1. There were 30 (16%) and 12 (16%) patients with a history of hemorroidal bleeding or inflammatory bowel disease in the rectal balloon and hydrogel spacer cohorts, respectively, and they were not counted in grade 1 bleeding events (but were counted for grade 2+ events). More patients in the rectal balloon cohort had high-risk and/or World Health Organization grade 5 disease owing to exclusion of ECE, SVI, or T4 disease for spacer application. More patients in the rectal balloon cohort were treated with US; this was related to our center switching to exclusively PBS after 2015. Sensitivity analyses excluding patients with high-risk, T3/4, or World Health Organization grade 5 disease or those treated with US did not change the primary outcomes (Fig. E1, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026).

Patients tolerated application of rectal hydrogel well. Only 11% reported transient, low-grade (no intervention) symptoms beyond those experienced by patients undergoing fiducial placement alone (hematuria and perineal pain). This is similar to the 10% rate reported by Mariados et al.[18] These symptoms typically resolve by time of simulation CT 2 to 3 weeks after placement. Qualitatively, symptoms reported by patients treated with rectal spacer but not by patients treated with rectal balloon immobilization included low pelvic pressure (n = 4), smaller stool calibers (n = 2), and mild tenesmus or dyschezia (n = 2).

Rectal dose DVH parameters were significantly superior in patients treated with rectal hydrogel spacer (Fig. 1). Concurrently, there were no differences in target volume coverage between the 2 groups: The PTV receiving at least 95% of the prescription dose was 99.5% and 99.6% (P = .589), and the minimum dose to 95% of the PTV was 79.0 and 78.8 CGE (P = .374), respectively (Fig. E2, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026).

At 2-year follow-up, the actuarial rate of any rectal bleeding (grade 1+) was 35% and 13% in the rectal balloon and hydrogel spacer groups, respectively (Fig. E3, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026). The 2-year actuarial rate of grade 2+ bleeding was 19% and 3%, respectively. The cumulative incidence of grade 2+ bleeding (log-rank P = .003) was significantly lower in the hydrogel spacer group compared with the rectal balloon group (Fig. 2). There were 2 grade 3 bleeding events in the balloon cohort versus 0 in the spacer cohort; there was no grade 4+ bleeding in either arm.

Inclusion of both rectal balloon and rectal spacer treatments was necessary to allow enough variance in the rectum parameters to robustly fit a logistic model. Among all patients, rectum (segment 1 cm inferior and superior to PTV) V65CGE, V70CGE, and V75CGE was associated with grade 2+ rectal bleeding (Table E2, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026). Rectum V81CGE(cc) was a poor parameter for regression because only 24% of treatments had a nonzero value. These normal tissue complication probability curves demonstrate both a volume and dose response (Fig. 3). Calibration plots showed that the prediction models were well fitted to observed data (Fig. E4, available online at https://doi.org/

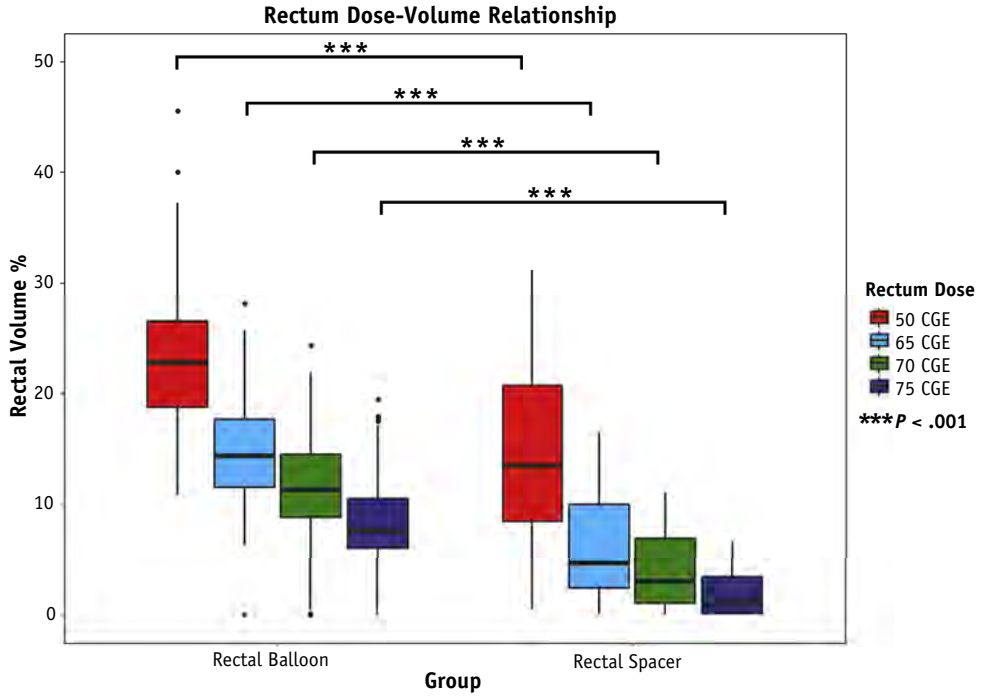

Fig. 1. Rectum dose-volume histogram comparison between rectal balloon and rectal spacer cohorts. Boxplot meridians and whiskers represent means and 1.5 times interquartile range, respectively. One-way analysis of variance (ANOVA) *P* values are shown.

10.1016/j.ijrobp.2020.01.026). On receiver operating characteristic analysis, rectum V75CGE (area under the curve, 0.672) was the best predictor of rectal bleeding (Fig. E5, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026). The predicted probability of grade 2+ bleeding can be limited to less than 15% if the rectum V65CGE, V70CGE, and V75CGE are constrained to less than 15%, 12%, and 8.6%, respectively. Concordantly, although 91%

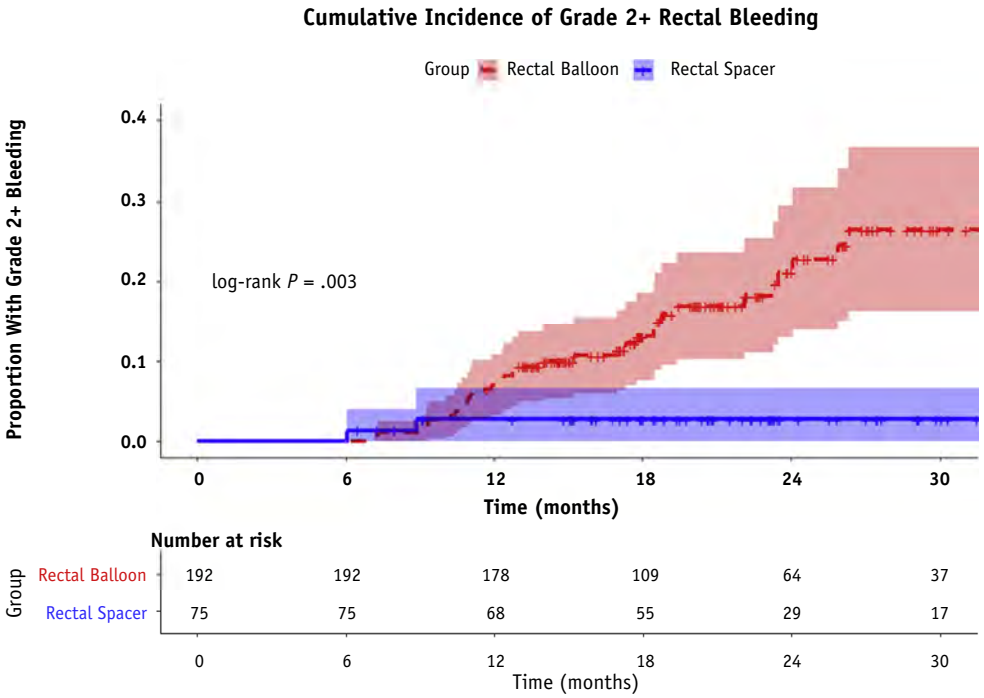

Fig. 2. Cumulative incidence of clinically significant bleeding (Common Terminology Criteria for Adverse Events [CTCAE] grade 2+, log-rank $P = .003$). Lines represent Kaplan-Meier estimates, and shaded area represents 95% confidence interval.

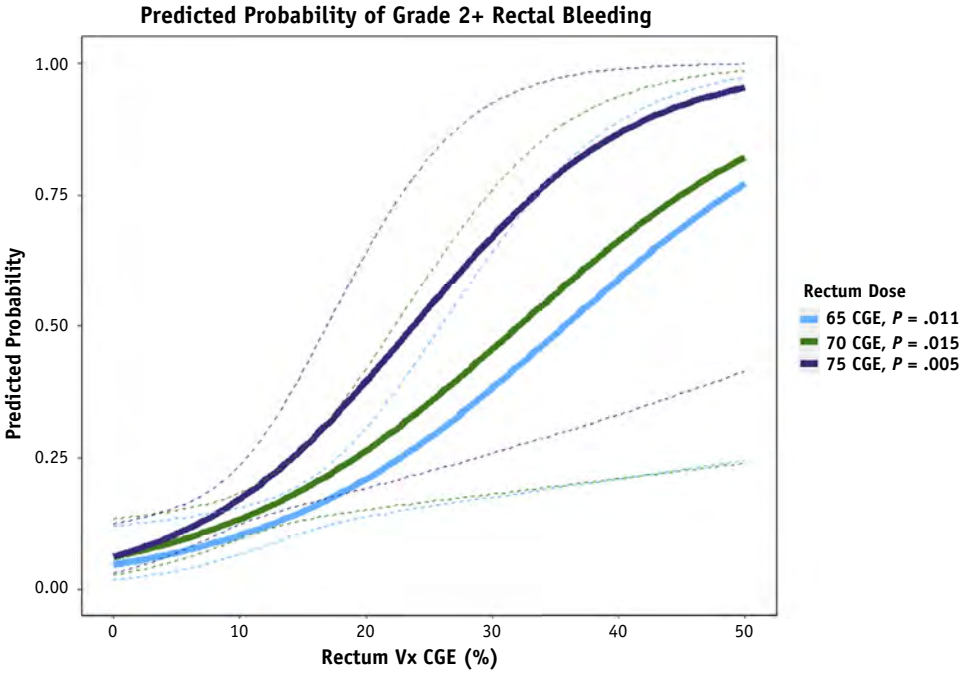

Fig. 3. Predicted probability of late grade 2+ rectal bleeding versus percent volume of rectum receiving at least 65 cobalt Gray equivalent (CGE), 70 CGE, or 75 CGE. Dashed lines represent 95% confidence interval. Logistic regression *P* values shown.

of treatments in the spacer cohort were able to achieve the V75CGE constraint, only 56% in the rectal balloon cohort conformed to this parameter.

In our Cox proportional hazards model, receipt of spacer hydrogel was significantly protective against late rectal bleeding (grade 1+: hazard ratio [HR], 0.287; $P < .001$; grade 2+: HR, 0.145; $P = .010$) whereas anticoagulation use was directly prognostic (grade 1+: HR, 3.001 [$P = .002$]; grade 2+: HR, 5.019 [$P < .001$]) (Table 2). There was a trend toward aspirin use and grade 2+ rectal bleeding (HR, 1.757; $P = .120$). The global Schoenfeld residuals *P* value was .305, confirming proportional hazards of the model. Rectal DVH parameters were not included in the final multivariable model owing to strong dependency of rectal dose on presence of hydrogel spacer (Fig. 1) and violation of the linearity assumption (Fig. E6, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026).

In the spacer cohort, the EPIC bowel questionnaires were prospectively completed by 72 of 75 (96%), 24 of 75 (32%), 41 of 75 (54%), 33 of 75 (44%), and 27 of 75 (36%) patients at baseline, 6, 12, 18, and 24-month follow-up, respectively. In the rectal balloon cohort, the EPIC bowel questionnaires were completed by 164 of 192 (85%), 68 of 192 (35%), 86 of 192 (45%), 81 of 192 (42%), and 43 of 192 (22%) patients at the same time points. There was no difference in pre-EBRT values between the spacer and balloon arms: Mean EPIC bowel score was 92.3 versus 93.4 ($P = .176$), respectively. However, patients in the rectal balloon arm had a larger posttreatment decrement in global bowel QOL compared with those in the spacer arm (Fig. 4). At 2-year follow-up, the absolute mean difference between groups was 5.5 ($P = .030$). On 2-way ANOVA, there were statistically significant differences between the spacer and nonspacer cohorts ($P = .0459$), with a significant interaction between receipt of spacer hydrogel and time of follow-up ($P = .0241$). Subdomain values of the EPIC bowel inventory (eg, rectal frequency or loose stools) were not specifically collected. However, the disparity in EPIC bowel scores was nearly preserved even after excluding patients with rectal bleeding, with an absolute mean difference of 5.0 favoring the spacer group after 2 years ($P = .072$; Fig. E7, available online at https://doi.org/10.1016/j.ijrobp.2020.01.026).

Discussion

Our results suggest that hydrogel spacer may improve rectal sparing compared with rectal balloon immobilization during PBT for prostate cancer. We showed that patients treated with rectal hydrogel spacer during PBT for prostate cancer had a significantly lower incidence of late grade 2+ rectal bleeding compared with those treated with rectal balloon immobilization. Those in the spacer group also reported superior global bowel symptoms after 2-year follow-up, compared with those in the rectal balloon group. These findings are significant because late rectal toxicity remains a limiting factor in EBRT for prostate cancer. Although toxicity grading is heterogeneous among different PBT studies, thus making direct comparisons imprecise, the rates of clinically significant late rectal toxicity range from 3% to higher than 20%,[6-9,19] with

Table 2 Cox proportional hazards multivariable model of any RB (CTCAE grade 1+ RB) or clinically significant bleeding (CTCAE grade 2 RB)

Covariate	HR grade 1+ bleeding (95% CI)	*P* value grade 1+ bleeding	HR grade 2+ bleeding (95% CI)	*P* value grade 2+ bleeding
Spacer (yes vs no)	0.287 (0.137-0.601)	<.001	0.145 (0.034-0.641)	.010
Risk				
Low (reference)	N/A	N/A	N/A	N/A
Intermediate	0.886 (0.479-1.64)	.698	0.738 (0.295-1.85)	.527
High	1.065 (0.487-2.33)	.8875	1.217 (0.406-3.64)	.726
T-stage				
T1 (reference)	N/A	N/A	N/A	
T2	0.725 (0.434-1.21)	.219	0.771 (0.366-1.62)	.494
T3/4	0.505 (0.108-2.37)	.386	0.297 (0.030-2.83)	.289
Hypertension (yes vs no)	1.253 (0.775-2.03)	.358	1.123 (0.546-2.31)	.753
Hemorrhoids (yes vs no)	0.584 (0.247-1.38)	.220	0.396 (0.091-1.72)	.216
Current smoking (yes vs no)	0.733 (0.257-2.09)	.561	1.470 (0.410-5.26)	.554
Anticoagulation (yes vs no)	3.001 (1.51-5.95)	.002	5.019 (1.94-12.97)	<.001
Aspirin (yes vs no)	1.400 (0.861-2.28)	.175	1.757 (0.863-3.57)	.120
PBS (yes vs no)	1.164 (0.639-2.12)	.623	1.031 (0.450-2.36)	.943

Abbreviations: CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; PBS = pencil beam scanning; RB = rectal bleeding.

several prominent series reporting rates closer to the latter, in line with that observed in our rectal balloon cohort. Specifically, rectal bleeding comprised the majority of late GI toxicity events in these reports. In this study, the use of hydrogel spacer led to a reduction of late grade 2+ rectal bleeding from 19% to 3% in PBT-treated patients. One potential reason for this may be use (or omission) of the rectal balloon spacer itself. Treatment with a rectal balloon may cause local pressure and irritation. In some cases, the balloon may deflect the rectal wall more anteriorly into the treatment field, increasing exposure. However, these concepts are speculative and there are no published data, to our knowledge, to support them. In future work, we will analyze patients undergoing treatment with neither device, though this comprises a small minority of our patients.

Rectal balloon immobilization theoretically reduces interfraction uncertainty introduced by variable rectal filling and gas.[20] This is important in PBT owing to the beam's range sensitivity to anatomic changes, particularly at air interfaces near a target. As such, a potential concern in using the rectal spacer in lieu of a rectal balloon is a diminished ability to control rectal filling. However, because our posterior CTV to PTV expansion is 4 mm whereas the hydrogel spacer typically creates an 8 to 13

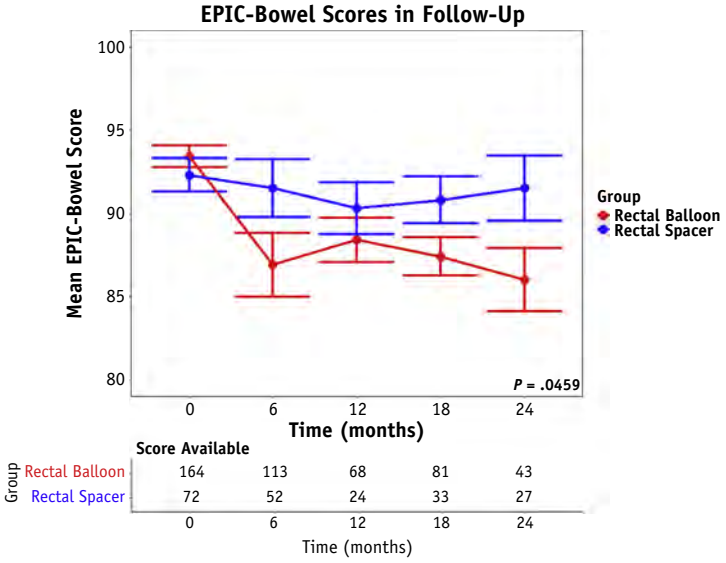

Fig. 4. Mean Expanded Prostate Cancer Index Composite (EPIC) scores, from pretreatment to 2 years posttreatment. Means ± standard error of the mean (error bars) are presented. Two-way analysis of variance (ANOVA) *P* values are shown.

mm separation between the anterior rectum and prostate,[21] PBT with spacer should have consistent rectal sparing despite modest daily variation in rectal filling. An analysis using midcourse QA scans performed in patients treated with PBT and hydrogel spacer demonstrated that high-dose exposure (≥V50%) to the rectum was within 2% of the initial planning values with use of a dietary regimen and stool softeners alone.[13]

A strength of this study was that patient-reported outcomes were prospectively collected. Patient-reported outcomes are increasingly recognized as relevant clinical trial endpoints.[22] In our study, there was a significant 5.5 point absolute difference after 2 years of follow-up in the EPIC bowel score favoring the rectal spacer cohort. Some authors have suggested a minimum difference of 5 as being clinically meaningful.[23] Furthermore, the statistically significant interaction term suggests that the differences in EPIC scores between treatment groups are also time dependent (ie, more separation with longer follow-up). Although subdomain values of the EPIC bowel inventory were not specifically collected, differences in patient-reported bowel QOL between groups were not likely driven solely by rectal bleeding because the disparity in EPIC bowel outcomes essentially persisted after adjusting for bleeding. A limitation of these data is the high drop-out rate in reporting with follow-up, although the rates are roughly similar between cohorts. A patient-level analysis of EPIC scores was not possible owing to the limited number of patients with scores at all time points.

Another significant result of this study is the generation of normal tissue complication probability curves for rectal bleeding. Retrospectively, the predicted probability of rectal bleeding can be limited to a particular threshold by constraining rectum V65CGE, V70CGE, and V75CGE below specific values. The performance of these predictors was modest, with the highest area under the curve being 0.672 for V75CGE. A limitation of this model was that rectal bleeding probabilities were simply estimated from single points on the rectum DVH, rather than from an integrated estimate of effective dose, as per the Lyman-Kutcher-Burman model.[24] Although the Lyman-Kutcher-Burman model is agnostic to any particular dose level, our model makes the a priori assumption that rectum V50CGE, V65CGE, V70CGE, and V75CGE are significant based on results of the Quantitative Analysis of Normal Tissue Effects in the Clinic.[25] Because this is a single-institution report, these constraints may not be generalizable, and further validation is required to confirm their predictive performance. Additionally, our conservative rectal DVH should be cautiously compared with series reporting whole rectum parameters. Nonetheless, these normal tissue complication probability curves are robust in the context of a single-institutional study for several reasons: They include data from 267 individual patients, they demonstrate an expected dose and volume response, and they have reasonable confidence intervals in the clinical range. Although many publications suggest normal tissue proton constraints extrapolated from those used in photon-based therapy, empirical rectal complication probabilities have not been previously reported for PBT.[26-28]

There are several other limitations in this study. First, incidences of rectal bleeding were retrospectively graded and thus subject to availability and heterogeneity of records. We would not expect this to bias the primary comparison because all patients were treated at the same institution, using the same electronic medical record and clinical protocols. During the follow-up window, there were very few intercurrent deaths in both groups, minimizing survivorship bias. A second limitation was that high-risk patients comprised a higher proportion in the rectal balloon immobilization group, in large part because patients with ECE, SVI, or local invasion were precluded from receiving hydrogel spacer. Excluding these patients from analyses did not affect the difference in incidence of rectal bleeding. Finally, although the use of rectal spacer is growing as insurance coverage increases, the added financial toxicity of this technology is an important dimension that was beyond the scope of this study.

Conclusions

We report that the incidence of rectal bleeding was significantly lower in patients treated with a rectal hydrogel spacer compared with those treated with a rectal immobilization balloon. The risk of bleeding was correlated with specific rectal dosimetric parameters. Furthermore, the former group appears to have an attenuated decrement in their global GI QOL compared with the latter. Use of hydrogel spacer and anticoagulation were significantly associated with rectal bleeding in multivariable analysis.

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