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Scientific Article

Quality Metric to Assess Adequacy of Hydrogel Rectal Spacer Placement for Prostate Radiation Therapy and Association of Metric Score With Rectal Toxicity Outcomes

Craig E. Grossman, MD, PhD, MSCE,[a] Michael R. Folkert, MD,[b] Stephanie Lobaugh, MS,[c] Neil B. Desai, MD, MHS,[d] Marisa A. Kollmeier, MD,[a] Daniel Gorovets, MD,[a] Sean M. McBride, MD, MPH,[a] Robert D. Timmerman, MD,[d] Zhigang Zhang, PhD,[c] and Michael J. Zelefsky, MD[a,*]

[a]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; [b]Department of Radiation Medicine, Northwell Health Cancer Institute, Lake Success, New York; [c]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; and [d]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas

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Abstract

Purpose: Although hydrogel spacer placement (HSP) minimizes rectal dose during prostate cancer radiation therapy, its potential benefit for modulating rectal toxicity could depend on the achieved prostate-rectal separation. We therefore developed a quality metric associated with rectal dose reduction and late rectal toxicity among patients treated with prostate stereotactic body radiation therapy (SBRT).

Methods and Materials: A quality metric consisting of prostate-rectal interspace measurements from axial T2-weighted magnetic resonance imaging simulation images was applied to 42 men enrolled in a multi-institutional phase 2 study using HSP with prostate SBRT (45 Gy in 5 fractions). A score of 0, 1, or 2 was assigned to a prostate-rectal interspace measurement of <0.3 cm, 0.3 to 0.9 cm, or ≥1 cm, respectively. An overall spacer quality score (SQS) was computed from individual scores at rectal midline and ±1 cm laterally, located at the prostate base, midgland, and apex. Associations of SQS with rectal dosimetry and late toxicity were evaluated.

Results: The majority of the analyzed cohort had an SQS of 1 (n = 17; 41%) or 2 (n = 18; 43%). SQS was associated with maximum rectal point dose (rectal Dmax; $P = .002$), maximum dose to 1 cc of rectum (D1cc; $P = .004$), and volume of rectum receiving ≥100% of prescription dose (V45; $P = .046$) and ≥40 Gy (V40; $P = .005$). SQS was also associated with a higher incidence of ($P = .01$) and highest-graded late rectal toxicity ($P = .01$). Among the 20 men who developed late grade ≥1 rectal toxicity, 57%, 71%, and 22% had an SQS of 0, 1, and 2, respectively. Men with an SQS of 0 or 1 compared with 2 had 4.67-fold (95% CI, 0.72-30.11) or 8.40-fold (95% CI, 1.83-38.57) greater odds, respectively, of developing late rectal toxicity.

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*Corresponding author: Michael J. Zelefsky, MD; E-mail: zelefskm@mskcc.org

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Conclusions: We developed a reliable and informative metric for assessing HSP, which appears to be associated with rectal dosimetry and late rectal toxicity after prostate SBRT.

Introduction

Given the anatomic proximity of the prostate to normal tissues such as the rectum, acute and late toxicities are possible with prostate cancer external beam or brachytherapy treatments. One such strategy to minimize toxicity is the insertion of a commercially supplied polyethylene glycol hydrogel rectal spacer, a polymerization solution injected transperineally under ultrasound-guidance to temporarily distance the rectum away from the prostate gland. This rectal spacer remains intact throughout a typical course of radiation therapy and is hydrolyzed 3 to 6 months after placement. The first prospective randomized clinical trial to evaluate the effect of the hydrogel rectal spacer in prostate cancer patients treated with conventionally fractionated external beam radiation therapy established its ability to increase the mean prostate-rectal separation by 1 cm; this translated into a lower rectal dose and reduced incidence of late grade 1 to 2 rectal toxicity.[1,2]

A systematic review and meta-analysis of 7 studies comparing over 1000 prostate cancer patients treated with dose-escalated external beam radiation therapy and/or brachytherapy with or without hydrogel rectal spacer placement (HSP) reported a 66% V70 rectal dose reduction with a corresponding decline in acute (RR 0.72) and late (RR 0.38) grade 1 and higher rectal toxicity, as well as superior patient-reported >3-month bowel quality of life in the presence of the spacer hydrogel.[3]

Attempts have been made to characterize the quality of HSP to accurately assess its true dosimetric- and toxicity-reduction effect given the variability of reported benefit across individual studies. However, these published HSP quality metrics[4-6] have not been universally adopted, as they are somewhat cumbersome to use and were not consistently evaluated for their utility in predicting late rectal toxicity. A secondary analysis of HSP quality in the pivotal phase 3 spacer trial demonstrated that 49% of patients had symmetrical hydrogel rectal spacers in all 3 axial slices analyzed, with a correlation between inferior composite symmetry scores and smaller rectal dose reduction relative to the prespacer plan.[4] Although informative, this metric does not assess the actual thickness of the prostate-rectal interspace (PRI) created by the spacer gel, which is more relevant to rectal dosimetry.

Because clinical observations have suggested the spacer's ability to reduce rectal dose is dependent on the quality of the implant, a universally adopted practical metric is needed. We therefore created a HSP quality metric that quantitatively characterizes the adequacy of the PRI at the prostate base, midgland, and apex, which also has the benefit of showing association with reductions in rectal dosimetry and late toxicity in men treated with prostate stereotactic body radiation therapy (SBRT).

Methods and Materials

Derivation of hydrogel rectal spacer quality metric

As previously described,[7] all patients had a 10-cc polyethylene hydrogel spacer (SpaceOAR System; Boston Scientific, Inc, Bedford, MA) introduced transperineally into the perirectal space between Denonvilliers' fascia and the anterior rectal wall under ultrasound guidance approximately 1 to 2 weeks before their magnetic resonance imaging (MRI) simulation session. Using the T2-weighted axial slices from the MRI simulation, the interspace between the posterior aspect of the prostate gland and the anterior rectal wall was measured in the anterior-posterior orientation parallel to anatomic midline. This total PRI thickness consisted of natural tissue space (ie, fat, soft tissue, and/or neurovasculature if present) and the implanted hydrogel rectal spacer (which is hyperintense on T2-weighted images). Measurements were made at rectal midline (along the left-right direction), as well as 1 cm to the right and left, as demonstrated in Fig. 1a; note, rectal midline did not necessarily correspond to the middle of the prostate gland (along the left-right direction). To obtain a representation of the PRI throughout the length of the prostate gland, measurements were made at the *base* (axial slice located 0.5-0.8 cm caudal to the most superior slice comprising the prostate base, excluding the median lobe within the bladder), *midgland* (axial slice located midway between the prostate *base* and *apex*), and *apex* (axial slice located 0.5-0.8 cm cranial to the most inferior slice comprising the prostate apex), as illustrated in Fig. 1b. Because of the occasional tortuous shape of the rectum, rectal midline was sometimes in a different location at the base, midgland, or apex slice.

PRI measurements (rounded to 1 decimal place) were assigned a value between 0 and 2 and entered into a 3 × 3 table. These numerical categories were defined as follows: a value of 0 for PRI measurements <0.3 cm, 1 for PRI measurements between 0.3 and 0.9 cm, and 2 for PRI measurements ≥1.0 cm (Fig. 2). A cutoff of 0.3 cm was chosen because this is a typical minimum planning target

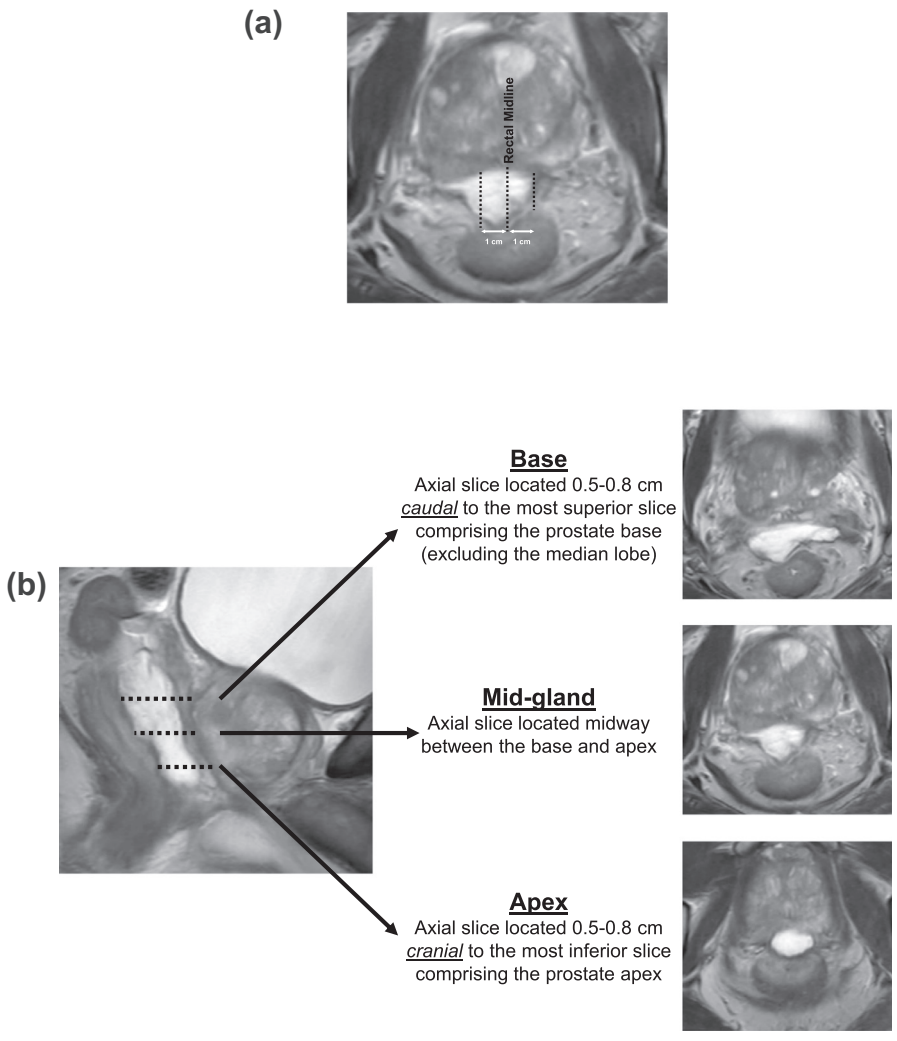


Figure 1 (a) Depiction of prostate-rectal interspace (PRI) thickness of hydrogel rectal spacer implant and natural space (ie, fat, soft tissue, and/or neurovasculature) between the anterior rectal wall and posterior prostate (or seminal vesicles, whichever is more posterior), measured in the anterior-posterior direction on magnetic resonance imaging T2-weighted axial slices. PRI measurements were obtained at rectal midline (which may not necessarily be anatomic midline), as well as 1 cm to the right and left of rectal midline. (b) Depiction of base, midgland, and apex PRI measurements along rectal midline.

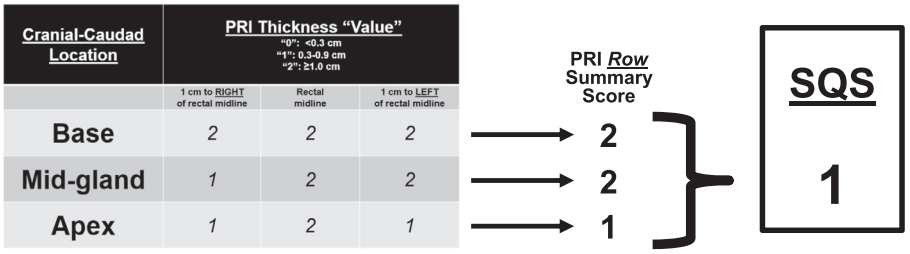
volume (PTV) posterior expansion for prostate SBRT treatments; a PRI of <0.3 cm would therefore result in overlap of the PTV with the rectum. A minimum threshold of 1.0 cm was used to define PRI category 2 because publications[3] have reported this value as the approximate mean perirectal space created by the hydrogel rectal spacer, and thus should be achievable with an optimal implant. The scores within the 3 × 3 table easily provide a synopsis of PRI symmetry along the left-right axis; adequacy of separation between the prostate and rectum at the base, midgland, and apex; and areas deficient of HSP where the hydrogel rectal spacer could have been implanted to increase prostate-rectal separation.

Cranial-Caudad Location	PRI Thickness "Value" "0": <0.3 cm "1": 0.3-0.9 cm "2": ≥1.0 cm		
	1 cm to RIGHT of rectal midline	Rectal midline	1 cm to LEFT of rectal midline
Base	2	2	2
Mid-gland	1	2	2
Apex	1	2	1

Figure 2 Example of a summary table of prostate-rectal interspace measurements.

We then created a hydrogel rectal spacer quality metric score for each patient, using the following rules (Fig. 3):

1. Step 1: Define a PRI summary score for each table row (ie, base, midgland, and apex) of a patient:
   a. If at least 2 cells within a table row have a value of 2, then assign that table row a summary score of 2.



Rules to generate an overall spacer quality score (SQS)

Step 1: Define a PRI *summary* score for each table row (i.e. base, mid-gland, & apex)
- *Assign a PRI row summary score of "2" if ≥2 cells within a table row have a value of "2"*
- *Assign a PRI row summary score of "0" if ≥2 cells within a table row have a value of "0"*
- *All other PRI rows are assigned a summary score of "1"*

Step 2: Define the SQS as the *lowest value* of the three overall row PRI scores

Figure 3 Rules for generating an overall spacer quality score (SQS) from the 3 × 3 prostate-rectal interspace thickness table.

b. If at least 2 cells within a table row have a value of 0, then assign that table row a summary score of 0.
c. Otherwise, a summary score of 1 is assigned to the table row.

2. Step 2: Define the PRI overall spacer quality score (SQS) for a patient as the lowest value of the 3 overall row PRI scores.

Patient cohort

The association between this SQS and late rectal toxicity was retrospectively evaluated in 42 men with low (11.6%) or intermediate (88.4%) risk prostate cancer enrolled on a multi-institutional phase 2 study using HSP with prostate SBRT to assess toxicity and tumor control.[8] One of the patients included in Folkert et al's article[8] was ineligible for this secondary analysis study due to the absence of follow-up data; our study cohort of 42 men had a median follow-up of 48 months. Patients had prostate glands ≤80 cc (2 patients had prior cytoreduction with bicalutamide), baseline American Urological Association Symptom Index score ≤18, no prior transurethral resection or cryotherapy of the prostate, and no history of inflammatory bowel disease. Greater than 95% of the PTV (a 0.3 cm isocentric expansion of the contoured prostate gland) received a total dose of 45 Gy over 5 fractions, delivered in 2 to 3 fractions per week on nonconsecutive days; concurrent or adjuvant androgen deprivation therapy was not allowed. Physician-reported late rectal toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0) was assessed up to 60 months, and the presence of rectal wall ulcers on anoscopies or sigmoidoscopies were assessed serially through 9 months post-SBRT. We then applied the SQS to all patients' HSP by measuring the PRI on the MRI simulation scans.

Statistical analysis

Using standard procedures, we calculated descriptive statistics, including median and ranges for continuous parameters, as well as percentages and frequencies for categorical variables. Differences in various baseline factors (including dosimetry and late rectal toxicity) between SQS groups were evaluated using Kruskal-Wallis tests for continuous factors and Fisher exact tests for categorical factors. Simple linear regression modeling was performed to assess associations between rectal dosimetric measures and the SQS. Univariable logistic regression was employed to evaluate the association between late rectal toxicity and the independent variable, SQS. The SQS was analyzed as a 3-level variable (0 is worst, 2 is best). Coefficients of determination (R^2) were computed for each model. To evaluate the predictive power of the SQS, we generated a univariable logistic model for each score under consideration: SQS with 3 levels (0, 1, and 2), SQS dichotomized as 0 to 1 versus 2, and SQS dichotomized as 0 versus 1 to 2. We computed Nagelkerke's adjusted pseudo R-square values to assess model fit, and qualitatively compared them between models. All statistical computations were performed and generated using SAS Software, version 9.4 (SAS Institute, Cary, NC).

This is a secondary analysis of data originally collected under an institutional review board–approved prospective study. Data remained deidentified and compliant with the Health Insurance Portability and Accountability Act.

Table 1 Rectal dosimetry and late rectal toxicity

		Total cohort N = 42
Rectal Dmax (cGy)	Median (range)	4418.0 (2927.6-5089.7)
	Mean (SD)	4288.8 (541.0)
Rectal D0.035cc (cGy)	Median (range)	4182.8 (2710.0-4990.0)
	Mean (SD)	4068.1 (619.4)
Rectal D1cc (cGy)	Median (range)	3337.5 (1473.4-4620.0)
	Mean (SD)	3369.8 (782.8)
Rectal V45Gy (cc)	Median (range)	0.0 (0.0-1.8)
	Mean (SD)	0.2 (0.4)
Rectal V40Gy (cc)	Median (range)	0.1 (0.0-6.5)
	Mean (SD)	0.8 (1.3)
Rectal V30Gy (cc)	Median (range)	2.5 (0.0-22.3)
	Mean (SD)	3.3 (4.0)
Presence of late rectal toxicity	Yes	20 (47.6)
	No	22 (52.4)
Late rectal toxicity (highest grade reported)	Median (range)	0 (0-2)
	Mean (SD)	0.6 (0.7)
	0	22 (52.4)
	1	14 (33.3)
	2	6 (14.3)

Abbreviations: rectal Dmax = maximum rectal point dose (cGy); rectal DXcc = maximum dose (cGy) to a certain (X) volume (cc) of rectum; rectal VXGy = volume (cc) of rectum receiving at least a certain (X) dose (Gy); SD = standard deviation.

Results

Rectal dosimetry and late rectal toxicity

Among the 42 men whose hydrogel spacer implants were evaluated in this study, 35 (83%) and 7 (17%) were enrolled by the University of Texas Southwestern Medical Center and Memorial Sloan Kettering Cancer Center, respectively. As reported in Table 1, among these patients who were treated to 45 Gy with SBRT in 5 fractions, the median and mean maximum dose to 1 cc of rectum (rectal D1cc) was 3337.5 (range, 1473.4-4620.0) and 3369.8 (SD, 782.8) cGy, respectively. The mean volume of rectum receiving 100% of the prescription dose (V45Gy) was 0.2 (SD, 0.4) cc. Over a median follow-up of 48 months, 20 men (48%) developed a late rectal toxicity, consisting of 14 and 6 patients with grade 1 and 2 as the highest reported late rectal toxicities, respectively; there were no grade 3 or higher late rectal toxicities.

Prostate-rectal interspace summary score and overall spacer quality score

As Table 2 shows, all patients had at least 0.3 cm of space between the prostate and rectum at the level of the prostate midgland (ie, PRI midgland summary score of 1-2). The majority of men had a PRI summary score of 2 at the base (74%), midgland (83%), and apex (64%). When a composite score consisting of individual PRI summary scores from the base, midgland, and apex was computed (defined as the SQS), 7 (17%), 17 (40%), and 18 (43%) men in this cohort had scores of 0, 1, and 2, respectively.

Associations between SQS and rectal dosimetric and late toxicity outcomes

All prostate SBRT rectal dosimetric measures analyzed (rectal Dmax, D1cc, V45Gy, and V40Gy) were associated with SQS (Table 3). Treatment planning scans with an SQS of 2 exhibited a lower (P = .002) rectal Dmax (median of 3920.8 cGy; range, 2927.6-4787.9) compared with a score of 0 (median of 4683.3 cGy; range, 3639.0-4896.2) or 1 (median of 4575.6 cGy; range, 3839.6-5089.7). We observed evidence that a higher SQS was associated with superior rectal dosimetry using simple linear regression modeling for rectal Dmax (P < .001) and D1cc (P = .002), as shown in Table 4. For example, a patient with an SQS of 1 had a rectal Dmax 661.8 cGy higher (95% CI, 362.6-961.0) than a patient with an SQS

Table 2 Prostate-rectal interspace scores and overall spacer quality score

		Total cohort N = 42
PRI base summary score	Median (range)	2 (0-2)
	Mean (SD)	1.7 (0.6)
	0, no. (col %)	2 (4.8)
	1, no. (col %)	9 (21.4)
	2, no. (col %)	31 (73.8)
PRI midgland summary score	Median (range)	2 (1-2)
	Mean (SD)	1.8 (0.4)
	1, no. (col %)	7 (16.7)
	2, no. (col %)	35 (83.3)
PRI apex summary score	Median (range)	2 (0-2)
	Mean (SD)	1.5 (0.7)
	0, no. (col %)	5 (11.9)
	1, no. (col %)	10 (23.8)
	2, no. (col %)	27 (64.3)
SQS	Median (range)	1 (0-2)
	Mean (SD)	1.3 (0.7)
	0, no. (col %)	7 (16.7)
	1, no. (col %)	17 (40.5)
	2, no. (col %)	18 (42.9)

Abbreviations: PRI = prostate-rectal interspace score; SD = standard deviation; SQS = overall spacer quality score.

of 2, and a patient with an SQS of 0 had a rectal Dmax 517.5 cGy higher (95% CI, 123.4-911.6) than a patient with an SQS of 2. Similarly, a patient with an SQS of 1 had a rectal D1cc 798.3 cGy higher (95% CI, 347.3-1249.3) than a patient with an SQS of 2, and a patient with an SQS of 0 had a rectal D1cc 894.3 cGy higher (95% CI, 300.3-1488.3) than a patient with an SQS of 2.

We observed an association between SQS and incidence of late rectal toxicity (P = .01), as illustrated in Table 3: 57%, 71%, and 22% of men with a score of 0, 1, and 2, respectively, developed late grade 1 to 2 rectal toxicity. Furthermore, men with an SQS of 0 or 1 had 4.67-fold (95% CI, 0.72-30.11) or 8.40-fold (95% CI, 1.83-38.57) greater odds of a late rectal toxicity compared with a score of 2 using univariable logistic regression modeling (Table 5). There was a weaker statistical association between late rectal toxicity and the individual PRI row summary scores at the base (P = .06), midgland (P = .04), and apex (P = .15), supporting the utility of this composite SQS which accounts for the entire length of prostate-rectum overlap within the treatment field.

Based on these observations that an SQS of 2 (compared with 0 or 1) was associated with superior rectal dosimetry and less late rectal toxicity, we also assessed whether the SQS should be reported as a 3-tier (0 vs 1 vs 2) or binary score (0-1 vs 2, or 0 vs 1-2). Based on qualitative comparison of the Nagelkerke's adjusted pseudo R-square values shown in Table 5, we found that the SQS reported as a 3-tier (R^2 = 0.25) or binary score of 0 to 1 versus 2 (R^2 = 0.24) were similar in terms of predictive power of grade 1 and higher late rectal toxicity. In comparison, a binary SQS of 0 versus 1 to 2 demonstrated weak predictive power of late rectal toxicity (R^2 = 0.01).

Discussion

By accounting for the PRI thickness created by the hydrogel rectal spacer at the level of the prostate base, midgland, and apex at midline and 1 cm peripherally, we have created an overall spacer quality score (SQS) that is associated with rectal dosimetry and late rectal toxicity after treatment with SBRT for prostate cancer. Forty-three percent of men had an SQS of 2, highlighting that the highest SQS score is achievable if the insertion of the hydrogel rectal spacer is performed by experienced users in a methodical fashion. An SQS of 2 not only was associated with lower radiation doses to the rectum (as measured by Dmax, D1cc, V45Gy, and V40Gy), but also significantly fewer incidences of late rectal toxicity compared with a score of 0 to 1 (22% vs 67%).

Although previously published HSP metrics have been widely adopted, we present a robust and practical instrument that both predicts for reduced rectal dose and late

Table 3 Associations between SQS and rectal dosimetry or late rectal toxicity

		SQS score			
		0 n = 7 (16.7%)	1 n = 17 (40.5%)	2 n = 18 (42.9%)	*P* value*
Rectal Dmax (cGy)	Median (range)	4683.3 (3639.0-4896.2)	4575.6 (3839.6-5089.7)	3920.8 (2927.6-4787.9)	.002
Rectal D1cc (cGy)	Median (range)	4340.0 (2755.0-4440.0)	3720.0 (2493.9-4620.0)	2884.0 (1473.4-4290.0)	.004
Rectal V45Gy (cc)	Median (range)	0.4 (0.0-0.8)	0.0 (0.0-1.8)	0.0 (0.0-0.3)	.046
Rectal V40Gy (cc)	Median (range)	1.8 (0.0-2.4)	0.4 (0.0-6.5)	0.0 (0.0-2.5)	.005
Presence of late rectal toxicity	Yes	4 (57.1)	12 (70.6)	4 (22.2)	.01
	No	3 (42.9)	5 (29.4)	14 (77.8)	
Late rectal toxicity (highest grade reported)	Median (range)	1 (0-1)	1 (0-2)	0 (0-2)	.01

Abbreviations: rectal Dmax = maximum rectal point dose (cGy); rectal D1cc = maximum dose (cGy) to 1 cc of rectum; rectal VXGy = volume (cc) of rectum receiving at least a certain (X) dose (Gy); SQS = spacer quality score.
* Kruskal-Wallis or Fisher exact test.

rectal toxicity. Fischer-Valuck et al[4] developed a symmetry score in which more asymmetrical implants correlated with less reductions in rectal dose compared with the treatment plan before insertion of the rectal spacer. However, hydrogel rectal spacer symmetry (relative to the prostate midline on axial images) does not always equate to the actual thickness of the PRI in the anterior-posterior direction which, as we demonstrate with our metric, is associated with reduced rectal dose. For example, a patient could have a symmetrical implant, but only minimal (<0.3 cm) space created between the prostate and rectum and therefore derive negligible dosimetric and toxicity benefit. In the Fischer-Valuck et al analysis of HSP quality in the published phase 3 spacer trial,[1,2] all but the most severe asymmetrical implants resulted in decreased rectal dose. This implies that inadequate separation between the prostate and rectum accounted for less dose-sparing to the rectum; less symmetry did result in a smaller rectal dose reduction, however. There was also no attempt by the authors to evaluate association of their symmetry score with rectal toxicity, highlighting the utility of our metric.

Hwang et al[5] used a more complicated model that accounted for implant symmetry in a 3-dimensional orientation and hydrogel rectal spacer volume. However, they did not identify an association between their metric and rectal toxicity in men treated with prostate SBRT.[5] The authors attributed this potentially to a small sample size of 22 patients, the moderate SBRT dose of 36.25 Gy delivered in 5 fractions, and inadequate duration of follow-up. However, we observed a similar rate of late grade 1 to 2 rectal toxicity (48% in our vs 30% in the Hwang et al studies) in a small sample size of 42 men that was still associated with late rectal toxicity. A mathematical equation consisting of 4 component equations (hydrogel volume, symmetry in the left-right and cranial-caudal orientations, and prostate-rectal space at midgland) was derived by Liu, et al,[6] to quantify HSP quality; no meaningful associations, however, were correlated with this score as well.

Increasing SBRT doses delivered to the prostate have been correlated with lower 2-year posttreatment positive biopsy rates[9] and superior biochemical control rates.[10] Thus, such measures used to attenuate dose to the rectum by anatomically separating the prostate and rectum via an implantable hydrogel rectal spacer are even more important. In a retrospective study from MSK of 551 men treated with SBRT for prostate cancer, those who had hydrogel rectal spacers implanted before treatment developed fewer late grade 2 and higher rectal toxicity (1%) compared with those without an implant (6%).[11]

Because studies using the hydrogel rectal spacer have not reported on the quality of the implant, it will be difficult to completely understand its benefits if a uniform QA metric is not widely used. Poor implants, which would be defined by an SQS of 0, will unnecessarily have placed a

Table 4 Simple linear regression modeling of SQS as the independent variable

Dependent variable	SQS value	No. (%)	β (95% CI)	*P* value*	R^2
Rectal Dmax (cGy)	2	18 (42.9)	Reference	<.001	0.34
	1	17 (40.5)	661.806 (362.562, 961.049)		
	0	7 (16.7)	517.520 (123.393, 911.647)		
Rectal D1cc (cGy)	2	18 (42.9)	Reference	.002	0.28
	1	17 (40.5)	798.337 (347.342, 1249.332)		
	0	7 (16.7)	894.344 (300.348, 1488.340)		
Rectal V45Gy (cc)	2	18 (42.9)	Reference	.06	0.13
	1	17 (40.5)	0.267 (0.017, 0.518)		
	0	7 (16.7)	0.323 (−0.007, 0.653)		
Rectal V40Gy (cc)	2	18 (42.9)	Reference	.09	0.12
	1	17 (40.5)	0.820 (−0.004, 1.644)		
	0	7 (16.7)	0.990 (−0.095, 2.075)		

Abbreviations: rectal D1cc = maximum dose (cGy) to 1 cc of rectum; rectal Dmax = maximum rectal point dose (cGy); rectal VXGy = volume (cc) of rectum receiving at least a certain (X) dose (Gy); SQS = spacer quality score.
* Overall analysis of variance.

Table 5 Univariable logistic regression of SQS (as binary or 3-tier scores) with late rectal toxicity

SQS		No. (no. of events)	Presence of late rectal toxicity OR (95% CI)	*P* value*	R-square†
(0 or 1) vs 2	2	18 (4)	Reference	.02	0.25
	0	7 (4)	4.67 (0.72, 30.11)		
	1	17 (12)	8.40 (1.83, 38.57)		
0-1 vs 2	2	18 (4)	Reference	.006	0.24
	0-1	24 (16)	7.00 (1.73, 28.34)		
0 vs 1-2	1-2	35 (16)	Reference	.58	0.01
	0	7 (4)	1.58 (0.31, 8.15)		

Abbreviations: CI = confidence interval; SQS = spacer quality score.
* Based on univariable logistic regression.
† Nagelkerke's adjusted pseudo R-square.

patient at risk of complications from the procedure without providing a reduced risk of developing toxicity from the actual treatment. Our SQS metric has the benefit of quantifying the total space between the prostate and rectum, which includes both the natural anatomic space and the additional space created by the hydrogel implant. It has been previously reported that fewer postbrachytherapy rectal complications occur with larger natural space present between the prostate and rectum.[12] Therefore, in men who have favorable anatomy in certain areas along the PRI, it could potentially be decided before implantation where the hydrogel rectal spacer should be focally inserted to enhance this separation.

Furthermore, we anticipate SQS's utility in not only reporting late rectal toxicity with external beam and brachytherapy prostate treatments in the presence of HSP, but also as a self-improvement tool for radiation oncologists to identify areas for refinement of the implant technique; visualization of the scores within the 3 × 3 table facilitates assessment of spacer symmetry both in the left-right and superior-inferior orientations. We anticipate that physicians who are more experienced with placement of the hydrogel rectal spacer will, on average, have implants with a higher SQS. For example, Pinkawa et al[13] assessed a group of 64 consecutive patients with rectal hydrogel spacers inserted at their institution over time and demonstrated that a learning curve existed: the latter half of patients had improved spacer symmetry, larger prostate-rectal separations, moderated rectal dose, and fewer acute rectal toxicity after radiation therapy.

A limitation of this study includes the small sample size, which may have weakened our ability to determine whether the SQS should be reported as a 3-tier or binary score (in which 0 and 1 are grouped together).

Furthermore, analysis of late toxicity did not account for follow-up time because this data was unavailable; therefore, we acknowledge that the results may be biased. Furthermore, we do not have data to assess whether SQS predicts which patients will have resolution of their late rectal toxicity. Another weakness of this study is that most patients who developed a late rectal toxicity had a grade of 1 (14 of 20 patients with toxicity), which we recognize as generally considered clinically insignificant. However, prostate SBRT, especially when a hydrogel rectal spacer is present, is a well-tolerated treatment with <5% late grade 2 and higher rectal toxicity rates.[11] Similarly, there was no grade 2 or higher late rectal toxicity in men with HSP treated with conventionally fractionated radiation to the prostate in the pivotal phase 3 spacer study.[1,2] Therefore, it is reasonable that our SQS metric can predict any graded late rectal toxicity. All of these shortfalls highlight the necessity to externally validate the SQS using a larger sample size, with more complete toxicity data, and with different radiation therapy techniques (ie, SBRT, moderate hypofractionation, and brachytherapy) to ensure its versatility and utility.

Although this comprehensive instrument that accounts for hydrogel spacer symmetry and thickness throughout the entire irradiated duration of the prostate-rectal interface was associated with both rectal dosimetry and late rectal toxicity in this small sample size, a more simplistic metric might achieve the same goals. Using the longer follow-up data from a published prospective randomized trial that compared rectal toxicity and dosimetry in patients treated with definitive radiation in the presence or absence of a hydrogel rectal spacer,[1] we plan to rigorously test the validity of the SQS and compare it to reduced metrics that describe the quality of separation at only one level of the prostate gland.

Conclusion

We have developed a metric to report on the overall quality of PRI created by HSP, that is significantly associated with rectal dosimetry and late rectal toxicity. This SQS will need to be validated using an external data set with a larger and more diverse patient cohort to corroborate its utility.

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