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Scientific Article

Patient Reported Quality of Life Outcomes After Definitive Radiation Therapy With Absorbable Spacer Hydrogel for Prostate Cancer

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Abstract

Purpose: SpaceOAR is a device approved for conventional radiation in prostate cancer. We sought to observe prospectively how SpaceOAR Hydrogel effected quality of life and dosimetry to organs at risk at our institution.

Methods and Materials: We prospectively enrolled patients with low risk or favorable-intermediate risk localized prostate cancer. Baseline Expanded Prostate Cancer Index Composite (EPIC-26) scores along with baseline American Urology Association Symptom Index (AUA-SI) scores were collected. SpaceOAR was placed for all patients who then received stereotactic body radiation therapy, low dose rate brachytherapy, conventionally fractionated radiation therapy, or moderately hypofractionated radiation therapy. We evaluated postimplant dosimetry to critical structures, and prospectively collected follow-up EPIC-26 and AUA-SI scores. We performed a repeated measures analysis of variance to compare patient-specific responses and correlated survey data with dosimetric metrics by generating linear regression models.

Results: We enrolled 59 patients in this study with a median follow-up of 366 days (interquartile range, 507). At final follow-up, the prostate-specific antigen had a significant decline compared with baseline ($P < .0001$). There were no grade 3 toxicities on treatment. There were no significant changes in the AUA-SI score ($P = .69$) at final follow-up compared with baseline, nor was there any change in EPIC-26 domain scores ($P = .19$) during the course of the study period. There were no significant associations between AUA scores and EPIC-26 scores and the dose to the rectum, bladder, or urethra with the exception being dose to the 2 mL rectum correlated with decline in EPIC-26 rectal score (β, -0.002; $P = .006$). Patient-reported declines in bowel domains were less than previously reported data.

Conclusions: Use of SpaceOAR results in favorable dosimetry to the organs at risk and portends excellent short-term quality of life as measured by the association with the patient reported outcome measures. Longer-term follow-up is ongoing and necessary to assess the long-term effect and association of the hydrogel.

Introduction

A large proportion of patients receiving definitive therapy for low or favorable intermediate risk localized prostate cancer receive external beam radiation therapy (EBRT) or brachytherapy. Given the proximity of the prostate to organs at risk such as the bladder, rectum, and

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urethra, methods to minimize dose and toxicity have become paramount. Patient-reported quality of life (QOL) metrics in the Expanded Prostate Cancer Index Composite (EPIC) surveyed from the PROTECT trial demonstrated higher rates of bowel dysfunction, nocturia, and urinary voiding in patients receiving radiation therapy at 6 months posttreatment compared with patients undergoing prostatectomy.[1]

Changes in modality of therapy such as proton therapy[2] and volumetric modulated arc therapy have been studied to minimize the side effect profile. Recently, the Food and Drug Administration has approved a temporary implant, SpaceOAR hydrogel (Boston Scientific, Marlborough, MA, formerly Augmenix, Waltham, MA), which was shown to reduce rates of rectal toxicity, urinary incontinence, and overall QOL for up to 3 years in a phase-3 randomized trial of patients with low- to intermediate-risk prostate cancer receiving conventional fractionated EBRT.[3,4] However, other radiation treatment modalities such as brachytherapy, stereotactic body radiation therapy (SBRT), and moderately hypofractionated radiation therapy (HFRT) are being used with increasing frequency.[5-7] Studies demonstrated that SpaceOAR is capable of improving the dosimetry received by OARs when using conventional radiation,[8] brachytherapy,[9] and with SBRT.[10]

Given the increasing use of SpaceOAR, we sought to further evaluate in a prospective observational fashion the effect of the hydrogel on patient reported outcomes (PROs) and QOL data up to 6 months after placement. We further sought to assess rates of acute toxicity by using validated metrics. Secondary endpoints included evaluation of dosimetry.

Methods

We initiated a prospective observational clinical trial to assess QOL in patients undergoing prostate radiation therapy. The Institutional Review Board approved this study (no. 161522). Patients selected for the study needed to be ≥18 years old with either low-risk or favorable-intermediate risk localized prostate cancer as defined by clinical stage T1 to T2a, and biopsy-proven Gleason ≤3 + 3 of any volume or up to 4 cores from a 12-core biopsy positive for Gleason 3 + 4 with <50% tissue of each core involved. Prostate-specific antigen (PSA) was required to be <15 ng/mL measured without androgen deprivation therapy or recent finasteride or dutasteride use. Performance status was required to be Eastern Cooperative Oncology Group of 0 to 2. No patients received androgen deprivation therapy. Patients with a prior history of transurethral resection of the prostate owing to advanced disease (T3-T4) were excluded.

Hydrogel placement

After informed consent, patients filled out a baseline American Urology Association Symptom Index (AUA-SI) and EPIC-26 questionnaires. All patients underwent transperineal placement of SpaceOAR by a certified practitioner using transrectal ultrasound guidance. Patients were administered regional anesthesia via a transperineal approach administered into the periprostatic nerves. If patients were planned for EBRT, a magnetic resonance image of the prostate was performed approximately 1 week later to delineate target volumes and assess the quality of the SpaceOAR implant. If patients were receiving brachytherapy, the SpaceOAR was placed after deployment of low-dose-rate permanent iodine-125 seeds. Otherwise, patients underwent computed tomography simulation for EBRT within 7 to 10 days of SpaceOAR placement. All patients received a magnetic resonance image after deployment.

Radiation therapy

All patients undergoing prostate brachytherapy were treated with radioactive iodine-125 seeds to a peripheral prescription dose of 14,500 cGy. Patients who received SBRT were given 4000 cGy in 5 fractions (57% consecutively vs 43% given every other weekday), and patients who received HFRT received doses between 6000 cGy and 7020 cGy in 20 to 26 fractions, respectively. For both brachytherapy and EBRT, at least 95% of the planned treated volume received the prescription dose. Lymph nodes were not included in the radiation field. Brachytherapy patients were also required to have a dose to 90% of the volume to be greater than 90% of prescription dose (D_{90} > 90%). Dosimetric plans for SBRT were within recommended constraints for Radiation Therapy Oncology Group (RTOG) 0938,[11] brachytherapy was within constraints for RTOG 0232,[12] and HFRT was within constraints consistent with the conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer (CHHiP) trial[6] and Pollack et al.[13] Planning for all EBRT plans limited hotspots to 110%. Patients receiving brachytherapy returned within 4 to 6 weeks after implantation for evaluation of postoperative dosimetry.

Patients were monitored weekly with on-treatment visits to evaluate for any acute toxicity, which was graded according to the common terminology of associated acute event version 4.0. Patients were scheduled for follow-up appointments at 1, 3, and 6 months to collect AUA-SI and EPIC-26 data. Dose-volume histogram data were extracted from the Varian Eclipse treatment planning software automatically via an Excel macro. All patient data were stored and tracked longitudinally in REDCap.[14]

Statistical analysis

The Shapiro-Wilk test was performed to assess for a normal distribution. Categorical variables were described as the absolute number and percentage, and continuous variables were described as the median and interquartile range. Changes in continuous survey metrics, such as EPIC-26 and AUA-SI, were compared across the study period by performing a repeated analysis of variance (ANOVA). Continuous variables were compared via a Wilcoxon signed-rank test. A one-sample binomial test was used to assess rates of a >5-point change in the EPIC-26 bowel domain or a change of at least 2 points in the urinary domain based on QOL data from RTOG 0413 and RTOG 0938. To compare changes in baseline PROs by modality, an ANOVA was used along with Tukey's range test. Linear regressions were performed between dosimetric predictors and changes in PRO within the AUA-SI and the EPIC-26 scores. Owing to issues of multicollinearity, only one dosimetric predictor was used in these models. All tests were 2-sided with a P value $\leq .05$ noted as being significant. Statistics were performed using R Studio software version 1.2.1335 (Boston, MA http://www.rstudio.org/).

Results

Patient baseline characteristics are presented in Table 1. The patients to date have been followed for a median of 366 days (interquartile range [IQR] 507). Of the patients with prospective follow-up data, 34 patients had SBRT, 17 had HFRT (3 received 6000 cGy, 14 received 7020 cGy), 6 received brachytherapy, and 2 had conventional fractionation. Among the patients with HFRT, the median age of enrollment was 68.4 (IQR 10.9). The median PSA value at enrollment was 5.47 ng/mL (IQR 6.5), with the current follow-up time of a median of 114 days (IQR 193). Most patients were T1c (91.5%) with a Gleason score of 3 + 4 (69.5%). The median prostate volume was 38.4 mL (IQR 23 mL). The perirectal placements were adequate, with a median midgland rectoprostatic separation of 1.22 cm and IQR of 0.32 cm, comparable to the mean of 1.26 cm reported in the phase 3 pivotal trial.[15] Initially, 12 (patients 20.3%) were taking Flomax before radiation therapy.

Table 1 Baseline characteristics

T stage, n (%)	
T1c	54 (91.5)
T2a	3 (50.8)
T2b	1 (1.7)
T2c	1 (1.7)
Gleason score, n (%)	
3 + 3	16 (27.1)
3 + 4	41 (69.5)
4 + 3	2 (3.4)
PSA ng/mL median (IQR)	5.47 (6.5)
Age median (IQR)	68.4 (10.9)
Prostate volume mL median (IQR)	38.4 (23.3)
SBRT	34
Moderate hypofractionated	17
Brachytherapy	6
Conventional	2

Abbreviations: IQR = interquartile range; PSA = prostate-specific antigen; SBRT = stereotactic body radiation therapy.

All patients thus far have had favorable outcomes by biochemical response. At last follow-up, the median PSA was 1.0 (IQR 1.3), which was significantly lower compared with baseline levels ($P < .00001$). Currently one patient is deceased from causes unrelated to his prostate cancer.

Table 2 describes various dosimetric parameters for the rectum, bladder, and urethra for SBRT, HFRT, and brachytherapy. Parameters such as dose to 50% of the rectum were a median of 693 cGy and 1965 cGy for patients receiving SBRT and HFRT, respectively. The doses to 50% of the bladder were 276 cGy and 890 cGy, for SBRT and HFRT, respectively. Among patients receiving brachytherapy, the median dose to 2 mL of the rectum was 7906 cGy (IQR 820).

While on treatment, there were few acute side effects. There were no grade 3 toxicities. There were 2 patients receiving SBRT who experienced a grade 1 diarrhea, and 1 patient receiving HFRT who experienced grade 2 diarrhea. In terms of genitourinary symptoms, there were 3 patients receiving SBRT who experienced a grade 2 toxicity and 1 who had a grade 1 toxicity. There were 2 patients who received brachytherapy who experienced a grade 1 genitourinary toxicity.

The baseline and last follow-up scores for the AUA-SI surveys are listed in Table 2. At the time of this analysis, 44 patients have presented for follow-up patient reported outcomes. When AUA-SI is analyzed continuously it showed no association at final follow-up compared with baseline. The total AUA-SI score showed a nonsignificant difference from the baseline scores to 6 months post-treatment ($P = .69$). When evaluated categorically, there were 28, 13, and 3 patients with mild, moderate, and severe scores, respectively, at baseline compared with 26, 15, and 4 patients at last follow-up ($P = .89$).

Patients generally had good baseline QOL scores for EPIC-26 scores, represented in Table 3. Of note, baseline bowel scores and urinary incontinence were at a median of 100 and 93.1. Even at last follow-up, patients maintained excellent bowel QOL and urinary incontinence scores with a median of 87.5. Repeated measures ANOVA did not demonstrate any differences over time with regard to the QOL across the study timeframe, which is displayed in Table 4. To demonstrate the

Table 2 Descriptive dosimetric statistics

Dosimetric parameter cGy	SBRT median (IQR)	Hypofractionated median (IQR)	Brachytherapy median (IQR)
Bladder 0.035 mL	4044 (139)	7348 (286)	13,000 (354)
Bladder 1 mL	3815 (230)	7213 (507)	8500 (300)
Bladder 2 mL	3651 (348)	7142 (675)	7000 (457)
Bladder 10 mL	2443 (424)	6081 (1,444)	3250 (227)
Bladder 20 mL	1678.5 (501)	4698 (2,012)	2900 (132)
Bladder 30 mL	1262.5 (685)	3995 (1983)	2440 (949)
Dose to 50% bladder	276 (282)	890 (1,792)	NA
Dose to 25% of bladder	774 (782)	2879 (2,241)	NA
Rectum 0.035 mL	3770 (248)	7003 (1,225)	15,000 (2,850)
Rectum 1 mL	3157 (462)	6323 (1102)	9316 (641)
Rectum 2 mL	2914 (604)	5891 (986)	7906 (820)
Rectum 10 mL	2029 (551)	3828 (1482)	4500 (186)
Rectum 20 mL	1526 (686)	2906 (1259)	2900 (208)
Rectum 30 mL	1158 (822)	2394 (1131)	2200 (167)
Dose 25% rectum	1611 (751)	2924 (756)	NA
Dose 50% rectum	693 (873)	1965 (627)	NA
Urethra 0.035 mL	4123 (120)	7335 (194)	23,100 (3000)
Urethra 1 mL	4021 (108)	7114 (1590)	14,250 (6430)

Abbreviations: IQR = interquartile range; NA = not applicable; SBRT = stereotactic body radiation therapy.

Table 3 EPIC-26 scores

EPIC-26 composite score	Baselinemedian (IQR)	First F/Umedian (IQR)	Second F/Umedian (IQR)	*P* value
EPIC bowel composite	100 (4.1)	91 (20)	100 (4.1)	.19
Sexual composite	68 (39)	57 (61)	72.5 (55)	.25
Urinary incontinence	93.1 (24)	81.2 (28.75)	87.5 (18)	.17
Urinary obstructive	93.7 (23)	81.25 (33)	87.5 (18)	.62
Urinary hormonal	87 (28)	90 (27.5)	95 (16)	.81

Abbreviations: EPIC = Expanded Prostate Cancer Index Composite; F/U = follow-up; IQR = interquartile range.

changes in scores by specific RT modality, Fig. 1 and 2 are boxplots of the changes at last follow-up in AUA-SI and EPIC-26 bowel domain from baseline. These scores did not reveal any significant difference in their means.

There were 8 patients (18.1%) who experienced a >5-point decrease in the bowel domain ($P = .17$). Six of those experienced the decline within the first 6 months, with 2 of them returning to near baseline within the first year. Six of those who did experience a decline in bowel score received SBRT. On the other hand, there were 11 patients (25%) who experienced a change of at least 2 points in the urinary domain ($P = .68$).

Table 4 AUA-SI review*

AUA question	Base line	Last F/U
Not emptying bladder	1 (2)	1 (1.5)
Urinate every 2 h	1 (3)	0.5 (1)
Stopped and started	1 (3)	1 (0.75)
Postponement of urine	1 (1)	0 (1.5)
Weak stream	1 (2)	0.5 (1)
Strain	1 (0)	0 (0)
Nocturia	1 (1)	1 (1.5)
Total	1 (2)	1 (2)

Abbreviations: AUA-SI = American Urology Association Symptom Index; F/U = follow-up.

* Values expressed as median and interquartile range.

Next, we assessed the relationship between the dosimetry to the OARs and the changes in both AUA-SI and EPIC-29 scores. Dosimetric predictors of AUA-SI decrease such as decreasing dose to 0.035 mL of the urethra had a beta (β) coefficient of change (change in dependent variable by the specified coefficient per each one decrease in cGy) of (β −0.0013, $P = .02$), bladder 0.035 mL (β −0.0011, $P = .022$), and bladder 1 mL (beta −0.0015, $P < .001$). Increasing dose to 2 mL of the rectum trended with changes in EPIC-26 bowel domain (β −0.005, $P = .07$) on univariate analysis. The best fit multivariable included age and prostate volume, which still maintained significance for rectal dose to 2 mL and EPIC-26 difference (β −0.002, $P = .006$). The effect sizes in these instances was the same as in the univariable

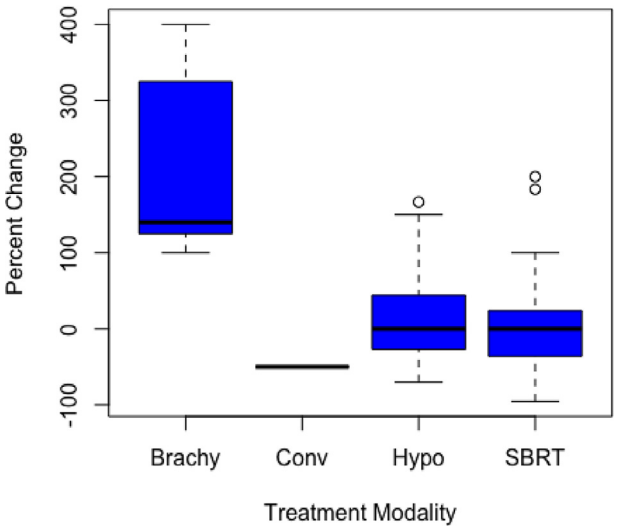

Figure 1 Box plot of the percent change in total American Urology Association Symptom Index scores. *Abbreviations:* Brachy = brachytherapy; Conv = conventional; Hypo = hypofractionation; SBRT = stereotactic body radiation therapy.

model. On multivariable analysis the changes in AUA-SI score correlated with bladder 1 mL. This indicates that for each 100-cGy increase in the dose to rectum it results in an average decrease of $\beta \times 100$ in survey scores.

Discussion

We performed a prospective observational study on patients at our institution receiving SpaceOAR along with prostate radiation therapy, including SBRT, HFRT, CFRT, and brachytherapy. As a whole, most patients had exceptional QOL life scores at follow-up. Although other studies have detailed the improved dosimetry with hydrogel,[15] this is the first to report PROs and QOL data.

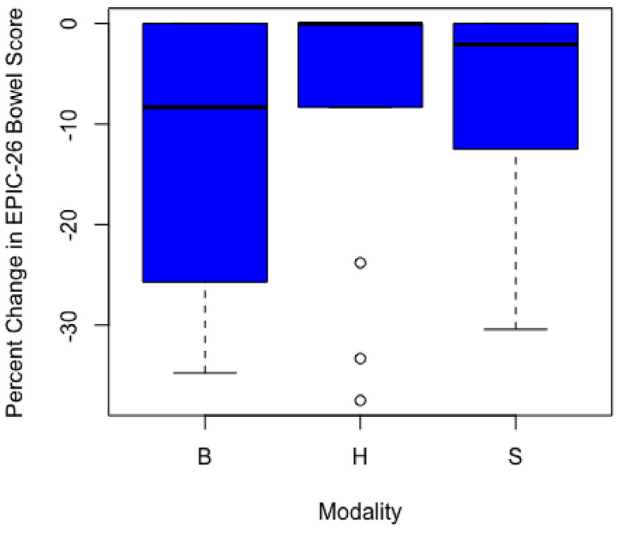

Figure 2 EPIC-26 change in scores by modality. *Abbreviations:* B = brachytherapy; EPIC = Expanded Prostate Cancer Index Composite; H = hypofractionation; S = stereotactic body radiation therapy.

In terms of dosimetry, SpaceOAR contributed to dramatic sparing of dose to the rectum and all dosimetric measurements were well within traditional dose constraints for studies evaluating HFRT and SBRT. In the RTOG 0415 study evaluating HFRT, for example, recommended constraints to the bladder are that no more than 25% and 50% of the organ receive 7500 cGy and 6500 cGy, respectively, which is considerably greater than the median doses in this study of 2924 cGy and 1965 cGy, respectively. Similarly, per RTOG 0938, the recommended dose to 50% of the rectum and 1 mL rectum are 1812 cGy and <3800 cGy, which were significantly larger than this study's doses of 693 cGy for 50% of the rectum and 3157 cGy to 1 mL of the rectum. These data are paramount considering another series on SBRT without SpaceOAR revealed increasing rates of rectal and urinary toxicity with higher dose to 50% of the organ and dose max.[16]

Although RTOG 0415 and QOL study of RTOG 0938 demonstrated rates of change in the bowel score of >5 points to be 29.8% and 35% at 1-year follow-up, respectively, we only had 8 patients experience a change ≥5 points for bowel toxicity within 6-months, with 2 of them improving on subsequent follow-up. Although the present study followed patients for a lesser amount of time, we found lower rates of bowel toxicity in our patient population. However, compared with these studies, the rates of change for urinary domain were similar to previous data. This is not unexpected given the action of the SpaceOAR primarily helps reduce dose to the rectum, with no effect on the urethra. In terms of longitudinal follow-up, patients had little change compared with their baseline scores, which likely is due to improved sparing of the OARs. Given the findings at 6 months in the PROTECT trial, lessening bowel toxicity in the first 6 months is paramount, and SpaceOAR appears to provide this benefit.

We do acknowledge some limitations to our study. This is a short-term follow-up of a median time just over a year. Although we have some patients who have followed for a longer amount of time given the IQR of 507, the understanding of the long-term patient reported outcomes will depend on further maturity of our data. We also acknowledge that at this point we did have an overall well-selected population at baseline. Patients as a whole did have good initial urinary scores and relatively small prostate gland sizes. We also did have heterogenous treatment modalities; however, we did attempt to review these by subset. Despite this, there was still no significant change to their baseline scores overtime.

This is one of the first studies to prospectively record QOL data on patients receiving SpaceOAR for hypofractionated radiation therapy courses. NRG-GU005 includes

patients who receive SpaceOAR and ascertaining the changes in QOL will be a secondary endpoint in that study. This population of patients will require further long term follow-up. Although the patient population was treated with different modalities, the overall positive QOL outcomes is still apparent throughout all groups. Continued follow-up will elucidate the outcomes at long-term time intervals.

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