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Basic Original Report

Salvage Stereotactic Body Radiation Therapy for Locally Recurrent Prostate Cancer: Quality-of-Life Outcomes From a Prospective Clinical Trial

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Purpose: Salvage stereotactic body radiation therapy (SBRT) for intraprostatic recurrence of prostate cancer is under study in early-phase clinical trials. Presently, the impact of this treatment on toxicity and health-related quality of life (HRQOL) is poorly defined. To our knowledge, we present the first report in the literature of HRQOL and psychometric outcomes from a mature, prospective clinical trial.

Methods and Materials: NCT03253744 was a phase 1 trial of focal salvage SBRT to doses of 40.0 to 42.5 Gy with target volume delineation guided by ^{18}F-DCFPyL positron emission tomography/computed tomography and magnetic resonance imaging. Secondary endpoints included longitudinal assessment of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 adverse events (AEs) and corresponding patient-reported outcome measures (PROMs). PROMs included the Expanded Prostate Cancer Inventory Composite (EPIC)-26, American Urologic Association Internal Prostate Symptom Score, Sexual Health Inventory for Men, Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety, PROMIS Depression, and PROMIS Psychosocial Illness Impact-Positive. Study assessments were conducted at baseline, 1 month, and at every 3-month interval post-SBRT until study completion or biochemical failure.

Results: Seventeen participants underwent salvage SBRT and were observed for a median of 24 months (min-max: 18-24 months). Toxicity assessment was completed in all participants, and the HRQOL response rate was 91%. Genitourinary (GU) toxicity was more common than gastrointestinal toxicity with a 24-month cumulative incidence of G2+ AEs of 76.5% (95% CI, 44.6%-90.0%) versus 29.4% (95% CI, 4.1%-48.1%) and G3+ AEs of 11.8% (95% CI, 0.0%-25.8%) versus 5.9% (0.0%-16.4%). GU toxicity peaked at 12 to 15 months and was associated most strongly with urethral reirradiation dose. PROMs were concordant with AEs, with significant differences from baseline noted in the American Urologic Association symptom index, EPIC GU irritation, and EPIC GU incontinence scores at 3 to 6 months, 6 to 9 months, and 9 to 18 months, respectively. No significant differences were noted in gastrointestinal PROMs or PROMIS measures.

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Research data are stored in an institutional repository and will be shared on request to the senior author. This trial is registered on clinicaltrials.gov under the NCT03253744 identifier.

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Conclusions: Salvage SBRT has a favorable treatment-related toxicity and HRQOL profile. Primarily, GU toxicities were observed corresponding to decrements in PROMs.

Introduction

Isolated local recurrence after primary radiation therapy (RT) is increasingly recognized as a clinical entity in modern practice. This is based in part on the advent of advanced prostate-specific imaging such as Prostate specific membrane antigen (PSMA)-based positron emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging to detect such recurrences and simultaneously aid in ruling out regional or distant recurrence. Many salvage options have been used for the treatment of patients with radiorecurrent prostate cancer including focal ablation, prostatectomy, and reirradiation, with reirradiation historically being administered with salvage, whole-gland low-dose-rate brachytherapy (BT) as studied in a multi-institutional phase 2 trial.[1] National guidelines, such as those from the National Comprehensive Cancer Network, have recently begun including salvage management options as recommendations for patients with this clinical presentation, including salvage surgery, salvage focal therapy (ie, cryotherapy or high-intensity focused ultrasound), and reirradiation.[2] An understanding of the toxicity and health-related quality of life (HRQOL) of these treatment options is important to prioritize therapeutic options and to inform patients regarding the risks of treatment.

Early-phase clinical trials have evaluated reirradiation with stereotactic body RT (SBRT).[3-6] These early prospective reports have defined the safety profile of prostate reirradiation and have also reported acceptable efficacy. However, the impact of prostate reirradiation with SBRT on toxicity and longitudinal HRQOL has not yet been reported. Here, we report the mature toxicity outcomes of NCT03253744 and to our knowledge, the first report of corresponding patient-reported outcome measures (PROMs) from a perspective clinical trial.

Methods and Materials

NCT03253744 was a phase 1 trial designed primarily to evaluate the maximum tolerable dose of reirradiation with SBRT for patients with local recurrence after primary RT for localized prostate cancer. All participants provided informed consent, and the trial was conducted with approval from the institutional review board of the National Cancer Institute. Eligible patients had biochemically recurrent (BCR) prostate cancer (defined by the Phoenix criteria[7]) and a biopsy-verified, intraprostatic recurrence with or without seminal vesicle invasion. Additional eligibility criteria included age ≥18 years and Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Exclusion criteria included ongoing grade 3+ toxicities from prior RT, distant metastases, or recurrence within 1 year of initial RT. All patients underwent staging with multiparametric magnetic resonance imaging, ^{18}F-NaF PET/CT or Technetium (99mTc) medronic acid-MDP bone scan, and ^{18}F-DCFPyL PET/CT. Participants were treated with a maximum prescription dose of 40 to 42.5 Gy to a planning target volume (PTV) defined by the gross tumor volume (GTV)+3 mm, as previously reported.[4,5] Particpants whose first course of RT was administered via BT were treated simultaneously to a dose of 30 Gy to the entire prostate.

Key secondary objectives were the longitudinal assessment of the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 toxicity burden of treatment and longitudinal PROMs. All patients were evaluated before treatment, at 1-month posttreatment, and at every 3 months posttreatment for the full 24-month study period or until biochemical failure. Acute toxicity was defined as occurring at or before the 3-month assessment and late toxicity thereafter. PROMs included the Expanded Prostate Cancer Inventory Composite (EPIC)-26, American Urologic Association (AUA) International Prostate Symptom Score, which includes the AUA symptom index (AUA-SI) and a single-item quality-of-life measure (AUA QOL), the Sexual Health Inventory for Men (SHIM), Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety, PROMIS Depression, and the PROMIS Psychosocial Illness Impact-Positive. Changes from pretreatment patient-reported outcome (PRO) score were interpreted using minimally clinically important difference (MCID) thresholds previously defined in the literature (Table E1). Each instrument was scored in accordance with its respective scoring manual, and PROMIS instruments were scored with the cancer-specific supplemental calibration.[8]

The frequency of treatment-related adverse events (TRAEs) by grade was reported as a proportion of the study population at each time point, and the cumulative incidence of G2+ and G3+ toxicity was reported at 24 months. The cumulative incidence of toxicity at study completion (24 months) was calculated via the Aalen-Johansen estimator with biochemical failure used as a competing risk. Based on the observed difference in toxicity by dose prescription, it was hypothesized that the exposure of organs-at-risk (OARs) was associated with dose. The one-sided Wilcoxon rank sum test was used to

test the hypothesis that ≥G2 toxicity had higher OAR exposure. Acute and late toxicity were tested separately against doses, which were transformed using the linear-quadratic model, using α/β ratios of 10 Gy and 3 Gy for acute and late toxicity, respectively. Logistic regression was used to evaluate the association between OAR exposure and ≥G2 acute and late toxicity. Univariable models were reported evaluating the impact of dose on toxicity, and models adjusted by trial cohort were also reported given the difference in baseline factors and protocol treatment between the 2 cohorts and the association of cohort with toxicity. The strength of each association was reported as an odds ratio with a corresponding profile likelihood-based 95% CI,[9] and hypothesis testing was conducted with the likelihood ratio test to evaluate the utility of each model. The performance of each model was quantified with a previously published pseudo-R^2 measure.[10] Further, the discrimination of each model was quantified using the area under the receiver operating curve metric and corresponding bootstrap 95% CI. The distribution of each PROM at each timepoint was reported along with the prevalence of the degree of change from baseline at each timepoint as referenced against the MCID (Table E1). The Wilcoxon rank sum test was used to compare each timepoint to baseline, pairwise. P values <.05 were considered statistically significant. As these analyses were exploratory in nature, adjustment for multiple comparisons via the Bonferroni method was made only when a single hypothesis was tested multiple times based on previous recommendations.[11]

Results

Trial population

In total, 17 patients were enrolled, 9 with BCR after prior BT-based treatment (cohort 1) and 8 with BCR after initial treatment with external beam RT alone (cohort 2). The reirradiation interval was a median of 8.2 years (min-max: 3.7-11.0 years) in cohort 1 and a median of 9.1 years (min-max: 6.3-16.4 years) in cohort 2. All patients were followed for 24 months with the exception of a single patient who experienced 2nd BCR at the 18-month timepoint and thus taken off study per protocol. Further details of the study population are provided in Table 1. Missing PROM responses were 8% for each instrument throughout the trial.

Toxicity

Genitourinary toxicity

The majority of patients had ≥G1 genitourinary (GU) adverse events (AEs) at baseline, most commonly urinary frequency (n = 15), urgency (n = 9), and weak stream (n = 5). The prevalence of ≥G2 GU toxicity during treatment was 65% (n = 11) consisting most commonly of noninfective cystitis (n = 5) and urinary frequency (n = 5). Two G3 AEs were observed: hematuria (duration: 4 days; latency: 3 months) and urinary incontinence (duration: 1.8 months; latency: 13.2 months). The corresponding 24-month cumulative incidence of G2+ and G3 + GU toxicity was 76.5% (95% CI, 44.6%-90.0%) and 11.8% (95% CI, 0.0%-25.8%), respectively. Regarding the longitudinal prevalence, ≥G2 GU toxicity peaked at approximately 12 to 15 months. The observed 3-, 12-, and 24-month prevalence of ≥G2 GU AEs of 35%, 47%, and 12%, respectively. At the 12- to 15-month peak, the most common ≥G2 AEs were urinary frequency (n = 4), noninfective cystitis (n = 3), and urinary incontinence (n = 3) (Fig. 1A). A difference in the time-to G2+ GU toxicity was noted between study cohorts ($P < .05$; Fig. E4).

Gastrointestinal and sexual/hormonal toxicity

Similar to the GU domain, the majority of patients had ≥G1 gastrointestinal (GI) toxicity at baseline, which were most commonly hemorrhoids (n = 11) and constipation (n = 4). G2+ GI toxicity was uncommon with a prevalence of 6% at 3 months and no observed AEs at 24 months. The 24-month cumulative incidence of G2+ GI toxicity was 29.4% (95% CI, 4.1%-48.1%), and the corresponding cumulative incidence of G3+ GI toxicity was 5.9% (95% CI, 0.0%-16.4%) representing a single G3+ GI AE, a rectal fistula that was successfully surgically repaired (latency: 12.5 months; duration: 5 months). No difference in the time-to G2+ GI toxicity was observed between study cohorts ($P > .05$; Fig. E4). Treatment-related sexual/hormonal AEs were uncommon (n = 4), and all were G1 in severity. No acute sexual/hormonal toxicities were observed, and a single potentially related toxicity persisted at study completion (G1 penile and perineal discomfort).

Predictors of toxicity

Toxicity attributable to treatment appeared to be associated with prescription dose level (40 Gy [Fig. 1B] vs 42.5 Gy [Fig. 1C]). Urethral D_{Max} and D_{Mean} were associated with both acute and late GU toxicity (Fig. E1), and, additionally, bladder D_{1cc}, and bladder D_{5cc} were associated with late GU toxicity (Fig. 2; Table 2). In an adjusted analysis for trial cohort, the only factors associated with acute and late toxicity were urethral D_{Max} (late toxicity) and urethral D_{Mean} (acute and late toxicity), respectively (Table E2). Although similar dosimetric factors appeared to be associated with acute and late toxicity, the emergence of ≥G2 acute toxicity was not associated with the development of ≥G2 late toxicity for either the GU or GI organ systems (both $P > .05$). No association between the use of α-blockers at pretreatment baseline and the occurrence of ≥G2 GU toxicity was observed (odds ratio, 3.50; 95% CI, 0.34-81.9; $P > .05$). Lastly, no association between pretreatment symptom burden, prostate volume, or reirradiation interval with acute or late GU or GI toxicity was observed (all $P > .05$).

Table 1 Baseline characteristics

	Cohort 1: brachytherapy	Cohort 2: EBRT	Total
Number enrolled	9 (52.9%)	8 (47.1%)	17 (100%)
Race			
Black	1 (11.1%)	4 (50.0%)	5 (29.4%)
White	8 (88.9%)	4 (50.0%)	12 (70.6%)
Age at study enrollment			
Median (min, max)	68.8 (59.9-77.1)	73.0 (62.3-82.3)	69.4 (59.9-82.3)
Initial course of therapy			
T-stage at initial diagnosis			
T1c	8 (88.9%)	4 (50.0%)	12 (70.6%)
T2a	1 (11.1%)	3 (37.5%)	4 (23.5%)
T2c	0 (0%)	1 (12.5%)	1 (5.9%)
PSA before initial treatment			
Median (min, max)	5.40 (4.10-15.2)	12.9 (4.67-33.4)	7.53 (4.10-33.4)
ISUP grade at initial treatment			
GG1	5 (55.6%)	3 (37.5%)	8 (47.1%)
GG2	3 (33.3%)	3 (37.5%)	6 (35.3%)
GG3	1 (11.1%)	0 (0%)	1 (5.9%)
GG4	0 (0%)	0 (0%)	0 (0%)
GG5	0 (0%)	2 (25.0%)	2 (11.8%)
NCCN risk group at initial treatment			
Low risk	5 (55.6%)	1 (12.5%)	6 (35.3%)
Favorable intermediate risk	2 (22.2%)	0 (0%)	2 (11.8%)
Unfavorable intermediate risk	2 (22.2%)	2 (25.0%)	4 (23.5%)
Intermediate risk, NOS	0 (0%)	1 (12.5%)	1 (5.9%)
High risk	0 (0%)	4 (50.0%)	4 (23.5%)
Technique of initial treatment			
Cs-131	1 (11.1%)	0 (0%)	1 (5.9%)
I-125	2 (22.2%)	0 (0%)	2 (11.8%)
Ir-192	1 (11.1%)	0 (0%)	1 (5.9%)
Pd-103	4 (44.4%)	0 (0%)	4 (23.5%)
Pd-103 + EBRT	1 (11.1%)	0 (0%)	1 (5.9%)
EBRT	0 (0%)	8 (100%)	8 (47.1%)
Absorbed dose (Gy) of initial treatment			
Median (min, max)	125 (27.0-145)	76.5 (72.0-79.2)	79.2 (27.0-145)
RT volume of initial treatment			
Prostate only	8 (88.9%)	1 (12.5%)	9 (52.9%)
Prostate and seminal vesicles	0 (0%)	2 (25.0%)	2 (11.8%)
Prostate, seminal vesicles, and pelvic LNs	1 (11.1%)	5 (62.5%)	6 (35.3%)
Salvage SBRT			
Time from diagnosis to study treatment			
Median (min, max)	8.15 (3.67-11.0)	9.09 (6.34-16.4)	8.74 (3.67-16.4)

(*Continued*)

Table 1 (*Continued*)

	Cohort 1: brachytherapy	Cohort 2: EBRT	Total
Pretreatment PSA			
Median (min, max)	3.10 (2.10-19.5)	2.92 (2.05-7.92)	3.00 (2.05-19.5)
ADT with salvage SBRT			
None	8 (88.9%)	7 (87.5%)	15 (88.2%)
Short term (≤9 mo)	1 (11.1%)	1 (12.5%)	2 (11.8%)
Maximum dose of salvage SBRT			
40.0 Gy (5 fractions)	3 (33.3%)	6 (75.0%)*	9 (52.9%)
42.5 Gy (5 fractions)	6 (66.7%)	2 (25.0%)*	8 (47.1%)

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; GG = grade group; ISUP = International Society for Urological Pathologists; LNs = lymph nodes; NCCN = National Comprehensive Cancer Network; NOS = not otherwise specified; PSA = prostate-specific antigen; RT = radiation therapy; SBRT = stereotactic body RT.
*Patients with prior brachytherapy were also treated with a dose of 30 Gy in 5 fractions simultaneously to the entire prostate gland based on the pre-specified treatment protocol.

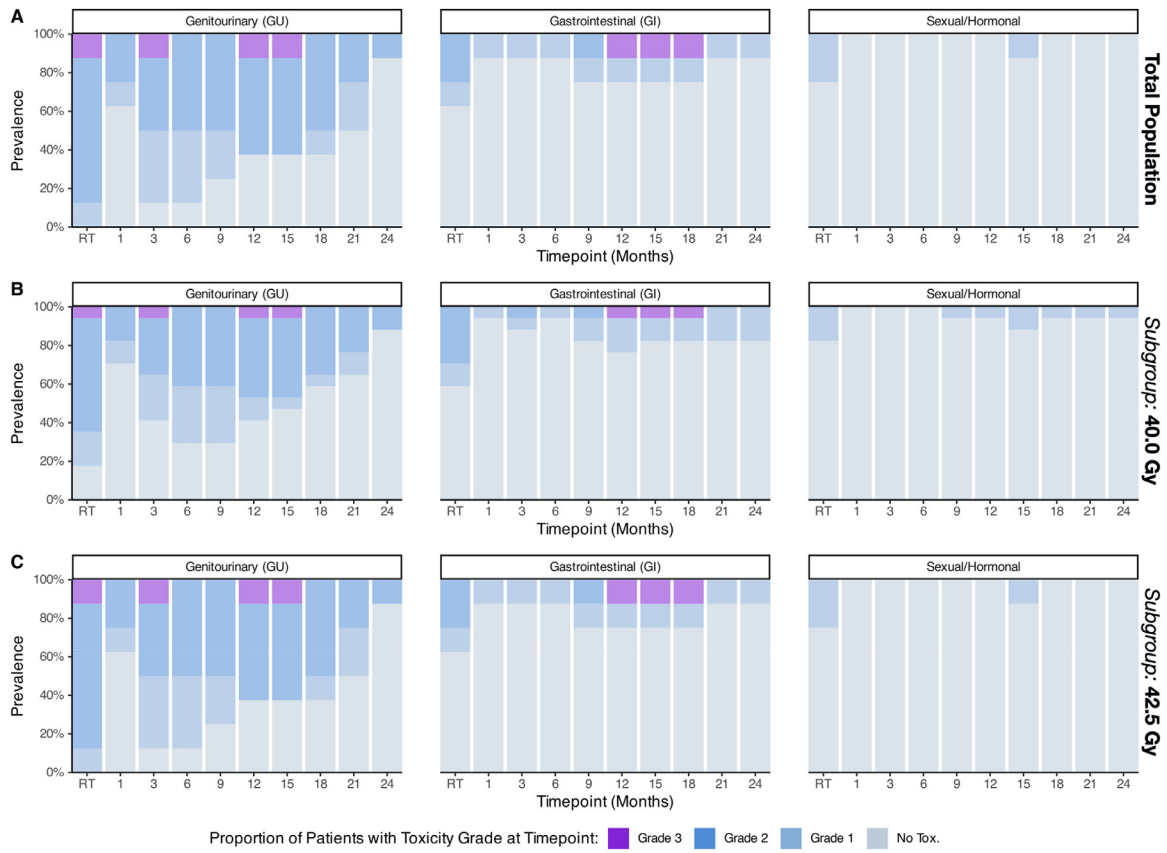

Figure 1 Treatment-related toxicity for the overall study cohort (A), patients treated with a prescription dose of 40.0 Gy (B) and patients treated with a prescription dose of 42.5 Gy (C). In this figure, the prevalence of toxicity attributable to salvage SBRT by grade and organ system is depicted over time. Each timepoint represents a range: RT from start to end of treatment, 1 month from end of treatment to 6 weeks posttreatment, and each subsequent interval the 3-month interval centered at that timepoint. All toxicities shown are those judged to be related to salvage SBRT.
Abbreviations: RT = radiation therapy; SBRT = stereotactic body radiation therapy.

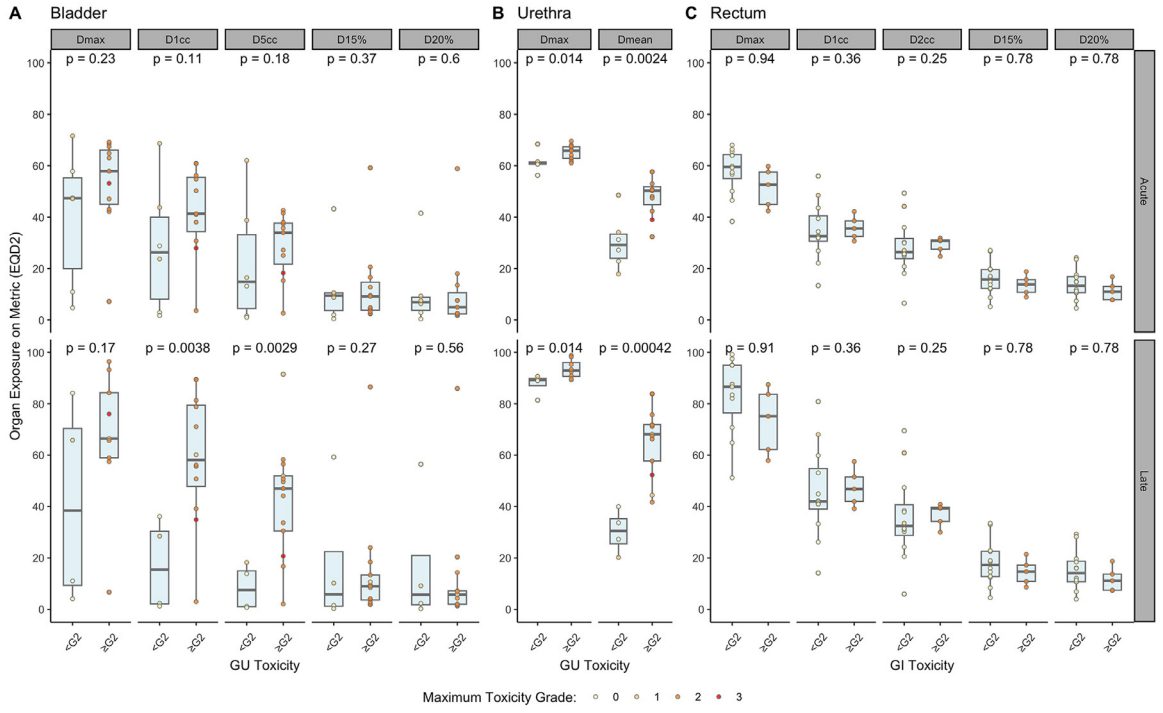

Figure 2 Organ-at-risk (OAR) exposure by physician-rated CTCAE version 5.0 Toxicity Grade. Dose is represented in EQD2 using an α/β ratio of 10 Gy for acute and 3 Gy for late toxicity. For each panel, *P* values correspond to one-sided hypothesis testing conducted with the Wilcoxon rank sum test (H_0: no difference in OAR exposure on a given metric between toxicity categories; H_a: The ≥G2 toxicity category has higher OAR exposure on the given metric).
Abbreviations: CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; EQD2 = XXX; GI = gastrointestinal; GU = genitourinary.

PRO measures

Genitourinary subdomain. At baseline, patients had low levels of self-reported urinary symptom burden (Fig. 3A). Median EPIC GU incontinence and irritation scores were >90 (incontinence: 100 [Q1-Q3: 100-100]; irritation 94 [Q1-Q3: 81-100]). The median baseline AUA-SI score was 5 (Q1-Q3: 2-12) and baseline AUA QoL score of 1.5

Table 2 Association between organ-at-risk exposure and grade 2+ toxicity

	OR	95% CI	*P*⋆	$R^{2,\dagger}$	AUC (95% CI‡)	OR	95% CI	*P*⋆	$R^{2,\dagger}$	AUC (95% CI)‡
	Acute G2+ GU Toxicity					*Late G2+ GU Toxicity*				
Urethra D_{Max}	**1.48**	**1.04-2.60**	**.026**	**0.29**	**0.83(0.50-1.00)**	**2.57**	**1.17-27.20**	**.002**	**0.52**	**0.94 (0.79-1.00)**
Urethra D_{Mean}	**1.21**	**1.06-1.52**	**.001**	**0.54**	**0.91 (0.73-1.00)**	§		**<.001**	**1.00**	**1.00 (1.00-1.00)**
Bladder D_{Max}	1.03	0.98-1.09	.22	0.09	0.62 (0.30-0.91)	1.03	0.999-1.08	.053	0.23	**0.78 (0.54-1.00)**
Bladder D_{1cc}	1.04	0.99-1.10	.17	0.12	0.70 (0.35-0.97)	**1.08**	**1.02-1.19**	**.005**	**0.44**	**0.94 (0.79-1.00)**
Bladder D_{5cc}	1.03	0.96-1.10	.42	0.05	0.65 (0.32-0.97)	**1.14**	**1.03-1.40**	**.002**	**0.47**	**0.94 (0.81-1.00)**
Bladder $D_{15\%}$	1.00	0.94-1.09	.93	0.00	0.44 (0.15-0.79)	0.99	0.95-1.06	.82	<0.01	0.62 (0.19-1.00)
Bladder $D_{20\%}$	1.00	0.93-1.08	.97	0.00	0.53 (0.29-0.75)	0.99	0.95-1.05	.72	<0.01	0.52 (0.23-0.79)

Abbreviations: AUC = area under the receiver operating curve; BT = brachytherapy; D_{Max} = maximum point dose; D_{Mean} = mean dose; $D_{xx\ cc}$ = minimum dose to xx cc volume receiving the most radiation dose; $D_{zz\ \%}$ = minimum dose to zz % volume receiving the most radiation dose; EQD2 = XXX; GU = genitourinary; OR = odds ratio.
The Association Between Organ-At-Risk Exposure and Grade 2+ Toxicity Adjusted for Trial Cohort is presented in Supplemental Table 2.
Bold values represent measures with $p<0.05$.
⋆Likelihood ratio test (LRT) is conducted against the null model.
†Pseudo-R^2 value for each model calculated for each logistic regression using the method published by Tjur, 2009.[10]
‡Area under the receiver operating curve when for logistic regression trained and measured on the entire patient cohort. Bootstrap CIs reported.
§Data perfectly separable by urethral D_{Mean} EQD2 (see Fig. E D). The patient with the maximum D_{Mean} who was observed to have grade 2+ GU toxicity had a D_{Mean} of 40 Gy_3 EQD2 and the patient with the minimum D_{Mean} who was observed to have grade 2+ GU toxicity had a plan with urethral D_{Mean} of 41.7 Gy_3 EQD2.

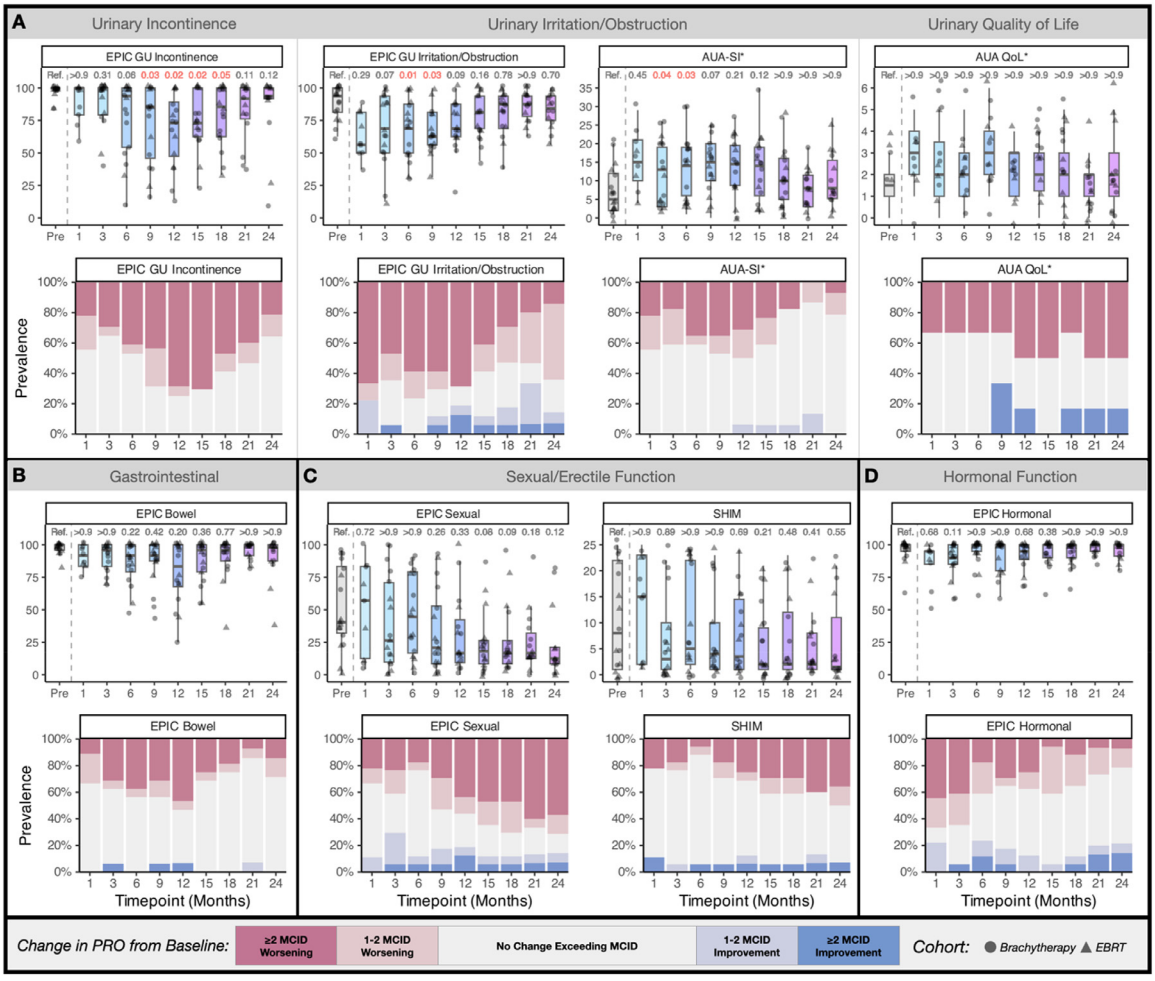

Figure 3 Patient-reported outcomes for genitourinary (A), gastrointestinal (B), sexual (C), and hormonal function (D). Top panels represent the distribution of raw scores while bottom panels represent the proportion of patients with a decline from their baseline at each timepoint. *P* values represent paired, 2-sided Wilcoxon rank sum hypothesis testing and are adjusted in each panel for 9 comparisons. On each scale, higher values represent better function within a domain (ie, less severe symptoms) with the exception of measures marked with an asterisk (*) where higher scores represent worse function.

(Q1-Q3: 1.0-2.0), representing a response between "pleased" and "mostly satisfied." A subacute decline in patient-reported urinary function was noted from the 3-month to 18-month timepoint, matching the trend in TRAEs (Fig. 1A). PROMs indicated an initial increase in urinary irritation with a significant difference from baseline in the distribution AUA-SI score at the 3- and 6-month timepoint (both $P_{adjusted} < .05$) and EPIC GU irritation at 6 and 9 months (both $P_{adjusted} < .05$). This most often was driven by patient-reported increases in weak stream/incomplete emptying (EPIC item #31) and urinary frequency (EPIC item #33), congruent with the most common physician-reported AEs during this period. As urinary irritation began to resolve, EPIC GU incontinence began to decline with statistically significant changes from baseline observed from 9 to 18 months (all $P_{adjusted} <$ .05). This was driven by patient-reported increases in leaking (EPIC item #26 & #28) and dribbling (EPIC item #28). During this period, 12 patients experienced a gradable GU toxicity, 2 of which were observed to have urinary incontinence. The distribution of patient-reported GU QOL (AUA QOL) did appear to increase (worsen) from baseline at these timepoints, although this difference was not statistically significant (all $P_{adjusted} > .05$). These changes in subacute GU function manifested in population-level reductions in EPIC GU incontinence and GU irritation ≥1 × MCID, which peaked at 12 months and 6-12 months, respectively, and were observed in approximately 75% of the patient population for each of these subdomains. This corresponded to a worsening in GU QOL (AUA QOL) ≥MCID in one-third to one-half of participants during this time period. The time to a ≥MCID decline in EPIC GU incontinence appeared shorter in patients in the BT cohort than the external beam RT cohort ($P < .01$); however, no corresponding difference was observed in the time to a ≥MCID decline

in EPIC GI incontinence ($P > .05$; Fig. E5). An association was observed between physician-reported GU toxicity grade and patient-reported change in GU HRQOL at each timepoint with the median difference between toxicity category groups (≥G2 vs <G2) exceeding the MCID for each measure (Fig. E2). The time-to-≥MCID decline is reported in Figure E3.

GI subdomain. Similarly, patient-reported GI function was high at baseline with all patients reporting a score >80 (median: 100 [Q1-Q3: 96-100]) (Fig. 3B). No significant changes in the distribution of patient-reported EPIC bowel scores were observed at any timepoint. Despite this, a similar temporal trajectory in patient-reported HRQOL was noted with a peak in patients reporting an ≥MCID decline in HRQOL at 12 months observed in 53% of the overall cohort. This temporal pattern was congruent with the few GI AEs observed in the overall population (Fig. 1A). At this timepoint, 29% of patients had GI toxicity, of which 2 were ≥G2 (grade 2 rectal pain of 9-month duration and a grade 3 rectal fistula of 5-month duration). No difference between the time to an ≥MCID decline in EPIC bowel subscore was noted between study cohorts ($P > .05$; Table E5). An association was observed between physician-reported GI toxicity grade and patient-reported change in EPIC bowel HRQOL at each timepoint with a median difference of 19 (Fig. E2).

Sexual/hormonal subdomain. In contrast to the GU and GI subdomains, baseline erectile dysfunction (ED) varied widely among participants (median EPIC sexual score 40 [Q1-Q3: 32-83]) (Fig. 3C). This same variability was seen on the SHIM at baseline where 42% had ≤ mild ED, 12% had moderate ED, and 47% had severe ED. A trend representing a decline of patient-reported sexual function over time was observed as indicated by increasing proportions of participants reporting an ≥MCID decline from baseline in EPIC sexual HRQOL or SHIM score. On both instruments, the observed proportion with a clinically significant decline from baseline peaked at the last study follow-up at 71% and 50%, respectively. Despite this, no significant differences in the distribution of scores were observed at any timepoint (all $P_{\text{adjusted}} > .05$). Hormonal subdomain outcomes are reported in Figure 3D.

Patient-reported psychometric measures. At baseline, patients reported better function than a reference cancer patient population on the PROMIS Anxiety, Depression, and Psychosocial Illness Impact instruments (ie, less anxiety, less depression, and greater positive psychological impact of illness). Minimal longitudinal change in PROMIS score was observed over the 24-month span of observation with less than one-third of the population reporting a change from baseline ≥MCID at any timepoint (Fig. 4).

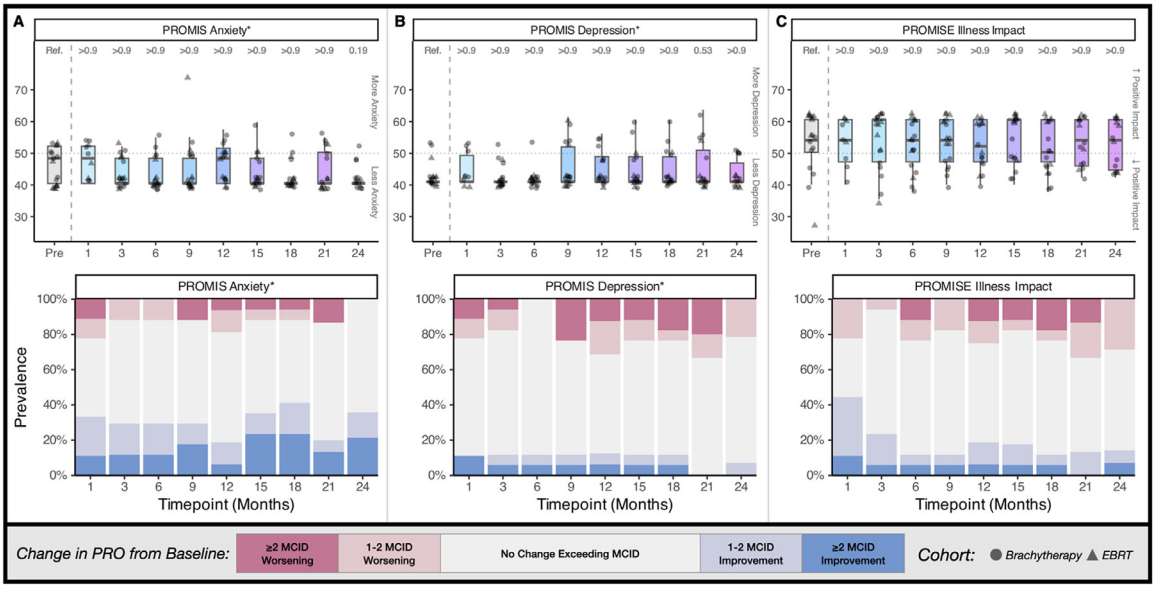

Figure 4 PROMIS patient-reported outcome (PRO) measures for anxiety (A), depression (B), and positive psychosocial illness (C). The T-score distribution for each measure is represented in the top panel with the corresponding prevalence of change in PRO measure from baseline at each timepoint in the bottom panel. Of note, on each scale, the T-score is centered at a mean of 50 with an SD of 10 for the population. *P* values represent paired, 2-sided Wilcoxon rank sum hypothesis testing and are adjusted in each panel for 9 comparisons. On the PROMIS illness impact measure, higher values represent better function within a domain (ie, more positive psychological impact). For the PROMIS anxiety.

Abbreviations: EBRT = external beam radiation therapy; MCID = minimally clinically important difference; PROMIS = Patient-Reported Outcomes Measurement Information System.

Discussion

To our knowledge, this study is the first mature report of a prospective clinical trial of salvage SBRT profiling both the longitudinal physician-rated toxicity burden and patient-reported HRQOL within the GU, GI, and sexual subdomains. This study demonstrates that the predominant physician-rated toxicities after salvage SBRT for radiorecurrent prostate cancer are GU toxicities that peak in the subacute period and then decline in prevalence through 24 months of follow-up. Further, this study demonstrates that the temporal pattern of physician-scored toxicity correlated with changes in patient-reported HRQOL in corresponding domains. Collectively, these data provide an estimate of toxicity that has relevance for informing patients about the expected impact of salvage SBRT and in the design of future clinical trials.

Several salvage treatment options have been evaluated for locally radiorecurrent prostate cancer, such as prostatectomy, focal therapy (ie, cryotherapy or high-intensity focused ultrasound), and reirradiation. There is a lack of consensus on the most appropriate treatment of these options for the management of localized radiorecurrence. This results, in part, from the paucity of mature clinical trial data to understand both the toxicity profile and HRQOL impact of salvage treatments. A recent systematic review and meta-analysis[11] concluded that reirradiation may be the favored salvage modality based in part on the suggestion that this treatment modality may carry the most limited toxicity burden. However, some have been reticent to make practice recommendations on the basis of this evidence given the retrospective nature of many of the studies on which this meta-analysis was based.[12] Thus, we aimed to address this knowledge gap in the literature with the present study, the first mature report of a prospective clinical trial of salvage SBRT profiling both the longitudinal objective toxicity burden as well as, more significantly, the corresponding HRQOL within the GU, GI, and sexual subdomains, which is considered a gold-standard measure of a treatment in oncology by the US Food and Drug Administration.[13]

In this study, we report several novel findings in regard to both toxicity and HRQOL after salvage SBRT. We observed that the burden of physician-reported GU toxicity was much greater than GI toxicity and that grade 3 TRAEs were generally rare. These findings recapitulate prior studies, which reported outcomes after salvage whole-gland BT[1] and focal SBRT.[14,15] We also report that acute toxicity during RT rapidly resolved by 1 month after treatment. Thereafter, treatment-related symptoms, most often within the GU domain, emerged gradually after treatment, peaking at approximately 12 months and often resolving by the 24-month timepoint. In addition, GU toxicity appeared to be related to prescription dose. Evaluation of the reirradiation plans in this trial seems to suggest the hypothesis that exposure to the urethra may be implicated in the development of GU toxicity as recently suggested for first-course treatments[16]; however, additional study is required to confirm causality.

Additionally, this is the first report of a comprehensive, longitudinal assessment of HRQOL on a prospective trial evaluating salvage prostate SBRT. These data demonstrate that the patient-reported symptom burden after salvage SBRT mirrors physician-rated toxicity assessment. Specifically, patients appear to encounter both self-reported urinary incontinence and urinary irritation in the subacute period from approximately 3 to 18 months. Bowel HRQOL appears to follow a similar trajectory, and sexual HRQOL appears to progressively decline, although changes from baseline in these domains were not statistically significant. The prevalence of participants with a decline $\geq$MCID in HRQOL was lower than the cumulative incidence of this decline by the end of treatment in all EPIC subdomains, resulting from transient declines in HRQOL in many patients, and this difference was significant in some cases (eg, EPIC GU incontinence). This observation suggests that future trials that seek to define the impact of salvage prostate SBRT on HRQOL may benefit from the use of prevalence at a landmark timepoint as opposed to the use of survival analysis, as planned in ongoing trials. Lastly, patients do not report changes in anxiety or depression from the beginning of treatment and in general report no psychosocial impact from treatment. One hypothesis consistent with his observation is that patients' familiarity with RT from their first course of treatment or trust in our quaternary referral center may minimize the psychological impact of treatment.

Limitations

There are several limitations to this study. First, the sample size limited the power to detect differences in groups as well as our ability to conduct exploratory analyses to generate hypotheses regarding potential factors, which influenced the development of toxicity. Second, the follow-up period may be considered a limitation. To offset this, the follow-up on trial was rigorous with 92% of PRO questionnaires completed. Additionally, this patient cohort was followed clinically after completion of this trial, and, despite the lack of systematic toxicity assessments, no additional serious treatment-related toxicities were noted. Finally, the findings regarding the potential dosimetric predictors of toxicity were obtained from a post hoc analysis on a limited sample and thus should be considered strictly hypothesis generating. In addition, the area under the receiver operating curves reported for each model were calculated based on the model development cohort, given the available sample size, and this is expected to produce a biased estimate of this metric, which should be considered in its interpretation.

Conclusions

In this report of a mature, prospective, clinical trial evaluating salvage SBRT after primary RT, we found that salvage SBRT had a 24-month cumulative incidence of G3 toxicity of 17.6% (95% CI, 0.0%-33.9%) representing 3/17 patients with resolving grade 3 toxicities. Patients commonly experienced G2 GU toxicity (24-month cumulative incidence: 76.5% [95% CI, 44.6%-90.0%]), which translated into reductions in HRQOL between 3 and 18 months on measures of obstructive/irritative symptoms and incontinence. The burden of treatment on GI toxicity and HRQOL impact was negligible, and no psychological impact of salvage SBRT was observed on measures of PROMIS anxiety, depression, or positive psychosocial impact.

Disclosures

Baris Turkbey received royalties from the National Institutes of Health; multiple patents in AI (details available on request); cooperative research and development agreements with NVIDIA and Philips. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2025.09.002.

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