Original Article

Predictors of Multidomain Decline in Health-Related Quality of Life After Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer

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BACKGROUND: Stereotactic body radiation therapy (SBRT) for localized prostate cancer involves high-dose-per-fraction radiation treatments. Its use is increasing, but concerns remain about treatment-related toxicity. The authors assessed the incidence and predictors of a global decline in health-related quality of life (HRQOL) after prostate SBRT. **METHODS:** From 2008 to 2014, 713 consecutive men with localized prostate cancer received treatment with SBRT according to a prospective institutional protocol. Expanded Prostate Cancer Index Composite (EPIC-26) HRQOL data were collected at baseline and longitudinally for 5 years. EPIC-26 is comprised of 5 domains. The primary endpoint was defined as a decline exceeding the clinically detectable threshold in $\geq$4 EPIC-26 domains, termed *multidomain decline*. **RESULTS:** The median age was 69 years, 46% of patients had unfavorable intermediate-risk or high-risk disease, and 20% received androgen-deprivation therapy. During 1 to 3 months and 6 to 60 months after SBRT, 8% to 15% and 10% to 11% of patients had multidomain declines, respectively. On multivariable analysis, lower baseline bowel HRQOL (odds ratio, 1.8; 95% confidence interval, 1.2-2.7; $P < .01$) and baseline depression (odds ratio, 5.7; 95% confidence interval, 1.3-24.3; $P = .02$) independently predicted for multidomain decline. Only 3% to 4% of patients had long-term multidomain declines exceeding twice the clinical threshold, and 30% of such declines appeared to be related to prostate cancer treatment or progression of disease. **CONCLUSIONS:** Prostate SBRT has minimal long-term impact on multidomain decline, and the majority of more significant multidomain declines appear to be unrelated to treatment. This emphasizes the importance of focusing not only on the side effects of prostate cancer treatment but also on other comorbid illnesses that contribute to overall HRQOL. ***Cancer* 2017;123:1635-42**. © *2016 American Cancer Society.*

KEYWORDS: Expanded Prostate Cancer Index (EPIC), health-related quality of life (HRQOL), Patient-reported outcomes (PRO), prostate cancer, stereotactic body radiation (SBRT).

INTRODUCTION

Prostate stereotactic body radiation therapy (SBRT) is an emerging treatment for localized prostate cancer. Promising results from single-institution[1-3] and multi-institutional[4] experiences with intermediate term follow-up have been reported, and phase 3 trials are ongoing.[5,6] SBRT is convenient, because it is delivered over just 5 treatments instead of the more standard 44 treatments, it appears to be cost effective,[7] and its use is on the rise in the United States.[8]

Despite encouraging tumor control results, concerns remain about the long-term toxicity associated with ultrahypofractionated treatment (ie, SBRT) to the prostate.[9,10] Others have reported more promising results. Widely regarded as the "gold standard" for assessing health-related quality of life (HRQOL) in prostate cancer, the Expanded Prostate Cancer Index Composite (EPIC-26) inventory captures 5 different domains of quality of life: urinary incontinence, urinary irritative, bowel, sexual, and vitality.[11] Pooled multi-institutional results to date have demonstrated minimal impact of prostate SBRT on select and solitary HRQOL, including the urinary, bowel, and sexual domains.[12] However, no data exist on

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patients who experience declines in multiple concurrent domains—a side-effect profile that may be more burdensome for patients and more difficult to manage for physicians.[13] Furthermore, the vast majority of published studies to date have focused on patients with low-risk disease, and less is known about HRQOL in men who have unfavorable intermediate-risk and high-risk disease after prostate SBRT, especially with the addition of androgen-deprivation therapy (ADT). Therefore, more work is needed to better understand the implications of SBRT on HRQOL.

We hypothesized that there is an underappreciated group of men who have clinically detectable, multidomain HRQOL decline after treatment. We used a novel framework to analyze a large, diverse cohort of men with prostate cancer who received SBRT and had prospectively collected data on HRQOL. The objective of this study was to assess the incidence of multidomain decline and to determine the associated patient and treatment factors.

MATERIALS AND METHODS

Patients

Between January 2008 and September 2014, 830 consecutive men with localized, biopsy-proven prostate cancer received SBRT according to 2 institutional protocols (National Clinical Trials NCT01766492 and NCT01618851; clinicaltrials.gov) or on a prospective registry according to protocol. Patients who had lymph node-negative, nonmetastatic disease were eligible (T1c-T3b disease, Gleason score 6-10, and prostate-specific antigen <50 ng/mL). Patients with high-risk disease were staged with a bone scan and computed tomography (CT) scans of the abdomen and pelvis. Baseline prostate-specific antigen levels were obtained before the initiation of therapy.

According to the protocol, HRQOL data were prospectively collected using the EPIC-26.[11] HRQOL data collection occurred at baseline. Post-SBRT data collection occurred at 1 month, then every 3 months for 2 years, and every 6 months thereafter. Of the 830 patients, 117 received ADT before baseline HRQOL collection, confounding the baseline results, and were excluded, leaving a final study cohort of 713 eligible patients who were available for analysis.

Treatment

Volume delineation of the prostate and seminal vesicles was defined using registration of the pretreatment magnetic resonance image (MRI) with the pretreatment CT simulation. Treatment-planning details of prostate SBRT alone as well as external-beam radiotherapy (EBRT) plus SBRT boost (intensity-modulated radiotherapy [IMRT] plus SBRT boost) have been previously described.[14,15] The prescribed dose was 35 to 36.25 grays (Gy) in 5 fractions for SBRT. Certain patients with higher risk disease received IMRT plus SBRT boost, with the prescribed dose including IMRT at 45 to 50.4 Gy in 1.8-Gy fractions plus SBRT at 19.5 Gy in 3 fractions. Treatment was delivered using a CyberKnife (Accuray, Sunnyvale, Calif) and gold fiducials aided with imaged-guided delivery. Neoadjuvant ADT consisted of a luteinizing hormone-releasing hormone agonist. ADT was prescribed primarily for 3 to 6 months to patients who had unfavorable intermediate-risk and high-risk disease.

Endpoints

The EPIC-26 is divided into 5 major symptom domains: urinary incontinence, urinary irritative, bowel, sexual, and vitality.[11] Individual question results within each domain are transformed and averaged to generate a summary score ranging from 0 to 100, and higher scores represent better HRQOL.

Minimally important difference (MID) thresholds are used to establish levels beyond which changes in quality-of-life measures are considered clinically detectable.[16] In their recent work, Skolarus et al used distribution-based and anchor-based techniques to establish specific MID thresholds for each of the EPIC-26 domains.[17] We used the midpoint of the Skolarus et al MID estimates for each domain: urinary incontinence (MID = 7.5), urinary irritative (MID = 6.0), bowel (MID = 5.0), sexual (MID = 11.0), and vitality (MID = 5.0); and each was defined as 1× MID change.

Our primary endpoint was defined as concurrent declines equal to or exceeding the MID threshold in 4 or 5 domains (termed *1× multidomain decline*). Patients who had greater global declines, defined by concurrent declines equal to or exceeding twice the MID threshold in any 4 or 5 domains (termed *2× multidomain decline*), also were documented.

Covariates

Pretreatment covariates included age (continuous), body mass index (in kg/m^2, continuous), prostate volume (in cm^3, continuous), baseline diabetes (binary, yes or no), current smoker (binary, yes or no), anticoagulation (binary, yes or no), Charlson comorbidity score[18] (binary, >2 or ≤2), baseline depression (binary, yes or no), and partner status (binary, yes or no). Pretreatment HRQOL variables included baseline incontinence, irritative, and bowel

TABLE 1. Patient Characteristics (N = 713)

Characteristic	No. of Patients (%)
Age: Median [IQR], y	69 [64-73]
Tumor classification	
T1c-T2a	575 (81)
T2b-T2c	132 (19)
T3	6 (1)
Gleason score	
≤6	247 (36)
3 + 4	250 (37)
4 + 3	121 (18)
4 + 4	59 (9)
9-10	36 (8)
Pretreatment PSA, ng/dL	
≤10	519 (73)
>10 to ≤20	135 (19)
>20	59 (8)
Risk group[a]	
Low	174 (24)
Favorable intermediate	214 (30)
Unfavorable intermediate	193 (27)
High	132 (19)
ADT[b]	
Yes	145 (20)
No	568 (80)
Prostate volume: Median [IQR], cm^3	37 [28-50]
BMI: Median [IQR], kg/m^2	27 [25-31]
Baseline HRQOL: Median [IQR]	
Urinary incontinence	100 [86-100]
Urinary irritative	88 [75-100]
Bowel	100 [92-100]
Sexual	61 [26-83]

Abbreviations: ADT, androgen-deprivation therapy; BMI, body mass index; HRQOL, health-related quality of life; IQR, interquartile range; PSA, prostate-specific antigen.
[a] Risk groups were adapted from National Comprehensive Cancer Network (NCCN) risk classification and the intermediate-risk classification proposed by Zumsteg et al.[19]
[b] All ADT was administered as neoadjuvant therapy for 3 to 6 months.

domains (continuous). Treatment-related covariates included ADT use (binary, use or nonuse, because all patients received short-term ADT).

Statistical Analysis

Descriptive statistics were used to describe the incidence of 1× and 2× multidomain declines over time and are reported as percentages and 95% confidence intervals (CIs). Univariable and multivariable logistical regressions were performed to generate models of predictors of 1× multidomain decline at 36 months after SBRT. Complete HRQOL data were available for 299 men at 36 months (88% response rate); and, of those 299 men, baseline comorbid characteristics were available for 72% (n = 215) (Supporting Table 1; see online supporting information). Odds ratios (ORs), adjusted ORs (AORs), and 95% CIs are reported. Two-sided *P* values of .05 were considered statistically significant. Statistical analyses were performed using IBM SPSS version 24.0 (IBM Corporation, Armonk, NY).

TABLE 2. Expanded Prostate Cancer Index-26 Response Rates

	Follow-Up, mo						
Variable	1	3	6	12	24	36	60
No. of respondents	659	616	570	503	401	299	133
Total no.[a]	697	665	624	559	449	339	141
Response rate, %	95	93	91	90	89	88	94

[a] Totals represent the total number of men who had follow-up at or beyond the time point.

RESULTS

Table 1 provides the characteristics of the patient cohort.[19] The median age was 69 years (interquartile range [IQR], 64-73 years). Most patients who received treatment had intermediate-risk (57%; n = 407) or high-risk (19%; n = 132) disease. Twenty percent of patients (n = 145) received short-term ADT. Response rates among those who had complete HRQOL information were ≥88% at all time points and remained consistent over time (Table 2). Before treatment, most men had excellent urinary incontinence, bowel, and vitality domains, with a median function of 100 (Table 1). The urinary irritative domain was slightly more impaired at baseline, with a median of 88 (IQR, 75-100). Sexual dysfunction was common and highly variable at baseline, with a median of 61 (IQR, 26-83).

Individual-Domain HRQOL Decline

The incidence of urinary irritative, bowel, and vitality domain 1× and 2× MID declines generally improved after an initial decrement post-treatment (Fig. 1A,B). For example, at 1 month, 54% of patients (95% CI, 50%-58%) had a 1× MID decline in the urinary irritative domain, which improved to 28% (95% CI, 20%-35%) at 5 years post-SBRT ($P < .001$). In contrast, sexual domain 1× and 2× MID declines worsened over time. One month after treatment, 39% of patients (95% CI, 35%-43%) reported a 1× MID sexual domain decline, which increased to 56% reporting a decline (95% CI, 47%-64%) at 5 years post-SBRT ($P < .001$). The urinary incontinence domain remained stable over time.

Rates of Multidomain Decline

In the acute setting (1 to 3 months after SBRT), approximately 10% to 15% of patients exceed the threshold for clinical detectable decline in 4 or more domains and meet

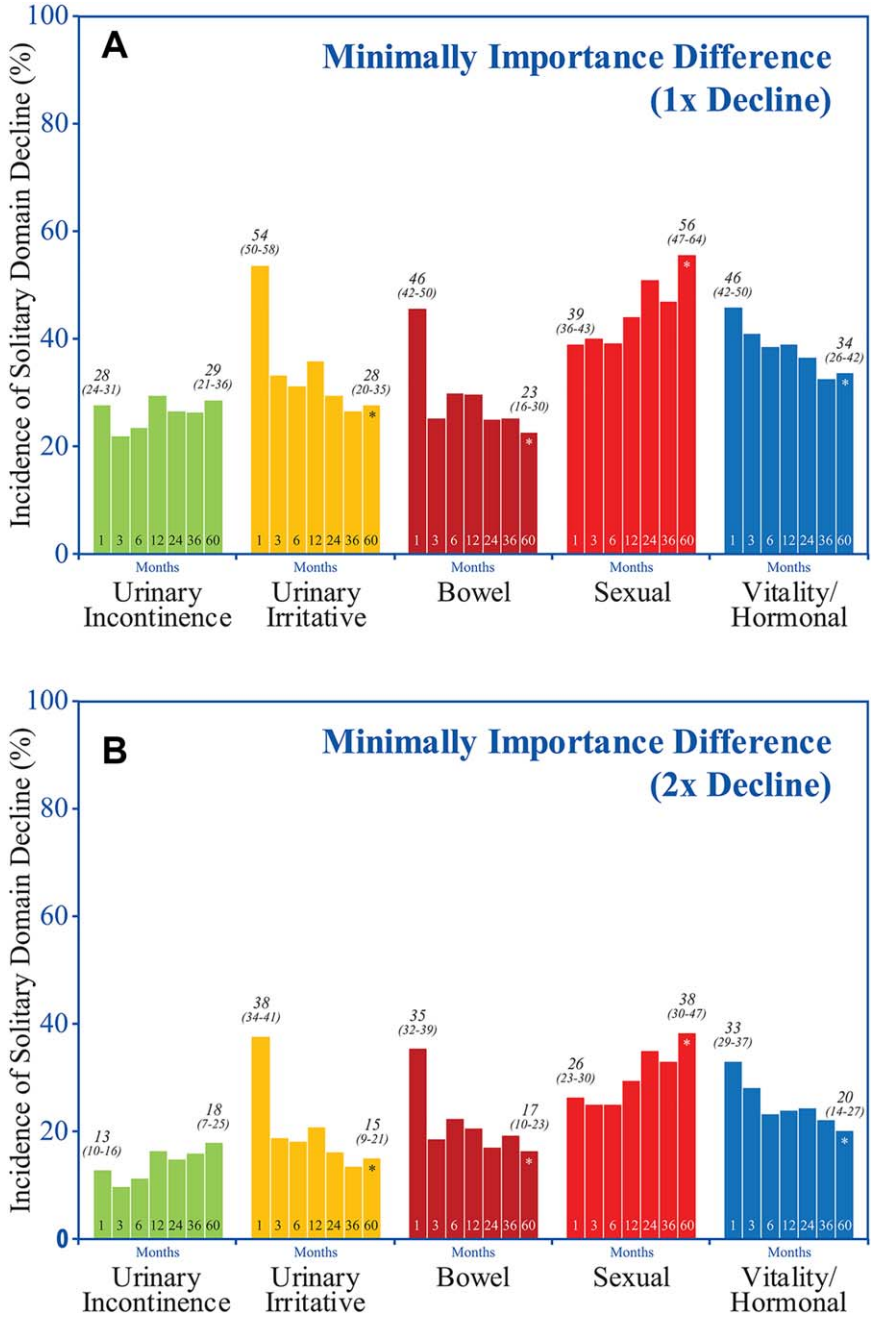

Figure 1. Solitary domain decline according to the Expanded Prostate Cancer Index (EPIC) is shown. Charts illustrate the incidence of a decline in a solitary EPIC domain (A) equal to or exceeding the threshold for clinical detection, estimated as described by Skolarus et al[17] (minimally importance difference 1x decline), and (B) a decline equal to or exceeding twice the clinical threshold for detection (minimally importance difference 2x decline). The results indicate percentages with 95% confidence intervals in parentheses; 1-month post-treatment declines are compared with declines at 60 months. An asterisk indicates $P < .01$.

our definition of 1× multidomain decline (Fig. 2A). Between 3 and 6 months, the incidence of 1× and 2× multidomain decline is lower, because the acute bowel and urinary irritative side effects from SBRT subside, and sexual domain declines have not yet peaked. In the long term (2 to 5 years after treatment), approximately 10% of patients continue to report 1× multidomain declines. Among those patients who have more significant declines, approximately 5% experience 2× multidomain declines in the acute setting, and this decreases to 3% to 4% from

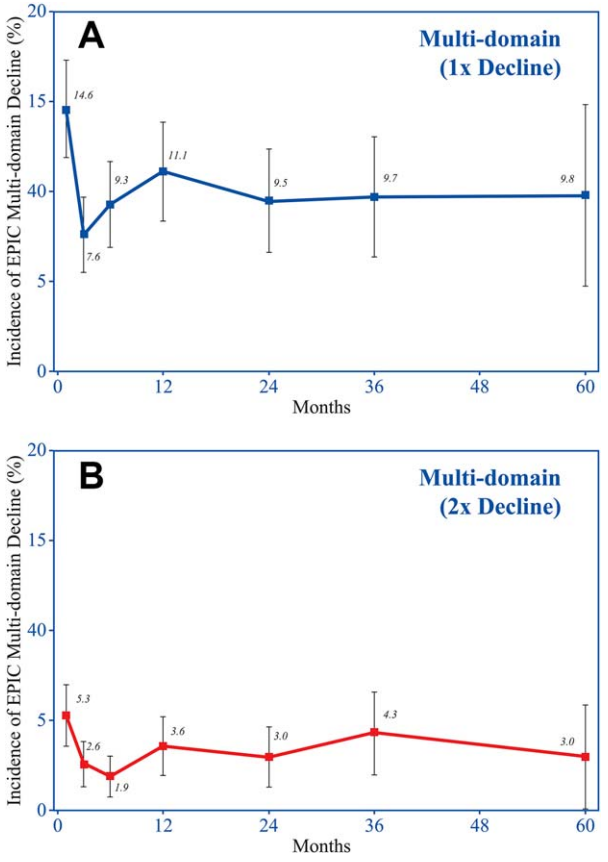

Figure 2. Multidomain decline according to the Expanded Prostate Cancer Index Composite (EPIC) is shown. Charts illustrate the incidence of a multidomain decline (A) equal to or exceeding the threshold for detection, estimated as described by Skolarus et al,[17] in 4 or more of the 5 EPIC domains (multidomain 1x decline) and (B) equal to or exceeding twice the threshold for clinical detection in ≥4 of the 5 EPIC domains (multidomain 2x decline). Error bars represent 95% confidence intervals.

2 to 5 years after treatment (Fig. 2B). Of the 29 patients who reported 1× or 2× multidomain declines at 36 months, 79% (n = 23) reported a "moderate" or "big" problem in at least 1 domain.

Predictors of Multidomain Decline

On univariable analysis, lower baseline bowel HRQOL (OR, 1.38 per 10-point decrease; 95% CI, 1.02-1.87 per 10-point decrease; $P = .04$) and a baseline diagnosis of depression (OR, 4.13; 95% CI, 1.00-17.01; $P = .05$) were significantly associated with multidomain decline (Table 3). Age, body mass index, prostate volume, baseline diabetes, smoking status, anticoagulation use, Charlson comorbidity score, partner status, baseline urinary incontinence or irritative HRQOL, and receipt of ADT were not significantly associated with multidomain decline.

On multivariable analysis, men who had worse baseline bowel HRQOL had an increased likelihood of having 1× multidomain decline (AOR, 1.82 per 10-point decrease; 95% CI, 1.21-2.73 per 10-point decrease; $P < .01$). Of those who had 1× multidomain declines, 7 had baseline bowel function in the lowest quartile; and 5 of those 7 men (71%) had identifiable bowel disease (2 had a prior history of colorectal cancer, 1 had hemophilia and chronic small-bowel obstructions, 1 had severe hemorrhoids and incontinence, and 1 had chronic diverticulitis). One of the 2 patients without bowel disease had a clinical diagnosis of depression but no overt diagnosis of irritable bowel syndrome. In addition to poor bowel function before treatment, a baseline clinical diagnosis of depression was significantly associated with a >5-fold increase in 1× multidomain decline (AOR, 5.65; 95% CI, 1.31-24.26; $P = .02$).

Among the 3% of patients (n = 13) who reported a more significant 2× multidomain decline at 36 months, 53% (n = 7) experienced concomitant declines in their health status unrelated to prostate cancer or treatment. These declines included a new pituitary tumor, a new diagnosis of pulmonary fibrosis, and a recurrent bladder tumor, among others (Table 4). Thirty percent of these patients (n = 4) experienced either a disease-related decline (metastasis and ADT) or persistent radiation side effects, such as radiation cystitis or urinary incontinence. Others reported a global decline without clear etiology that may or may not have been treatment related (n = 2).

DISCUSSION

The modern definition of prostate cancer treatment success involves cure with preserved quality of life.[20] Reports from Sanda et al, Resnick et al, and the recent Prostate Testing for Cancer and Treatment (ProtecT) randomized trial all indicate that patient-reported outcomes differ among definitive treatment strategies.[21-23] Men who undergo radical prostatectomy are more likely to report declines in urinary incontinence and sexual function, whereas those who receive conventionally fractionated radiation (EBRT) are more likely to report rectal bleeding. Less is known about the side-effect profile of SBRT, particularly its impact on global decline. Therefore, as we await randomized data from trials like Prostate Advances in Comparative Evidence (PACE, NCT01584258),[5] which will compare SBRT with radical prostatectomy and EBRT, our data provide insight into the expected patient-

TABLE 3. Univariable and Multivariable Analysis of Predictors of Multidomain Decline at 36 Months

	36 Months					
	Univariable Analysis			Multivariable Analysis		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Age[a]	1.02	0.97-1.08	.46			
BMI[a]	0.99	0.93-1.06	.78			
Prostate volume	1.00	0.98-1.02	.95			
Baseline diabetes (yes vs no)	1.38	0.43-4.40	.59			
Current smoker (yes vs no)	0.44	0.06-3.43	.43			
Anticoagulation use (yes vs no)	0.94	0.37-2.40	.89			
Charlson comorbidity score >2	1.43	0.56-3.68	.46			
Baseline depression (yes vs no)	4.13	1.00-17.01	.05	5.65	1.31-24.26	.02
Partner status (yes vs no)	0.42	0.16-1.10	.08			
Baseline incontinence HRQOL[b]	1.17	0.94-1.44	.15			
Baseline irritative HRQOL[b]	0.87	0.68-1.13	.30			
Baseline bowel HRQOL[b]	1.38	1.02-1.87	.04	1.82	1.21-2.73	< .01
ADT use (yes vs no)	0.70	0.20-2.44	.58			

Abbreviations: ADT, androgen-deprivation therapy; BMI, body mass index; CI, confidence interval; HRQOL, health-related quality of life; OR, odds ratio; PSA, prostate-specific antigen.
[a] Age and BMI were considered continuous variables.
[b] HRQOL values shown are per 10-point decrease in HRQOL.

TABLE 4. Detail of Patients With 2x Multidomain Decline at 36 Months[a]

Reason for Decline	No. of Patients
Unrelated to treatment	7
Hypogonadism secondary to pituitary tumor	1
Major depressive episode	1
New diagnosis of pulmonary fibrosis	1
Recent nephrolithiasis diagnosis	1
Recurrent bladder cancer	1
Unemployed and alcohol abuse	1
Worsening of morbid obesity and metabolic syndrome	1
Disease or treatment related	4
Metastasis and initiation of androgen-deprivation therapy	1
Radiation cystitis	1
Recent urinary tract infection and sepsis	1
Urinary incontinence	1
Unclear or unknown	2

[a] These include all patients with incidence of a decline equal to or exceeding twice the clinical threshold for detection estimated by Skolarus et al[17] in ≥4 of the 5 Expanded Prostate Cancer Index domains at 36 months (2× multidomain decline).

reported outcomes post-SBRT and address concerns related to treatment with high doses per fraction.

Our results from novel, patient-level analyses support the finding that prostate SBRT is generally well tolerated with a low incidence of global decline after treatment. With up to 5 years of follow-up, 90% of patients did not meet the minimum threshold for detection of multidomain decline using EPIC-26, a gold standard in patient-reported HRQOL. In the subset of 3% to 4% of patients who had more substantial multidomain declines at 3 years, >50% experienced a decline in their general health status that likely was unrelated to prostate cancer or treatment. To our knowledge, this is the first comprehensive report of global HRQOL after SBRT and is particularly unique given the diverse patient population and detailed patient-level comorbidity details.

Our findings are consistent with other investigations of the impact of SBRT on select and solitary domains of HRQOL. In 2013, King et al reported their multi-institutional pooled analysis of HRQOL after prostate SBRT indicating that tumor-control outcomes were promising, and there were acceptable rates of sexual, urinary, and bowel domain HRQOL declines.[12,24] Evans et al reported that HRQOL after prostate SBRT was similar to that after brachytherapy and IMRT with respect to mean urinary ($P > .5$) and sexual ($P = .57$) domains but was associated with better mean bowel function (6.7 points; $P < .01$).[25] Unfortunately, most studies published to date have not provided enough information on baseline comorbidity to clarify the impact of these factors on HRQOL. Our study provides further support that SBRT is well tolerated, with rates of solitary domain decline comparable to those reported in the published literature, and also demonstrates that there is minimal multidomain decline in our higher risk population, 20% of which received ADT. Furthermore, our baseline comorbidity details provide additional key insight regarding those who are most likely to report decline.

Several studies have demonstrated that pre-existing anal disease (fissures, hemorrhoids)[26] and bowel disease

(Crohn disease, ulcerative colitis, irritable bowel syndrome [IBS])[27] are associated with bowel toxicity after treatment with conventionally fractionated radiotherapy. Although previous studies have suggested that patient-reported bowel function is affected less by SBRT than by conventional fractionation,[25] our findings suggest that patients who have poor baseline function remain at higher risk of multidomain decline (AOR, 1.8 per 10-point decline; 95% CI, 1.21-2.73 per 10-point decline). It is unknown whether these patients have inherently radiosensitive tissue and, thus, that generalized, radiation-induced dysfunction is more likely in these patients or that poor bowel function itself impacts other domains (ie, urinary problems, avoiding sexually activity, and fatigue). Of the patients who had multidomain decline and bowel function in the lowest quartile, 71% had identifiable preexisting bowel disease. These patients with poor baseline bowel function should be counseled about the risks of treatment and aggressively managed in the acute and long-term settings. Although it was not prospectively documented in our cohort, patients with IBS should also be of concern, because most studies demonstrate that the prevalence of concurrent psychiatric disorders in patients with IBS is $\geq$90%.[28] The most common psychiatric diagnosis associated with IBS is major depression, which is also an important comorbidity to keep in mind based on our results.

Baseline depression was associated with a >5-fold increase in multidomain decline at 36 months. This finding is consistent with Mohamed et al, who reported that pretreatment depressive symptoms were associated with patient-reported HRQOL declines in urinary and sexual function in a group of 1370 men who underwent either radical prostatectomy, brachytherapy, or EBRT.[29] Because this increased side-effect profile appears to be prevalent across multiple definitive modalities, pretreatment counseling and optimized psychiatric care should be prioritized. Furthermore, >50% of patients who experienced a 2$\times$ multidomain decline had an unrelated decline in their general health, highlighting the importance of comprehensive survivorship care after treatment and stressing the importance of treating the patient and not simply their prostate cancer.

Several limitations of our study are worthy of discussion. With conventionally fractionated radiotherapy, symptoms stabilize at 3 years[30]; however, less is known about the late side effects of ultrahypofractionated treatment. Although >100 patients had more than $\geq$5 years of follow-up, most of our patients had $\leq$3 years of follow-up, and continued close monitoring of long-term side effects is warranted. It is possible that unaccounted for confounding variables, such as insurance status, may have affected our results.[31] We are limited in making conclusions regarding dose-volume correlations, because such data were not available for analysis. Preliminary work suggests that there is minimal dosimetric impact on MID declines across most domains.[32] Finally, our models have not been independently validated.

Conclusion

In summary, prostate SBRT appears to have minimal long-term impact on clinically detectable, multidomain declines up to 5 years after treatment. Further follow-up and independent validation are warranted to confirm these promising findings. Moreover, we eagerly await the long-term results from randomized controlled trials, such as PACE (NCT01584258), which will compare both the efficacy and the HRQOL of radical prostatectomy, SBRT, and conventionally fractionated radiotherapy in patients with low-risk and intermediate-risk disease. In addition to solitary-domain comparisons, we recommend cross-modality comparisons of multidomain decline and capturing of baseline comorbidities, including depression, to better understand the impact of treatment itself on HRQOL.

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CONFLICT OF INTEREST DISCLOSURES

Felix Y. Feng reports grants from Varian, Medivation/Astellas, and Celgene and serves on the advisory boards of Medivation/Astellas, GenomeDx, Nanostring, and Celgene, outside the submitted work. Sean P. Collins is a clinical consultant for Accuracy outside the submitted work, and Accuracy also provides educational grants to the Department of Radiation Medicine at Georgetown University. Daniel E. Spratt reports grants from the Prostate Cancer Foundation, outside the submitted work.

AUTHOR CONTRIBUTIONS

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