Original Article

Predictors of Multi-Domain Decline in Health Related Quality of Life after Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer

Running Title: Multi-domain Decline and Prostate SBRT

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Precis for use in the Table of Contents (2 sentences)

In a cohort of over 700 patients with prospective health related quality of life information, prostate stereotactic body radiation therapy has minimal long-term impact on clinically detectable declines in global quality of life. Baseline poor bowel function and clinical depression are associated with an increased rate of multi-domain decline.

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Abstract

Background: Stereotactic body radiation therapy (SBRT) for localized prostate cancer involves high dose per fraction radiation treatments. Utilization is increasing, but concerns remain about treatment-related toxicity. We assess the incidence and predictors of a global decline in health-related quality of life (HRQOL) after prostate SBRT.

Methods: From 2008-2014, 713 consecutive men with localized prostate cancer were treated with SBRT per 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 ≥4 EPIC-26 domains, termed "multi-domain decline".

Results: Median age was 69 years old, 46% were unfavorable intermediate- or high-risk, and 20% received androgen deprivation therapy. During 1-3 and 6-60 months post-SBRT, 8-15% and 10-11% of patients had a multi-domain decline, respectively. On multivariable analysis, lower baseline bowel HRQOL (odds ratio 1.8 [95%CI 1.2-2.7], p<0.01) and baseline depression (odds ratio 5.7 [95%CI 1.3-24.3], p=0.02) independently predicted for multi-domain decline. Only 3-4% of patients had long-term multi-domain decline exceeding twice the clinical threshold, of which 30% appeared to be related to prostate cancer treatment or progression of disease.

Conclusions: Prostate SBRT has minimal long-term impact on multi-domain decline, and of those with more significant multi-domain decline, the majority appear to be unrelated to

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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.

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Introduction:

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

Despite encouraging tumor control results, concerns remain about the long-term toxicity associated with ultra-hypofractionated treatment (i.e. SBRT) to the prostate.[9,10] Others have reported more promising results. Widely regarded as the 'gold standard' for assessing HRQOL in prostate cancer, the Expanded Prostate Cancer Index Composite (EPIC) 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 exists on 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 with unfavorable intermediate and high risk disease after prostate SBRT, especially with the addition of androgen deprivation therapy. As such, more work is needed to better understand the implications of SBRT on HRQOL.

We hypothesize that an underappreciated group of men exists with clinically detectable, multi-domain HRQOL decline following treatment. Using a novel framework, we analyze a large, diverse cohort of men with prostate cancer, all treated with SBRT with prospectively

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collected HRQOL. We aim to assess the incidence of and determine patient- and treatment-factors associated with multi-domain decline.

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Methods and Materials

Patients

Between January 2008 and September 2014, 830 consecutive men with localized biopsy-proven prostate cancer were treated with SBRT per two institutional protocols (ClinicalTrials.gov NCT01766492, NCT01618851) or on a prospective registry per protocol. Node negative, non-metastatic patients were eligible (T1c-T3b disease, Gleason score 6-10, and PSA <50 ng/mL). High risk patients were staged with a bone scan and CT of the abdomen and pelvis. Baseline prostate-specific antigen (PSA) levels were obtained prior to initiation of therapy.

Per protocol, Health Related Quality of Life (HRQOL) data were prospectively collected utilizing the EPIC-26 [11]. HRQOL data collection occurred at baseline. Post-SBRT data collection occurred at 1 month, 3 months for 2 years, and every 6 months thereafter. Of the 830 patients, 117 were administered androgen deprivation prior to baseline HRQOL collection confounding the baseline results and were excluded leaving 713 eligible patients available for analysis that forms the study cohort.

Treatment

Volume delineation of the prostate and seminal vesicles was defined using a registration of the pretreatment MRI with the pretreatment CT simulation. Treatment planning details of prostate SBRT alone as well as external beam radiotherapy plus SBRT boost (IMRT+SBRT

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boost) have been previously described.[14,15] Dose prescription was 35-36.25 Gy in 5 fractions for SBRT. Certain higher risk patients were treated with IMRT+SBRT boost; dose prescription included 45-50.4 Gy in 1.8 Gy fractions of IMRT plus 19.5 Gy in 3 fractions of SBRT. Treatment was delivered using Cyberknife (Accuray, Sunnyvale CA) and gold fiducials aided with imaged-guided delivery. Neoadjuvant androgen deprivation therapy (ADT) consisted of an LHRH agonist. ADT was prescribed primarily to unfavorable intermediate and high risk patients for 3-6 months duration.

Endpoints

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; higher scores represent better HRQOL.

"Minimally Important Difference" (MID) thresholds establish levels beyond which changes in quality of life measures are considered clinically detectable.[16] Recent work by Skolarus et al utilized distribution-based and anchor-based techniques to establish specific MID thresholds for each of the EPIC-26 domains.[17] We utilized the midpoint of the Skolarus et al MID estimates for each domain: urinary incontinence (7.5), urinary irritative (6.0), bowel (5.0), sexual (11.0), and vitality (5.0); each defined as 1x MID change.

Our primary endpoint was defined as patients with declines equal to or exceeding the MID threshold in 4 or 5 domains concurrently (termed 1x multi-domain decline). Those with greater global declines, defined by declines equal to or exceeding twice the MID threshold in any 4 or 5 domains concurrently, were also documented (termed 2x multi-domain decline).

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Covariables

Pretreatment covariables included age (continuous), body mass index (BMI, kg/m2, continuous), prostate volume (cubic centimeters (cc), continuous), baseline diabetes (binary, yes or no), current smoker (binary, yes or no), anticoagulation (binary, yes or no), Charlson Comorbidity [18] (binary, greater than or less than 2), baseline depression (binary, yes or no), and partner status (binary, yes or no). Pretreatment HRQOL variables included baseline incontinence, irritative, and bowel domains (continuous). Treatment-related covariables included ADT use (binary, use or non-use, as all patients were treated with short-term ADT).

Statistical Analysis

Descriptive statistics were used to describe the incidence of 1x and 2x multi-domain decline over time, reporting the percentage and 95% confidence interval (CI). Univariable and multivariable logistical regression was performed to generate models of predictors of 1x multi-domain decline at 36-months post-SBRT. Complete HRQOL data were available in 299 men at 36 months (88% response rate), and of the 299 men, baseline comorbid characteristics were available for 72% (n = 215) (**Supplementary Table 1**). Odds ratios (OR), adjusted OR (AOR), and 95% CI are reported. Two-sided P values of 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS version 24.0 (SPSS Inc., Chicago, IL USA).

Results

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Table 1 demonstrates the characteristics of the patient cohort. Median age was 69 years old (IQR 64-73). Most patients treated were intermediate risk (57%, n=407) or high risk (19%, n = 132). Twenty percent (n = 145) of patients received short-term ADT. Response rates with complete HRQOL information were 88% or greater at all time points, and remained consistent over time **(Table 2).** Prior to treatment, most men had excellent urinary incontinence, bowel, and vitality domains with median function of 100 **(Table 1)**. The urinary irritative domain was slightly more impaired at baseline with a median of 88 (interquartile range (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 1x and 2x MID decline generally improved after an initial decrement post-treatment (**Figure 1A and 1B**). For example, at 1 month 54% (95% CI 50-58%) of patients had a 1x MID decline in the urinary irritative domain, which improved to 28% (95% CI 20-35%) of patients at 5-years post-SBRT, $p<0.001$. In contrast, the sexual domain 1x and 2x MID decline worsened over time. At 1-month post treatment 39% (95% CI 35-43%) of patients reported a 1x MID sexual domain decline, which increased to 56% reporting a decline (95% CI 47-64%) at 5-years post-SBRT, $p<0.001$. The urinary incontinence domain remained stable over time.

Rates of multi-domain decline

In the acute setting 1-3 months post SBRT, approximately 10-15% of patients exceed the threshold for clinical detectable decline in 4 or more domains and meet our definition of 1x

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multi-domain decline (**Figure 2A**). Between 3-6 months, the incidence of 1x and 2x multi-domain decline is lower as the acute bowel and urinary irritative side effects subside from SBRT, and before sexual domain declines peak. Long-term, 2-5 years post-treatment, ~10% of patients continue to report 1x multi-domain declines. As for those patients with more significant declines, ~5% of men experience 2x multi-domain decline in the acute setting, which decreased to 3-4% 2-5 years post-treatment (**Figure 2B**). Of the 29 patients reporting 1x or 2x multi-domain decline at 36 months, 79% (n = 23) reported "moderate" or "big" problem in at least one domain.

Predictors of Multi-domain decline

On univariable analysis, lower baseline bowel HRQOL (OR 1.38 per 10 point decrease [95%CI 1.02-1.87], p=0.04) and a baseline diagnosis of depression (OR 4.13 [95% CI 1.00-17.01], p=0.05) were significantly associated with multi-domain decline (**Table 3**). Age, BMI, prostate volume, baseline diabetes, smoking status, anticoagulation use, Charlson comorbidity, partner status, baseline urinary incontinence or irritative HRQOL and use of ADT were not significantly associated with multi-domain decline.

On multivariable analysis, those with worse baseline bowel HRQOL had an increased likelihood of having 1x multi-domain decline (AOR of 1.82 per 10 point decrease [95% CI 1.21-2.73], p<0.01). Of the patients with 1x multi-domain decline, seven had baseline bowel function in the lowest quartile. Five of the seven (71%) had identifiable bowel disease (two with prior history of colorectal cancer, one hemophilia and chronic small bowel obstructions, one with severe hemorrhoids and incontinence, and one with chronic diverticulitis). One of the two without bowel disease had a clinical diagnosis of depression, but no overt diagnosis of irritable bowel syndrome. In addition to poor bowel function prior to treatment, a baseline clinical

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diagnosis of depression was significantly associated with a >5-fold increase in 1x multi-domain decline (AOR 5.65 [95%CI 1.31-24.26], p=0.02).

Of the 3.0% of patients (n = 13) reporting a more significant, 2x multi-domain decline at 36 months, 53% of patients (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, a recurrent bladder tumor, among others (**Table 4**). Thirty percent (n = 4), experienced either disease related decline (metastasis and ADT) or persistent radiation side effects such as radiation cystitis or urinary incontinence. Others reported a global decline without a clear etiology that may or may not be treatment related (n = 2).

Discussion

The modern definition of prostate cancer treatment success involves cure with preserved quality of life.[19] As noted by Sanda et al, Resnick et al, and the recently reported Prostate Testing for Cancer and Treatment (ProtecT) randomized trial, patient reported outcomes differ amongst definitive treatment strategies.[20-22] Those undergoing radical prostatectomy (RP) are more likely to report declines in urinary incontinence and sexual function whereas those receiving 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. As we await randomized data from trials such as Prostate Advances in Comparative Evidence (PACE, NCT01584258)[5] which will compare SBRT to RP and EBRT, our data provides insight as to the expected patient-reported outcomes post-SBRT and addresses concerns related to treatment with high doses per fraction.

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Using a novel patient-level analysis, our findings support that prostate SBRT is generally well tolerated with low incidence of global decline following treatment. With up to 5 years of follow-up, 90% of patients do not meet the minimum threshold for detection of multi-domain decline using EPIC-26, a gold standard in patient reported HRQOL. In the subset of the 3-4% patients with more substantial multi-domain decline at 3 years, over 50% of patients experienced a decline in their general health status likely unrelated to prostate cancer or treatment. To our knowledge, this is the first comprehensive report of global HRQOL following SBRT and is particularly unique given the diverse patient population and detailed patient-level comorbidity detail.

Our findings are consistent with others investigating the impact of SBRT on select and solitary domains of HRQOL. In 2013, King et al reported their multi-institutional pooled analysis of HRQOL following prostate SBRT. Tumor control outcomes were promising, and there were acceptable rates of sexual, urinary, and bowel domain HRQOL declines.[12,23] Evans et al reported HRQOL was similar to brachytherapy and IMRT with respect to mean urinary ($p > 0.5$) and sexual domains ($p = 0.57$), but was associated with better mean bowel function (6.7 points, $p < 0.01$).[24] Unfortunately, most studies published to date often do not provide baseline comorbidity to understand the impact of these factors on HRQOL. Our study provides further support that SBRT is well tolerated with comparable rates of solitary domain decline to the published literature, and demonstrate there is also minimal multi-domain decline in our higher-risk population, 20% of which received ADT. Furthermore, our baseline comorbidity detail provides additional key insight as to those most likely to report decline.

Several studies have demonstrated preexisting anal disease (fissures, hemorrhoids) [25] and bowel disease (Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS)) [26] have been

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associated with bowel toxicity following treatment with conventionally fractionated radiotherapy. While previous studies suggest that patient-reported bowel function is less affected by SBRT compared to conventional fractionation [24], our findings suggest that those with poor baseline function remain at higher risk of multi-domain decline (AOR 1.8 [95% CI 1.21-2.73] per 10 points). It is unknown whether these patients have inherently radiosensitive tissue and generalized radiation-induced dysfunction is thus more likely in these patients or that poor bowel function itself impacts other domains (i.e. urinary problems, avoiding sexually activity, and fatigue). Of the patients with multi-domain decline and bowel function in the lowest quartile, 71% had identifiable preexisting bowel disease. These patients with poor baseline bowel function should be counseled as to the risks of treatment and aggressively managed in the acute and long-term setting. While not prospectively documented in our cohort, patients with IBS should also be of concern, given that most studies demonstrate the prevalence of concurrent psychiatric disorders in IBS to be 90% or higher.[27] The most common psychiatric diagnosis associated with IBS is major depression, which is also an important comorbidity to be mindful of based on our results.

Baseline depression was associated with a >5-fold increase in multi-domain 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 1,370 men treated with either radical prostatectomy, brachytherapy, or external beam radiation.[28] As 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 2x multi-domain decline had an unrelated decline in their general health, highlighting the importance of comprehensive

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survivorship care following treatment, and stresses 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 [29], however less is known about the late side effects of ultra-hypofractionated treatment. While over 100 patients had longer than 5 years of follow-up, the majority of our patients had 3 or less years of follow up and continued close monitoring of long-term side effects are warranted. It is possible that unaccounted for confounding variables, such as insurance status, may have affected our results.[30] We are limited in making conclusions regarding dose-volume relationships as they were not available for analysis. Preliminary work suggest minimal dosimetric impact on MID declines across most domains.[31] Finally, our models have not been independently validated.

Conclusion

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

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Figure 1: EPIC Solitary Domain Decline

Panel (A) represents the incidence of patients with a solitary domain decline equal to or exceeding the threshold for clinical detection estimated by Skolarus et al [17] (Minimally Importance Difference (MID) 1x Decline). Panel (B) represents incidence of a decline equal to or exceeding twice the clinical threshold for detection (Minimally Importance Difference 2x Decline). Parenthesis represent 95% confidence intervals. 1-month post-treatment declines are compared to the decline at 60 months; * represents p-value < 0.01. Abbreviations: EPIC, Expanded Prostate Cancer Index Composite.

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Figure 2: EPIC Multi Domain Decline

Panel (A) represents the incidence of patients with a multi-domain decline equal to or exceeding the threshold for detection estimated by Skolarus et al [17] in 4 or more of the 5 EPIC domains (Multi-domain 1x Decline). Panel (B) represents the incidence of patients with a decline equal to or exceeding twice the threshold for clinical detection in 4 or more of the 5 EPIC domains (Multi-domain 2x Decline). Abbreviations: EPIC, Expanded Prostate Cancer Index Composite. Error bars represent 95% confidence intervals.

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Table 1: Patient Characteristics

Abbreviations: PSA, prostate specific antigen; ADT, androgen deprivation therapy; BMI, body mass index; HRQOL, health related quality of life

* Risk group adapted from National Comprehensive Cancer Network (NCCN) risk classification and the intermediate risk classification proposed by Zumsteg and Spratt.[32]

** All ADT administered neoadjuvantly for 3-6 months.

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Table 2: EPIC-26 Response Rates

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite.

* Represent total men with follow-up at or beyond time point.

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Table 3: Univariable and Multivariable Analysis of Predictors of Multi-Domain Decline at 36 Months

* Continuous variables; † Per 10 point decrease in HRQOL.
Abbreviations: BMI, body mass index; HRQOL, health related quality of life; ADT, androgen deprivation therapy; OR, odds ratio; CI, confidence interval

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Table 4: Detail of Patients with 2x Multi-domain Decline at 36 months

Includes 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 or more of the 5 EPIC domains at 36 months (2x Multi-domain decline). Abbreviations: EPIC, Expanded Prostate Cancer Index Composite.

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Table 1: Patient Characteristics

Patients	**N= 713**	**%**
Age (years)		
Median (IQR)	69.0	(64-73)
T-Stage		
T1c-T2a	575	81%
T2b-c	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%
Pretreat PSA (ng/dl)		
≤10	519	73%
>10 to ≤20	135	19%
>20	59	8%
Risk Group *		
Low	174	24%
Favorable Intermediate	214	30%
Unfavorable Intermediate	193	27%
High	132	19%
ADT **		
Yes	145	20%
No	568	80%
Prostate Volume (cc)		
Median (IQR)	37	(28-50)
BMI (kg/m2)		
Median (IQR)	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)

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Table 2: EPIC-26 Response Rates

	Follow-up Time period (months)						
	1	3	6	12	24	36	60
Number of Respondents	659	616	570	503	401	299	133
Total *	697	665	624	559	449	339	141
Response rate	95%	93%	91%	90%	89%	88%	94%

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Table 3: Univariable and Multivariable Analysis of Predictors of Multi-Domain Decline at 36 Months

	Univariable Analysis				*Multivariable Analysis*			
	36 months				*36 months*			
	OR	*CI*		*p*	*OR*	*CI*		*p*
Age *	1.02	0.97	1.08	0.46				
BMI *	0.99	0.93	1.06	0.78				
Prostate Volume *	1.00	0.98	1.02	0.95				
Baseline Diabetes (yes vs no)	1.38	0.43	4.40	0.59				
Current smoker (yes vs no)	0.44	0.06	3.43	0.43				
Anticoagulation use (yes vs no)	0.94	0.37	2.40	0.89				
Charlson Cormorbidity > 2	1.43	0.56	3.68	0.46				
Baseline Depression (yes vs no)	4.13	1.00	17.01	0.05	5.65	1.31	24.26	0.02
Partner status (yes vs no)	0.42	0.16	1.10	0.08				
Baseline Incontinence HRQOL †	1.17	0.94	1.44	0.15				
Baseline Irritative HRQOL †	0.87	0.68	1.13	0.30				
Baseline Bowel HRQOL †	1.38	1.02	1.87	0.04	1.82	1.21	2.73	<0.01
ADT use (yes vs no)	0.70	0.20	2.44	0.58				

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Table 4: Detail of Patients with 2x Multi-domain Decline at 36 months

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)

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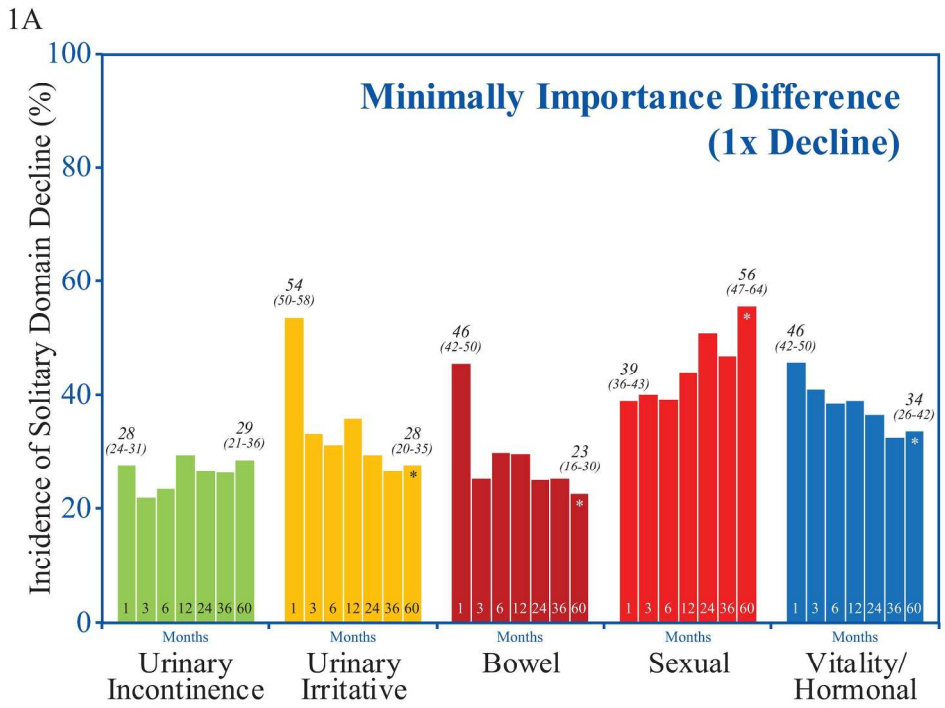

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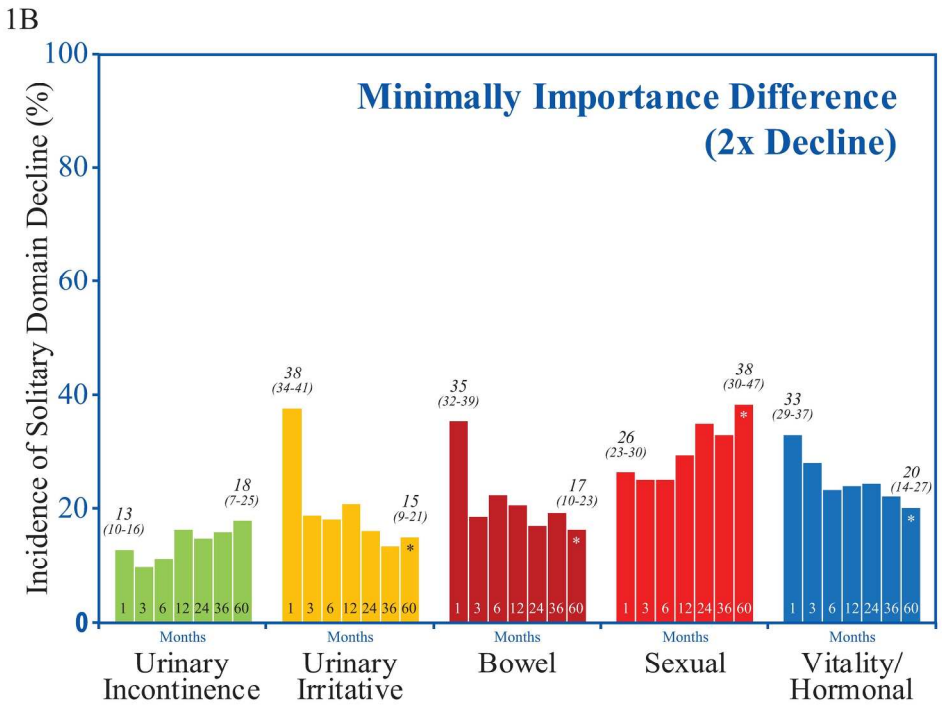

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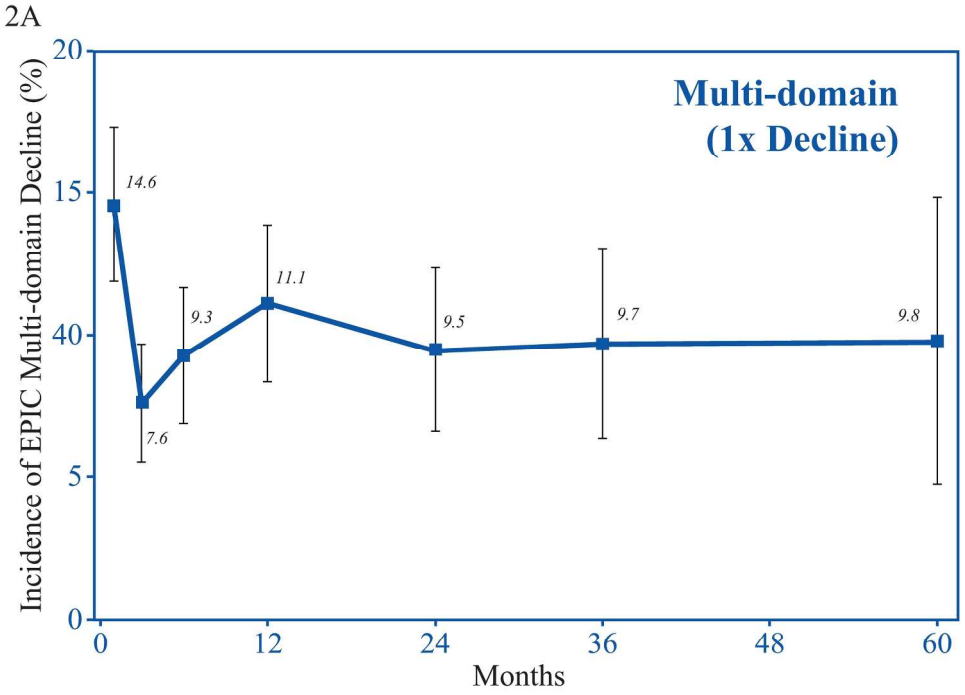

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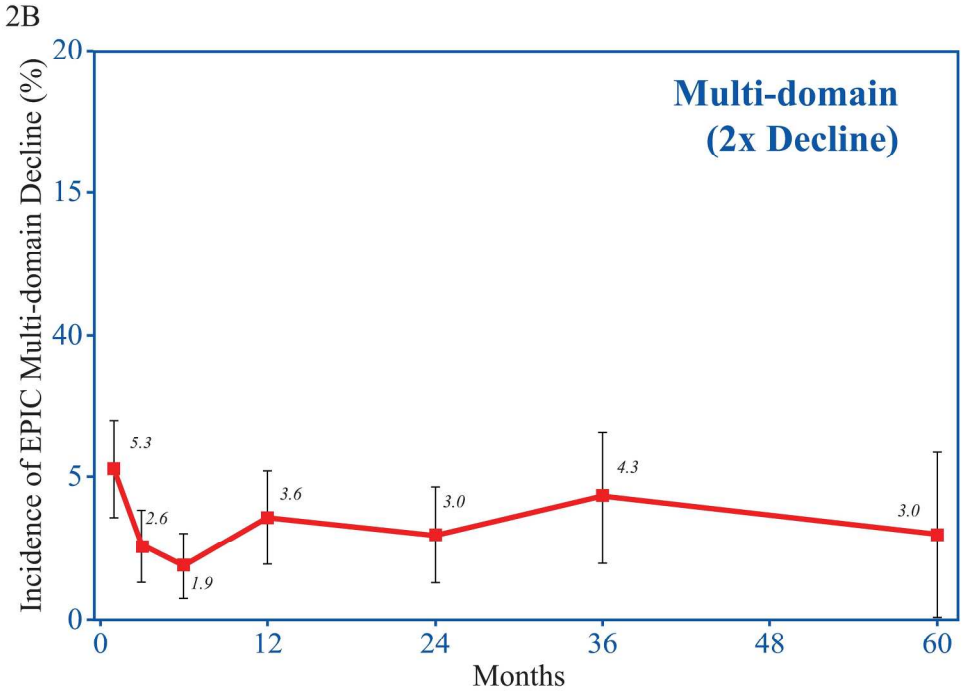

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Supplemental Table 1: Baseline Comorbidities

Age		
Mean (IRQ)	69	(64-73)
BMI		
Mean (IRQ)	29	(25-31)
Prostate Volume		
Mean (IRQ)	41	(28-50)
Baseline Diabetes *		
Yes	34	16%
No	181	84%
Current Smoker *		
Yes	22	10%
No	193	90%
Anticoagulation *		
Yes	89	41%
No	126	59%
Charslon Comorbidiy *		
≤ 2	70	33%
> 2	145	67%
Baseline Depression *		
Yes	11	5%
No	204	95%
Partner Status *		
Yes	164	76%
No	51	24%
Baseline Incont HRQOL		
Mean (IQR)	92	(86-100)
Baseline Incont HRQOL		
Mean (IQR)	85	(81-100)
Baseline Bowel HRQOL		
Mean (IQR)	95	(96-100)
ADT (neoadjuvant 3-6 mos)		
Yes	258	86%
No	41	14%

* Unknown in 84 patients

Abbreviations: BMI, body mass index; HRQOL, health related quality of life; ADT, androgen deprivation therapy

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