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Association between adherence to radiation therapy quality metrics and patient reported outcomes in prostate cancer

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Abstract

Background: Prior studies have shown significant variability in the quality of prostate cancer care in the US with questionable associations between quality measures and patient reported outcomes. We evaluated the impact of compliance with nationally recognized radiation therapy (RT) quality measures on patient-reported health related quality of life (HRQOL) outcomes in the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) cohort.

Methods: CEASAR is a population-based, prospective cohort study of men with localized prostate cancer from which we identified 649 who received primary RT and completed HRQOL surveys for inclusion. Eight quality measures were identified based on national guidelines. We analyzed the impact of compliance with these measures on HRQOL assessed by the 26-item Expanded Prostate Index Composite at pre-specified intervals up to 5 years after treatment. Multivariable analysis was performed controlling for demographic and clinicopathologic features.

Results: Among eligible participants, 566 (87%) patients received external beam radiation therapy and 83 (13%) received brachytherapy. Median age was 69 years (interquartile range: 64–73), 33% had low-, 43% intermediate-, and 23% high-risk disease. 28% received care non-compliant with at least one measure. In multivariable analyses, while some statistically significant associations were identified, there were no clinically significant associations between compliance with evaluated RT quality measures and patient reported urinary irritative, urinary incontinence, bowel, sexual or hormonal function.

Conclusions: Compliance with RT quality measures was not meaningfully associated with patient-reported outcomes after prostate cancer treatment. Further work is needed to identify patient-centered quality measures of prostate cancer care.

Keywords

prostate cancer; patient reported outcomes; radiation therapy; health services research

Introduction

There is considerable variability in the delivery and quality of prostate cancer (PCa) care in the United States[1–3]. Quality measures are increasingly used to incentivize transparency,

efficacy, and efficiency in PCa care[4]. Radiation therapy (RT) is commonly delivered for PCa and is known to impact health-related quality of life[5]. RT quality can be assessed by previously defined, nationally recognized quality measures[6,7] and compliance with these measures in the United States is variable[8].

Prior studies evaluating the impact of compliance with quality indicators for localized prostate cancer have failed to demonstrate an association with clinically important changes in patient reported outcomes[9,10] which has highlighted the need for more patient-centered measures of quality. However, these studies only focused on those who were treated surgically and did not evaluate the quality of care with respect to radiation therapy. The effect of compliance with RT quality measures on patient-reported health-related quality of life (HRQOL) outcomes is not known.

We evaluated the association between compliance with eight RT quality measures (5 for external beam RT and 3 for brachytherapy) and patient-reported HRQOL outcomes in the prospective population-based Comparative Effectiveness Analysis of Radiation and Surgery (CEASAR) study. We hypothesized that noncompliance with RT quality measures would be associated with poorer HRQOL Outcomes.

Methods

The CEASAR study is a population-based, prospective cohort study that enrolled 3709 men with clinically localized PCa from January 2011 to February 2012. 649 men received RT for initial therapy, completed at least one HRQOL survey, and had data available on the defined quality metrics and were therefore included in the analytic cohort. A complete inclusion and exclusion flow diagram is available in supplementary figure 1. The CEASAR study design has been described previously[11]. Patients were accrued from five population-based Surveillance, Epidemiology and End Results (SEER) registry catchment areas (Atlanta, Los Angeles, Louisiana, New Jersey, and Utah), as well as an additional prostate cancer patient registry (Cancer of the Prostate Strategic Urologic Research Endeavor, CaPSURE™). Institutional review board approval was obtained from Vanderbilt University Medical Center (coordinating center) and from each site. Informed consent was obtained from each participant and this study was conducted in accordance with the Declaration of Helsinki.

Exposure: Quality Measures

Five quality measures for external beam radiation therapy (EBRT) and three for brachytherapy (BT) in place at time of cohort treatment (2011–12) which were measurable using available data were pre-specified at the time of initial study design. These measures were selected due to broad national adoption, feasibility of data measurement, and based on recommendations from multiple nationally-recognized governing bodies including the National Comprehensive Cancer Network prostate cancer guidelines[12], American Brachytherapy Society[13], Quality Research in Radiation Oncology (QRRO)[7], Physician Quality Reporting Initiative[4], and National Radiation Oncology Registry[14]. Selection of, and compliance with, the quality measures utilized in our study has been previously reported in this cohort[8].

For men who received EBRT alone, adherence to the following quality measures was assessed: (1) use of image-guided radiotherapy (IGRT), (2) prescription dose 75Gy if treated with conventional fractionation, (3) no pelvic field irradiation for low-risk disease, (4) no use of androgen-deprivation therapy for patients with low-risk disease and (5) use of androgen-deprivation therapy in patients with high-risk disease. Men were classified as receiving IGRT based on review of the medical record. IGRT included fiducial, ultrasound, and CT alignment.

Men who received BT alone (without EBRT) were evaluated for: (1) documentation of postimplant dosimetry, (2) prescription dose of 140 Gy to 160 Gy for iodine 125 (I125), and (3) prescription dose of 110 Gy to 125 Gy for palladium 103 (Pd103). Compliance was based on adherence to the guidelines established in 2011 at the time of study enrollment. Data collection on compliance was performed via chart abstraction by trained abstractors. Abstractor training was conducted in a series of face-to-face and web-based conferences, followed by monthly phone calls throughout the data collection period. Each site was required to double-abstract 3–5% of all cases to evaluate for inter-rater reliability of key abstracted items. Table 2 lists the selected quality measures and their respective sources.

Outcomes

We assessed patient-reported disease-specific HRQOL using the validated 26-item Expanded Prostate Index Composite (EPIC-26)[15]. The EPIC-26 survey characterizes HRQOL outcomes in several prostate cancer-specific domains (sexual function, urinary incontinence, urinary irritation/obstruction, bowel function, and hormone therapy-related symptoms) scored from 0–100 with 100 being better HRQOL. Minimum clinically important differences (MCID) in sub-scale scores have been quantified as 6 points in the bowel domain, 9 points in the urinary domains, 12 points in the sexual domain, and 6 points in the hormone domain[16]. Men completed surveys at baseline, 6 months, 12 months, 3 years, and 5 years after treatment.

Baseline characteristics

To describe the study cohort, a number of clinically important covariates were collected from self-report and medical records including age, race, educational achievement, marital status, income, health insurance status, employment, D'Amico disease risk classification, serum PSA at diagnosis (continuous), clinical tumor stage, biopsy Gleason score, use of androgen deprivation therapy, and geographic site of treatment and corresponding baseline HRQOL survey scores. Comorbidity was measured using the Total Illness Burden Index (TIBI), with higher scores indicating more severe comorbidity burden.[17] Previously described validated instruments were used to assess patient-reported social support, depression (CESD-9), and decision-making style.[15]

Statistical Analysis

Patients' demographic and clinical characteristics were compared in patients who received RT quality measure compliant and non-compliant care, using medians (quartiles) for continuous variables and frequencies (proportions) for categorical variables. Differences in demographic and clinical characteristics between the two groups were assessed using the

Wilcoxon rank-sum (continuous variables) and Pearson χ^2 tests (categorical variables). The difference in changes from baseline HRQOL at each time interval between the compliant and non-compliant groups were examined using the Welch two-sample t-test. To evaluate the association of compliant vs. non-compliant care with PROs, multivariable longitudinal linear regression models were used. All models accounted for patients' compliant care category (compliant vs. non-compliant), time since treatment (restricted cubic splines), and baseline function in the PRO domain of interest (linear). Restricted cubic splines on time since treatment were included in regression models to model the potential non-linear associations, and its interactions with compliant care category were also included in the models to allow the varying of compliant-PRO-association along with time since treatment. No baseline demographic variable was included in these regression models as small sample sizes prevented a stable estimation from complex models. All these decisions were made a priori, informed from previous CEASAR investigations. Mean differences of EPIC-26 scores between patients receiving compliant and non-compliant care were estimated using these models and presented with corresponding 95% confidence intervals. Statistical significance was evaluated at $p < 0.05$; however, given the large number of significance tests, clinical significance was also evaluated. All analyses were conducted using R version 4.0.

Results

The final analyzed dataset included 649 patients treated with primary RT of which 566 (87%) received EBRT alone and 83 (13%) received LDR brachytherapy alone. Forty-three percent of men received any ADT in the initial year after receiving primary RT. Demographic and clinical characteristics for the cohort are shown in Table 1. Median age was 69 years (Quartiles: 64–73). With respect to race/ethnicity, 72% of the cohort were non-Hispanic white, 18% black, 6% Hispanic, and 3% Asian. Low-, intermediate and high-risk disease was observed in 33%, 43% and 23% of study participants, respectively.

Overall, 180 (28%) men received care that was non-compliant with at least one of the selected quality measures. Of men who received BT, 33 (40%) received care that was non-compliant with at least one quality measure; of men who received EBRT, 147 (26%) received care that was non-compliant with at least one measure. Men who received non-compliant care were more likely to have low-risk disease (44% vs. 29%, p < 0.001). Compliance with individual quality metrics is shown in table 2 and ranged from 68% (use of postimplant CT dosimetry) to 96% (no pelvic field irradiation for low-risk disease).

Overall, compliance with the RT quality measures tested in our study did not have a clinically significant association with the surveyed PROs (Table 3). Compliance with IGRT use and withholding of ADT in low-risk disease had no clinically or statistically significant association with EPIC-26 outcomes. Noncompliance with EBRT dose prescription > 75 Gy was associated with a small statistically significant decrement in the bowel function domain at 1 year (−4.5, 95% CI −7.9 to −1.0), but this relationship was not identified at any other time point. Similar isolated relationships met statistical significance on univariable analysis for compliance with the use of ADT in high-risk disease and the sexual (−16.1, 95% CI −26.3 to −5.9) and hormone function (−9.5, 95% CI −17.4 to −1.5) domains, compliance with post-implant CT dosimetry and the urinary irritative domain at 5 years (−10.6, 95%

CI −18.4 to −2.7), and compliance with dose prescription of 140–160 Gy in I125 BT and the incontinence domain at 5 years (−20.1, 95% CI −34.6 to −5.5). Receipt of pelvic field radiation for low-risk disease was associated with a statistically significant reduction in the bowel function domain and 3 and 5 years (−5.1, 95% CI −7.4 to −2.8 and −3.4, 95% CI −5.6 to −1.3 respectively), the sexual function domain at 3 years (−51.5, 95% CI −96.1 to −6.8), and the hormone function domain at 6 months (−4.7, 95% CI −8.9 to −0.5). Most of these isolated statistically significant associations also met clinical significance as defined by their respective MCIDs. Some of the estimated mean score were clinically significant by MCID, but small sample size led to statistically insignificant estimates due to wide confidence intervals. This was most notable for the urinary irritative domain among patients receiving care non-compliant with I125 BT dose prescription 140 – 160 Gy and the bowel and sexual function domains among patients receiving pelvic field radiation for low-risk disease.

Multivariable regression evaluating the association between quality metric noncompliance and PROs is shown in table 4. Due to sample size constraints with limited numbers of patients with non-compliant treatment regimens, multivariable adjusted analyses were only conducted for the use of IGRT in patients receiving EBRT, prescription dose 75Gy if treated with conventional fractionation, and use of post-implant dosimetry. None of the analyses of the association between non-compliant use of IGRT and PROs produced statistically significant results at any time during follow up. In patients who received care that was non-compliant with a dose prescription 75Gy in conventional fractionation, multivariable regression demonstrated a statistically significant association with worse irritative urinary symptoms at 6 months (−5.4, 95% CI −9.8 to −1.0, p=0.016), but the difference attenuated and was no longer statistically significant by the end of follow up (−4.6, 95% CI −9.7 to 0.5, p=0.1). There were no other statistically significant associations between this quality measure and any other PROs. There was a statistically significant decrement on the irritative urinary symptoms domain at 5 years (−8.8, 95% CI −15.3 to −2.3, p=0.008) and improved response in the bowel function domain at 5 years (7.2, 95% CI 0.8 to 13.5, p=0.027) in patients who received care non-compliant with use of post-implant dosimetry. These changes in PRO response were larger than their respective MCIDs but were not statistically significant at other survey time points.

Discussion

In this prospective cohort study of patients with prostate cancer treated with radiation therapy, we did not identify any clinically significant associations between compliance with nationally recognized radiation therapy quality measures and important patient-reported functional outcomes including urinary, bowel, and sexual function. Few associations in our analysis met the level of statistical significance and even fewer were clinically significant, indicating that there were no identifiable patterns.

Compliance with individual quality measures in our study was generally high, with most having > 85% compliance, though 28% of patients had care which was non-compliant with at least one quality measure. Holmes et al. found similar compliance rates with a different set of prostate cancer quality measures in a cohort of patients in North Carolina.[2] High rates of compliance with individual measures may be due to guidelines already followed by

clinicians prior to the establishment of the quality measures. It may also be evidence of the Hawthorne effect, whereby behavior—in this case, radiation oncology practice—is changed in response to the awareness of being observed as quality metrics are increasingly publicized and linked to reimbursement.

The different quality measures we tested would be expected to have distinct effects on patient reported HRQOL outcomes; compliance with some measures may worsen PROs while others may improve them. Delivery of dose-escalated radiation and administration of ADT with RT for men with high-risk prostate cancer are quality measures that were adopted because of high-level evidence demonstrating they improve cancer control but can negatively impact PROs. Pelvic field irradiation and use of ADT in patients with low-risk disease are both measures of overtreatment and noncompliance was expected to be associated with worse treatment-related PROs. IGRT is important for target margin reduction and treatment accuracy[12] and may improve PROs by reducing radiation dose to adjacent bowel and bladder. Documentation of postimplant dosimetry in brachytherapy may reflect higher-quality treatment as it allows physicians to adjust their technique for consistent results as they gain experience, allows for comparison in a research setting, and can be used when considering salvage therapy[13]. However, our analysis did not identify any clinically significant associations between these quality measures and PROs. Possible reasons for this include inadequate sample size, the inability of the survey instruments to capture transitory HRQOL changes that may resolve over time due to survey timing, and that the effect of RT and ADT on these domains is too small to capture.

Our results are similar to prior analyses in the CEASAR cohort demonstrating that adherence to general quality measures in prostate cancer care had no significant impact on PROs.[9] Previous studies similarly found no clinically significant association between quality measures and patient-reported outcomes in the CEASAR cohort among patients treated surgically.[10] Recently published data from the NRG/RTOG 0126 trial demonstrated, amongst other findings, no decrement in PROs with dose-escalated EBRT at 12 months[18]. Our study adds to these data with similar findings at 5 years of follow up in a population-based cohort.

The quality indicators used in this study are process measures. Understanding the impact of process measures—which are being used with increasing frequency to characterize prostate cancer care quality—on PROs remains an area of active investigation. Process measures are appealing because (1) they are easy to evaluate and benchmark at the same time as the clinical care they are measuring, (2) they are responsive to incentives, and (3) they do not require risk adjustment[19]. However, a process-outcome link can be difficult to establish, and our study adds to a body of literature suggesting that the link between some process measures and PROs in prostate cancer is weak. Moreover, process measures may be difficult to understand for patients and non-clinician stakeholders. In our study, benchmarks of postimplant dosimetry and specific RT dose prescriptions may not be immediately important to patients because of their technical nature and lack of association with patient-centered outcomes out to 5 years.

Our study has a number of important limitations. PRO data are subject to recall bias, though the EPIC-26 has been shown to have high test-retest reliability and internal consistency reliability[20]. Some subgroup analyses were not feasible due to small sample size and the overall high rate of quality measure compliance limits our power to detect differences in outcomes. However, we do not expect different results from the untested quality measures given the lack of identifiable patterns in the presented analyses and the multiplicity of tests performed would have increased our risk for type I error. We did not compare overall compliance with all measures as a binary regression outcome, but given the differential effect compliance with our tested quality measures are expected to have on HRQOL outcomes, we would not expect this model to have different clinically significant results. Our results should be interpreted in the context of the multiple *a priori* tests performed – the few associations that we did identify may have been due to chance. An investigation of reasons for non-compliance with quality measures was outside the scope of this study, but we controlled for other factors known to be associated with compliance including race and disease risk classification[8]. We did not have complete data to assess the association between hospital type, hospital volume, or physician volume on PROs, though we expect that the quality measures in our study captured some of the differences related to these exposures. We evaluated whether or not radiation dose to normal tissues was documented in the medical record, but we did not analyze the impact of specific radiation doses to the bladder and rectum via dose volume histogram data on patient reported function. We did not evaluate in this study what role compliance with these quality measures may have had on oncologic outcomes and how this may have influenced the PROs because follow up was limited to 5 years. We evaluated eight well-established quality measures that were available at the time of patient enrollment, but did not evaluate all of the quality measures that have been proposed for prostate radiation therapy[21]. These represent areas for further evaluation in future studies. Our limited overall sample size introduces risk of a type II error. Strengths of our study include drawing from a large and diverse cohort with granular, use of validated outcomes measures and long term follow up. Though there were some small statistically significant differences, we were careful to focus on the broader absence of clinically significant patterns in our data when determining the significance of our results.

Conclusion

In this prospective cohort study of men receiving RT for prostate cancer, we did not identify any clinically significant associations between adherence to nationally recognized quality measures and patient-reported functional outcomes. Defining high quality prostate cancer care requires further development of patient-centered outcomes. Further work is needed to identify the optimal ways to measure and benchmark prostate cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Statement:

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Table 1:

Baseline characteristics by type of radiation therapy

		EBRT (N=566)	LDR (N=83)	Combined (N=649)	P-value[a]
Age at diagnosis		69 (64, 74)	66 (63, 72)	69 (64, 73)	**0.009**
Race	White	396 (70%)	67 (83%)	463 (72%)	0.06
	Black	104 (18%)	10 (12%)	114 (18%)	
	Hispanic	36 (6%)	2 (2%)	38 (6%)	
	Asian	22 (4%)	0 (0%)	22 (3%)	
	Other	6 (1%)	2 (2%)	8 (1%)	
Education	Less than high school	91 (17%)	6 (7%)	97 (15%)	0.17
	High school graduate	114 (21%)	22 (27%)	136 (22%)	
	Some college	123 (22%)	23 (28%)	146 (23%)	
	College graduate	111 (20%)	15 (19%)	126 (20%)	
	Grad school	108 (20%)	15 (19%)	123 (20%)	
Marital status	Not married	141 (26%)	22 (28%)	163 (26%)	0.7
	Married	404 (74%)	57 (72%)	461 (74%)	
Any hormone therapy in yr 1	No	299 (53%)	69 (84%)	368 (57%)	**<0.001**
	Yes	265 (47%)	13 (16%)	278 (43%)	
Comorbidity score (TIBI)	0--2	97 (18%)	23 (28%)	120 (19%)	**0.03**
	3--4	223 (41%)	23 (28%)	246 (39%)	
	5 or more	230 (42%)	35 (43%)	265 (42%)	
Income	Less than $30,000	160 (32%)	23 (30%)	183 (32%)	0.4
	$30,001 -- $50,000	116 (23%)	12 (16%)	128 (22%)	
	$50,001 -- $100,000	132 (26%)	26 (34%)	158 (27%)	
	More than $100,000	95 (19%)	16 (21%)	111 (19%)	
Health insurance type	Medicare	392 (69%)	48 (58%)	440 (68%)	0.14
	Private / HMO	145 (26%)	33 (40%)	178 (27%)	
	VA / Military	4 (1%)	0 (0%)	4 (1%)	
	Medicaid	9 (2%)	1 (1%)	10 (2%)	
	Other	6 (1%)	0 (0%)	6 (1%)	
	None	10 (2%)	1 (1%)	11 (2%)	
Employment	Full time	123 (22%)	25 (31%)	148 (23%)	0.3
	Part time	46 (8%)	6 (8%)	52 (8%)	
	Retired	353 (63%)	46 (57%)	399 (62%)	
	Unemployed	37 (7%)	3 (4%)	40 (6%)	
D'Amico risk group	Low Risk	161 (28%)	55 (66%)	216 (33%)	**<0.001**
	Intermediate Risk	258 (46%)	23 (28%)	281 (43%)	
	High Risk	147 (26%)	5 (6%)	152 (23%)	
PSA at diagnosis, corrected		6 (5, 9)	5 (4, 7)	6 (5, 9)	**<0.001**
Clinical tumor stage	T1	405 (72%)	69 (83%)	474 (73%)	**0.028**
	T2	160 (28%)	14 (17%)	174 (27%)	

		EBRT (N=566)	LDR (N=83)	Combined (N=649)	P-value[a]
Biopsy Gleason score	6 or less	194 (34%)	61 (73%)	255 (39%)	**<0.001**
	3 + 4	193 (34%)	11 (13%)	204 (31%)	
	4 + 3	81 (14%)	8 (10%)	89 (14%)	
	8,9,10	98 (17%)	3 (4%)	101 (16%)	
Accrual Site	Utah	13 (2%)	11 (13%)	24 (4%)	**<0.001**
	Atlanta	42 (7%)	10 (12%)	52 (8%)	
	LA	135 (24%)	14 (17%)	149 (23%)	
	Louisiana	223 (39%)	40 (48%)	263 (41%)	
	NJ	129 (23%)	4 (5%)	133 (20%)	
	CaPSURE	24 (4%)	4 (5%)	28 (4%)	
General HRQOL scores (SF-36)	Physical (PF)	89 (65, 100)	95 (76, 100)	90 (70, 100)	**0.006**
	Emotional (EWB)	84 (68, 92)	84 (72, 92)	84 (68, 92)	0.9
	Energy (EF)	75 (55, 85)	70 (55, 85)	74 (55, 85)	0.9
	General (GH)	60 (60, 80)	80 (60, 80)	60 (60, 80)	0.11
Social support scores (MOS-SS)		95 (70, 100)	95 (61, 100)	95 (65, 100)	0.9
Depression score (CESD-9)		15 (4, 30)	11 (4, 33)	15 (4, 30)	0.4
Participatory decision-making score (PDM-7)		79 (64, 89)	86 (75, 93)	79 (64, 89)	**0.009**

[a] p-values correspond to univariate comparisons between EBRT and BT groups

Table 2 –

Rates of compliance with RT quality measures

Metric	Source	Compliant	Noncompliant
IGRT Utilization	NCCN, QRRO	468 (85%)	81 (15%)
Dose prescription > 75 Gy for conventional fractionation	NROR, QRRO	492 (92%)	40 (8%)
No pelvic field radiation for low risk disease	NCCN, NROR	154 (96%)	7 (4%)
No ADT for low risk disease	NCCN, NROR	145 (91%)	15 (9%)
Use of ADT for high risk disease	NCCN, NROR, PQRI, QRRO	124 (84%)	23 (16%)
Postimplant CT dosimetry	ABS, NCCN, NROR, QRRO	50 (68%)	24 (32%)
I125 dose 140–160 Gy	ABS	54 (87%)	8 (13%)
Pd103 dose 110–125 Gy	ABS	17 (89%)	2 (11%)

ABS = American Brachytherapy Society; NCCN = National Comprehensive Cancer Network; NROR = National Radiation Oncology Registry; PQRI = Physician Quality Reporting Initiative; QRRO = Quality Research in Radiation Oncology

Table 3 –

Differences in PRO (EPIC-26 domain score) changes from baseline in compliant and non-compliant participants

		IGRT Utilization	EBRT Dose > 75Gy	No pelvic field radiation for low risk disease	No ADT for low risk disease	Use of ADT for high risk disease	Post-implant CT dosimetry	I125 Dose 140–160 Gy
Urinary Incontinence	6 months	−2.9 (−6.8, 1.1)	−1.4 (−8.8, 5.9)	−3.2 (−13.8, 7.5)	−2.6 (−13.0, 7.8)	4.2 (−2.7, 11.1)	−0.8 (−8.8, 7.2)	−7.2 (−23.8, 9.5)
	1 year	−1.6 (−5.5, 2.4)	−3.7 (−11.4, 4.1)	−4.2 (−16.2, 7.9)	−5.1 (−14.0, 3.7)	2.8 (−3.4, 8.9)	−0.6 (−9.8, 8.5)	1.9 (−20.3, 24.1)
	3 years	3.1 (−3.0, 9.1)	3.1 (−8.0, 14.2)	−1.6 (−6.3, 3.1)	−2.9 (−11.4, 5.7)	1.8 (−6.9, 10.5)	4.4 (−6.9, 15.7)	−4.3 (−36.2, 27.6)
	5 years	1.5 (−4.8, 7.7)	−3.6 (−14.7, 7.5)	−5.6 (−21.6, 10.5)	−2.1 (−18.9, 14.7)	2.8 (−7.2, 12.8)	−2.4 (−15.8, 11.0)	**−20.1 (−34.6, −5.5)**
Urinary Irritative	6 months	−0.7 (−5.7, 4.3)	−5.8 (−12.4, 0.8)	−5.0 (−18.1, 8.2)	3.7 (−5.0, 12.4)	−4.2 (−11.9, 3.4)	1.8 (−8.8, 12.3)	−18.3 (−38.4, 1.7)
	1 year	−1.6 (−6.3, 3.1)	−5.9 (−13.8, 2.0)	−4.7 (−17.5, 8.2)	3.7 (−6.1, 13.4)	−3.2 (−9.4, 3.1)	−2.5 (−12.8, 7.8)	−16.2 (−37.8, 5.4)
	3 years	−0.3 (−4.8, 4.3)	−1.1 (−10.9, 8.6)	−2.2 (−23.7, 19.4)	−2.9 (−11.3, 5.6)	−3.9 (−11.5, 3.7)	−3.8 (−11.9, 4.3)	−13.6 (−38.7, 11.5)
	5 years	−2.0 (−7.2, 3.2)	−5.9 (−14.5, 2.7)	−3.8 (−16.4, 8.7)	−1.4 (−15.4, 12.5)	−2.0 (−10.2, 6.1)	**−10.6 (−18.4, −2.7)**	−28.9 (−58.7, 0.9)
Bowel Function	6 months	1.3 (−3.7, 6.2)	−4.0 (−8.1, 0.0)	−9.7 (−19.9, 0.6)	−1.1 (−5.8, 3.6)	−1.9 (−11.3, 7.6)	4.3 (−4.9, 13.4)	−5.3 (−11.9, 1.3)
	1 year	1.2 (−3.0, 5.4)	**−4.5 (−7.9, −1.0)**	−8.3 (−17.4, 0.7)	0.4 (−7.2, 8.0)	0.0 (−8.2, 8.2)	2.5 (−4.3, 9.2)	−3.7 (−11.2, 3.9)
	3 years	−1.6 (−5.6, 2.4)	1.0 (−3.8, 5.9)	**−5.1 (−7.4, −2.8)**	0.5 (−8.6, 9.6)	−2.5 (−9.9, 4.9)	−0.1 (−7.3, 7.2)	−3.8 (−10.1, 2.5)
	5 years	−2.3 (−6.9, 2.4)	−3.2 (−8.5, 2.1)	**−3.4 (−5.6, −1.3)**	−5.6 (−13.4, 2.2)	2.3 (−7.0, 11.6)	10.4 (2.2, 18.6)	−5.7 (−16.2, 4.9)
Sexual Function	6 months	−4.0 (−10.2, 2.2)	−7.1 (−18.1, 3.8)	−23.1 (−58.3, 12.1)	18.3 (−6.8, 43.4)	**−16.1 (−26.3, −5.9)**	6.2 (−8.8, 21.1)	−5.7 (−26.2, 14.7)
	1 year	−0.3 (−6.3, 5.7)	−6.3 (−16.3, 3.7)	−34.0 (−78.4, 10.4)	15.3 (−7.2, 37.8)	−9.7 (−19.5, 0.0)	−0.8 (−13.3, 11.8)	−1.8 (−25.6, 22.0)
	3 years	1.0 (−6.5, 8.4)	−3.6 (−16.9, 9.7)	**−51.5 (−96.1, −6.8)**	−0.2 (−30.8, 30.5)	−13.3 (−27.2, 0.6)	0.9 (−15.5, 17.4)	−29.5 (−65.4, 6.3)
	5 years	5.4 (−2.7, 13.5)	−4.4 (−17.5, 8.7)	−26.2 (−78.6, 26.3)	−3.0 (−26.3, 20.3)	−8.4 (−25.2, 8.4)	8.0 (−8.5, 24.5)	−12.0 (−72.7, 48.6)
Hormone Function	6 months	−1.4 (−5.7, 2.9)	−2.9 (−9.3, 3.6)	**−4.7 (−8.9, −0.5)**	9.3 (−2.6, 21.2)	**−9.5 (−17.4, −1.5)**	3.2 (−1.8, 8.3)	4.0 (−8.3, 16.3)
	1 year	2.2 (−2.4, 6.9)	−1.9 (−7.5, 3.6)	−4.8 (−19.7, 10.1)	6.7 (−3.8, 17.1)	−7.3 (−14.6, 0.1)	3.8 (−1.4, 8.9)	7.0 (−7.2, 21.3)
	3 years	2.0 (−3.7, 7.7)	8.9 (−0.3, 18.0)	−9.8 (−98.9, 79.2)	1.1 (−7.8, 10.1)	−5.2 (−11.1, 0.7)	1.3 (−4.6, 7.2)	−2.3 (−13.6, 9.1)
	5 years	0.1 (−4.9, 5.0)	3.2 (−4.5, 10.8)	−3.1 (−33.4, 27.2)	2.1 (−8.0, 12.2)	−4.0 (−13.5, 5.6)	0.7 (−6.0, 7.3)	−0.0 (−15.4, 15.3)

Bolded values are statistically significant (p < 0.05). All others are not statistically significant. Values represent point differences in EPIC-26 response between patients receiving non-compliant vs. compliant care. The EPIC-26 is scaled from 0–100 with higher scores representing better function. Minimum clinically important differences (MCID) in sub-scale scores: 6–9 points in the incontinence and irritative urinary domains, 4–6 points in the bowel domain, 10–12 points in the sexual domain, and 4–6 points in the hormone domain.

Table 4 -

Multivariable adjusted differences in PRO (EPIC-26 domain scores) in compliant and non-compliant participants

EPIC-26	Survey Time	IGRT Utilization			EBRT Dose > 75Gy			Post-implant Dosimetry		
		Effect	(95% CI)	p	Effect	(95% CI)	p	Effect	(95% CI)	p
Incontinence	6 months	-1.8	(-5.6 – 2.1)	0.4	-0.6	(-6.4 – 5.3)	0.8	-1.7	(-8.8 – 5.4)	0.6
	1 year	-0.1	(-3.7 – 2.7)	0.8	0.4	(-5.7 – 6.6)	0.9	-2.2	(-9.5 – 5.1)	0.6
	3 years	1.9	(-3 – 6.7)	0.4	0.7	(-6.9 – 8.3)	0.9	-2	(-11.9 – 7.9)	0.7
	5 years	1.4	(-5.3 – 8.1)	0.7	-3.0	(-11.4 – 5.5)	0.5	0.3	(-12.8 – 13.5)	0.9
Irritative	6 months	1.1	(-2.5 – 4.7)	0.5	-5.4	(-9.8 – -1.0)	**0.016**	2.1	(-6.8 – 11)	0.6
	1 year	1.5	(-1.6 – 4.6)	0.3	-3.4	(-7.5 – 0.7)	0.1	-0.3	(-7.5 – 6.8)	0.9
	3 years	1.4	(-2 – 4.8)	0.4	-1.1	(-7.1 – 4.9)	0.7	-6.4	(-13.6 – 0.8)	0.08
	5 years	-0.4	(-5.1 – 4.3)	0.9	-4.6	(-9.7 – 0.5)	0.1	-8.8	(-15.2 – -2.3)	**0.008**
Bowel Function	6 months	3.1	(-1 – 7.2)	0.1	-3.4	(-7.0 – 0.2)	0.1	-1.1	(-7.2 – 5.1)	0.7
	1 year	2.0	(-1.1 – 5)	0.2	-2.6	(-5.2 – 0.0)	0.1	-4.3	(-10.3 – 1.7)	0.2
	3 years	-0.4	(-3.4 – 2.6)	0.8	-0.7	(-4.5 – 3.2)	0.7	-4.8	(-11.6 – 1.9)	0.2
	5 years	-0.4	(-4.3 – 3.5)	0.8	0.2	(-4.2 – 4.6)	0.9	7.2	(0.8 – 13.5)	**0.027**
Sexual Function	6 months	-1.1	(-6.8 – 4.6)	0.7	-1.6	(-10.3 – 7.1)	0.7	-0.5	(-13.6 – 12.7)	0.9
	1 year	-1.0	(-5.9 – 3.9)	0.7	-2.1	(-10.9 – 6.7)	0.6	-4	(-14.6 – 6.7)	0.5
	3 years	1.1	(-5.6 – 7.9)	0.7	-2.3	(-13.2 – 8.6)	0.7	-5.8	(-19.1 – 7.5)	0.4
	5 years	4.9	(-3.4 – 13.3)	0.2	-0.7	(-12.5 – 11.1)	0.9	4.5	(-11.4 – 20.3)	0.6
Hormone Function	6 months	1.9	(-1.9 – 5.6)	0.3	-3.0	(-8.3 – 2.4)	0.3	-0.1	(-4.6 – 4.4)	0.9
	1 year	2.5	(-0.6 – 5.7)	0.1	-0.3	(-4.6 – 3.9)	0.9	-1.4	(-5.1 – 2.3)	0.5
	3 years	2.9	(-1.1 – 7)	0.2	4.7	(-1.5 – 11.0)	0.1	-3.1	(-7.4 – 1.2)	0.2
	5 years	1.0	(-3.1 – 5)	0.6	4.0	(-2.4 – 10.5)	0.2	-1.6	(-8.4 – 5.2)	0.6

Remaining quality measures were underpowered for multivariable regression analysis. Values represent point differences in EPIC-26 response between patients receiving non-compliant vs. compliant care. The EPIC-26 is scaled from 0–100 with higher scores representing better function. Minimum clinically important differences (MCID) in sub-scale scores: 6–9 points in the incontinence and irritative urinary domains, 4–6 points in the bowel domain, 10–12 points in the sexual domain, and 4–6 points in the hormone domain.