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Association between pelvic nodal radiotherapy and patient-reported functional outcomes through 5 years among men undergoing external-beam radiotherapy for prostate cancer: an assessment of the CEASAR cohort

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Abstract

Background: The role of pelvic irradiation in men receiving external beam radiotherapy (EBRT) for prostate cancer is unclear, in part due to a lack of data on patient-reported outcomes. We sought to compare functional outcomes for men receiving prostate and pelvic versus prostate-only radiotherapy, longitudinally over 5 years.

Materials and methods: We performed a population-based, prospective cohort study of men with clinically-localized prostate cancer undergoing EBRT. We examined the effect of prostate and pelvic (n=102) versus prostate-only (n=485) radiotherapy on patient-reported disease-specific (using the EPIC-26) and general health-related (using the SF-36) function, over 5 years. Regression models were adjusted for outcome-specific baseline function, clinicopathologic characteristics, and androgen deprivation therapy (ADT).

Results: 587 men (median [quartiles] age 69 [64–73] years) met inclusion criteria and completed ≥1 post-treatment survey. More men treated with prostate and pelvic radiotherapy had high-risk disease (58% vs. 18%, $p<0.01$) and received ADT (75% vs. 41%, $p<0.01$). These men reported worse sexual (6 months to 5 years), hormonal (at 6 months), and physical (6 months to 5 years) function. Accounting for baseline function, patient and tumor characteristics, and use of ADT, pelvic irradiation was not associated with statistically or clinically significant differences in bowel function, urinary incontinence, irritative voiding symptoms or sexual function through 5-years (all $p>0.05$). Marginally clinically important differences were noted in hormonal function at 3-years (adjusted mean difference 4.7, 95% confidence interval [1.2–8.3]; minimally clinically important difference (MCID) 4–6) and 5-years (4.2, [0.4–8.0]) following treatment. After adjustment, there was a transient statistically significant, but not clinically important, difference in emotional well

being at 6 months (3.0, [0.19–5.8]; MCID 6) that resolved by 1 year and no differences in physical functioning or energy and fatigue.

Conclusions: This prospective, population-based cohort study of men with localized prostate cancer treated with EBRT, showed no clinically important differences in disease-specific or general health-related quality of life with the addition of pelvic irradiation to prostate radiotherapy, supporting the use of pelvic radiotherapy when it may be of clinical benefit, such as men with increased risk of nodal involvement.

Keywords

Prostatic neoplasms; prospective studies; patient reported outcome measures; survey and questionnaires; cohort studies

INTRODUCTION

The role of pelvic radiotherapy in men undergoing external-beam radiotherapy for prostate cancer remains controversial[1]. Data on both oncologic and toxicity-related effects of this approach are conflicting[1], despite a number of published randomized controlled trials. Concerning toxicity, available studies have examined use of 3D-conformal radiotherapy or comprised small cohorts with physician-adjudicated toxicity assessment[2–6]. Recently, the POP-RT study reported improvements in biochemical failure-free survival and disease-free survival but not overall survival[7] for patients receiving pelvic radiotherapy with increased late genitourinary toxicity[8].

There are two main issues applying the available data to patient counselling. First, there is poor correlation between patient- and physician-reported symptoms among patients with prostate cancer[9]. Thus, given importance of patient-centered care, most available toxicity data have limited value. Second, it is well accepted that treatment effects observed in randomized controlled trials may differ substantially from their effects in clinical practice, the so-called efficacy-effectiveness gap[10,11]. To address each of these issues, we utilized data from the prospectively accrued Comparative Effectiveness Analysis of Surgery and Radiation study (CEASAR) to assess the effect of adding pelvic, to prostate, radiotherapy on longitudinal measures of patient-reported outcomes (PROs).

METHODS

From 2011–2012, the prospective population-based CEASAR study recruited men aged ≤80 years with clinically-localized prostate cancer (cT1-cT2, PSA<50ng/dL) from 5 population-based Surveillance, Epidemiology, and End Results registries and the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) within 6 months following diagnosis. Institutional review board approval was obtained from Vanderbilt University Medical Center (coordinating center) and from each participating sites.

The CEASAR study collected data on men treated with radiotherapy, surgery, ablation, and active surveillance utilizing baseline and follow-up surveys and medical chart abstraction

at 1 year following enrollment. This analysis relies on patients treated with EBRT. Our exposure variable was radiotherapy approach (prostate plus pelvic versus prostate-only).

We assessed patient-reported disease-specific and general health-related function using the validated 26-item Expanded Prostate Index Composite (EPIC)[12] and Short Form Health Survey (SF-36)[13], respectively. Each domain is scored from 0–100, with higher scores indicating better function. We interpreted results based on previously determined minimally clinical important differences for each functional domain: sexual, 12; urinary incontinence, 9; urinary irritative, 7; bowel, 6; and hormonal function, 6; physical functioning, 7; emotional well-being, 6; and energy and fatigue, 9[14,15]. Surveys were completed at baseline, 6-months, 1-, 3-, and 5-years after enrollment.

Important demographic, clinicopathologic, and treatment-related covariates were captured from patient-reported surveys and chart abstraction, as appropriate.

Patients' baseline demographic, tumor and treatment characteristics were summarized with median and interquartile range (continuous variables) or frequency and percentage (categorical variables) by receipt of Pelvic radiation treatment (Pelvic radiation versus No Pelvic radiation). Differences between treatments were assessed using Wilcoxon Rank-Sum or Pearson's chi-squared tests. The study endpoints (PROs including five EPIC domain scores and three SF-36 scores) were compared between treatments at each study time point using Wilcoxon Rank-Sum test. To further evaluate the associations between treatments and PROs over time, using the longitudinal survey data, we fit multivariable longitudinal linear regression models adjusting Gleason grade, clinical tumor stage, PSA, baseline PRO scores (outcome specific), and propensity score of receipt Pelvic radiation. To allow for variable estimation of treatment at different time points, we included the interaction terms between treatment and time since treatment in the models. To mitigate the confounding from differences in patients' baseline characteristics (including baseline PROs), we included the propensity scores in the multivariable models. By adjusting for the propensity scores, we further controlled patients' age (continuous, restricted cubic splines), race, insurance status, household income, marital status, Gleason grade, clinical tumor stage, PSA, ADT, D'Amico risk group, TIBI-CaP, study site, CESD score (continuous, linear), social support (continuous, linear), participatory decision-making index (continuous, linear), baseline EPIC-26, and SF-36 scores (continuous, linear). In all models, to account for the correlation due to repeated measurements collected on the same subjects from multiple time points, the Huber-White method[16,17] was implemented by *robcov* function in *rms* R package to estimate the variance-covariance matrices. Mean differences between treatments and associated 95% confidence intervals (CI) were reported as effect measurements. All missing covariate values were imputed 10 times using the MICE (multiple imputation using chained equations) implemented by *aregImpute* function in *rms* R package. Statistical significance was considered for all two-sided p values < 5%. All analyses were conducted using R version 4.0.2.

RESULTS

Among 587 men treated with EBRT who completed baseline and ≥1 post-baseline survey, 102 men received prostate and pelvic radiotherapy while 485 received prostate only radiotherapy (Figure). 99% of pelvic radiotherapy was delivered with IMRT. Patients who received pelvic radiotherapy were more likely to have high risk-disease (58% vs. 18%) driven by a higher proportion of patients with palpable disease (38% vs. 25%), and high-grade histology. Accordingly, these patients were more likely to receive androgen deprivation therapy (ADT). Further differences were observed with respect to age, marital status, income, and health insurance (Table 1).

In unadjusted analysis, patient-reported disease-specific functional outcomes were similar between prostate and pelvic radiotherapy and prostate-only radiotherapy groups from baseline through 5 years (Table 2), with the notable exception of worse sexual (from 6 months to 5 years) and hormonal function (at 6 months) among those receiving pelvic radiotherapy. In adjusted analyses, no significant differences were found in bowel, urinary incontinence, irritative voiding symptoms, or sexual function through 5-years between treatment groups, while marginally clinically significant differences were noted in hormonal function at 3-years (adjusted mean difference 4.7, 95% confidence interval [1.2–8.3]; minimally clinically important difference (MCID) 4–6) and 5-years (4.2, [0.4–8.0]) following treatment (Table 2).

Crude estimates of general health-related function using the SF-36 identified baseline differences in physical functioning, which persisted over time but not in emotional well being or energy and fatigue (Table 3). In adjusted analyses, we found a transient statistically significant, but not clinically important, difference in emotional well being at 6 months that resolved by 1 year and no differences in physical functioning or energy and fatigue (Table 3).

DISCUSSION

In this large, prospective cohort of men with localized prostate cancer, the use of pelvic IMRT, in addition to prostate, radiotherapy was not independently associated with clinically important differences in patient-reported functional and quality-of-life outcomes through five years. Observed crude differences in both hormonal and sexual function are likely attributable to the concomitant use of ADT, given its higher utilization in men receiving prostate and pelvic radiotherapy owing to higher rates of high-risk disease in this group.

Prior randomized controlled trials (GETUG-01, RTOG 9413, and POP-RT) have demonstrated conflicting results with respect to the oncologic benefit of whole pelvic radiotherapy[18,19]. As a result of these conflicting data on oncologic benefit, as well as toxicity-related concerns, the role of pelvic radiotherapy remains controversial. To date, most studies assessing this question have been small[2,3] or utilized outdated radiotherapy approaches (including GETUG-01 and RTOG 9413)[4–6]. Recently, the POP-RT trial demonstrated no differences in quality of life for patients receiving image-guided intensity modulated radiotherapy (IMRT) among 224 patients randomized to prostate only or whole

pelvis radiotherapy[8]. Differences between outcomes in randomized controlled trials and routine clinical practice are not uncommon, the so-called efficacy-effectiveness gap[10,11]. Further, the EORTC PR-25 tool utilized in this study has limited sensitivity for bowel dysfunction. The data from this study of patients in the CEASAR cohort demonstrates the generalizable observation that whole pelvic radiotherapy does not confer an added burden of patient-reported toxicity. Further corroboration can be found in the recent work of Parry and colleagues who examined the association between pelvic lymph node irradiation using IMRT and patient-reported outcomes in a cross-sectional analysis of men in the United Kingdom at least 18 months after diagnosis. These authors found a clinically insignificant difference in sexual function and no difference in other EPIC domains or health-related quality of life[20]. These results are similar to our analysis; however, in contrast, the authors of the UK study did not control for patient-reported baseline function (instead utilizing gastrointestinal and genitourinary procedures in the year prior to radiotherapy as a proxy) and did not account for the longitudinal nature of the symptoms due to the cross-sectional methodology.

Notably, in our study, fewer than one in five men undergoing EBRT received pelvic radiotherapy. This is somewhat less than previous analyses of the National Cancer Database[21]. While the observed utilization reflects practice patterns in the community at the time of study accrual, the CEASAR cohort, through the chosen inclusion criteria, excludes men with PSA ≥50 ng/mL and those with cT3 disease in whom the use of pelvic radiotherapy may be more common. Further, as has been previously noted[21], we observed significant geographic variation in the use of pelvic radiotherapy. Additionally, there were many differences in unadjusted demographic characteristics of patients receiving pelvic radiotherapy and not, again in keeping with prior work showing that demographic characteristics including ethnicity, geographic location, facility type, insurance status, and distance to treatment facility are independently associated with receipt of pelvic radiotherapy[21].

As with all observational research, this study is subject to confounding by indication. However, given the similarity in patient-reported outcomes at baseline and use of propensity scores in modeling, it is not clear that this would affect study conclusions. Second, patient surveys were collected at 6-, 12-, 36-, and 60-months following treatment. While this period is expected to capture the greatest treatment-related effects, there may be important differences at times not represented, including acute effects during treatment or important late effects, including secondary cancers[22]. Third, the relatively small study cohort raises the potential for type II error, however none of the statistically insignificant differences estimated from multivariable models are greater than the clinically important differences. Fourth, we are unable to capture the whole pelvic radiotherapy dose. Finally, while we can capture whether ADT was used concomitantly with radiotherapy, this was operationalized in a binary manner. This was done as chart abstraction was performed at one year following study enrollment and, thus, we could not accurately ascertain the duration of therapy. This may contribute to residual confounding due to within-group heterogeneity among those receiving ADT given higher rates of utilization among those receiving whole pelvic radiotherapy (and postulated longer durations). This is most likely to affect longer term (3- and 5-year) measures of hormonal function.

Maturing trials that randomize men to ADT and prostate radiotherapy with or without pelvic radiotherapy will provide additional information about patient-reported outcomes after pelvic radiotherapy. In the meantime, these data support the use of pelvic radiotherapy when it may be of clinical benefit, such as for men with increased risk of nodal involvement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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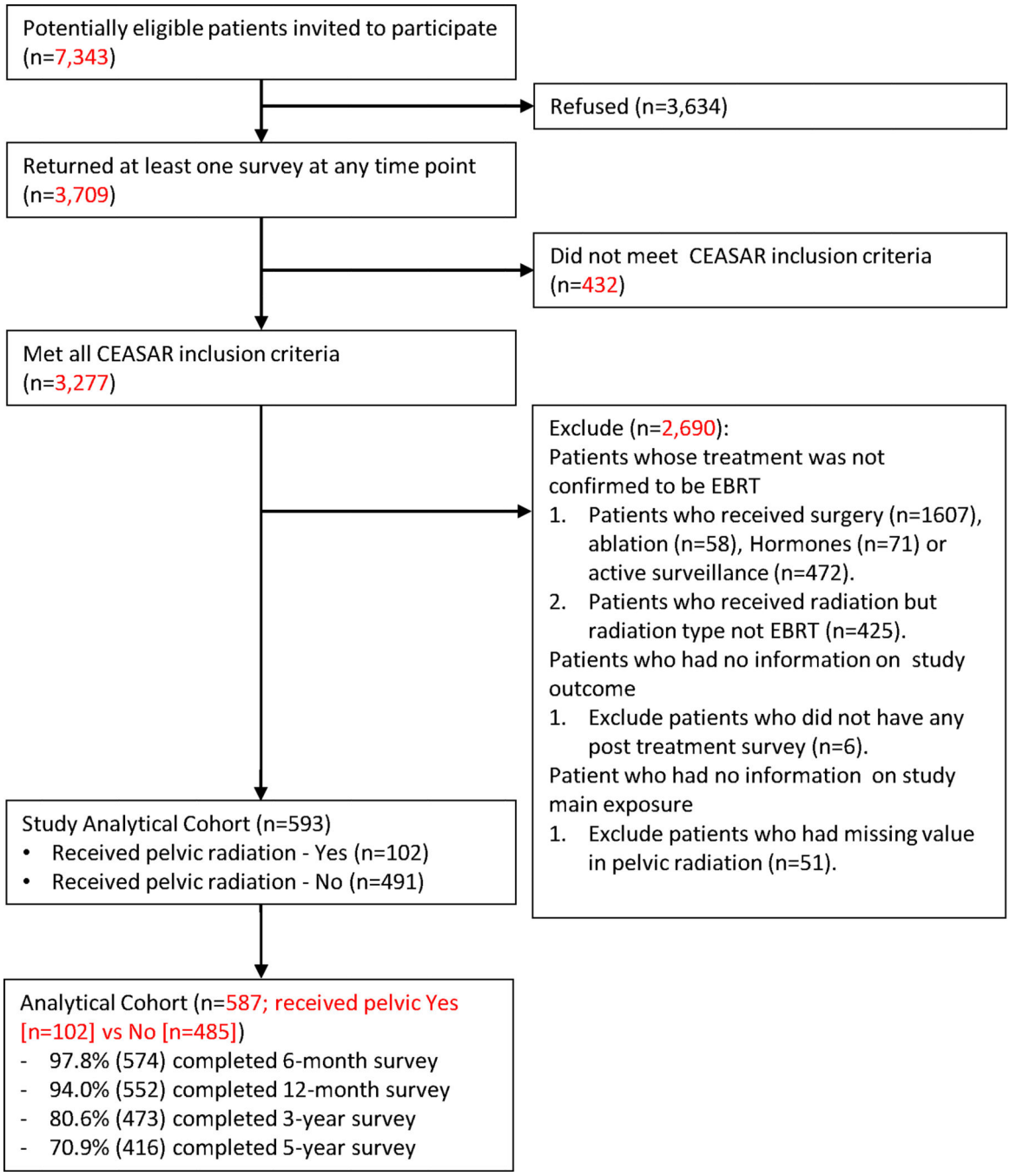

Figure.
Diagram of the Assembly of the Analytic Cohort based on CEASAR Study Cohort.

Table 1.

Baseline characteristics of cohort, stratified by receipt of pelvic radiotherapy.

	N	Pelvic Radiation (n=102)	No Pelvic Radiation (n=485)	Combined (n=587)	P-value
DEMOGRAPHICS					
Age at diagnosis, median (IQR), y	587	70 (65–75)	69 (64–73)	69 (64–73)	0.017
Race	585				0.137
White		69 (68%)	341 (70%)	410 (70%)	
Black		25 (25%)	82 (17%)	107 (18%)	
Hispanic		3 (3%)	35 (7%)	38 (6%)	
Asian		2 (2%)	21 (4%)	23 (4%)	
Other		2 (2%)	5 (1%)	7 (1%)	
Education	571				0.091
Less than high school		24 (24%)	70 (15%)	94 (16%)	
High school graduate		18 (18%)	98 (21%)	116 (20%)	
Some college		24 (24%)	104 (22%)	128 (22%)	
College graduate		20 (20%)	96 (20%)	116 (20%)	
Graduate/professional school		13 (13%)	104 (22%)	117 (20%)	
Marital status	569				<0.001
Not married		39 (39%)	109 (23%)	148 (26%)	
Married		60 (61%)	361 (77%)	421 (74%)	
Comorbidity score (TIBI)	574				0.056
0–2		13 (13%)	87 (18%)	100 (17%)	
3–4		34 (34%)	200 (42%)	234 (41%)	
5 or more		52 (53%)	188 (40%)	240 (42%)	
Income	527				0.001
Less than $30,000		42 (48%)	125 (28%)	167 (32%)	
$30,001 -- $50,000		19 (22%)	99 (23%)	118 (22%)	
$50,001 -- $100,000		19 (22%)	120 (27%)	139 (26%)	
More than $100,000		8 (9%)	95 (22%)	103 (20%)	
Health insurance	587				0.018
Medicare		78 (76%)	323 (67%)	401 (68%)	
Private/HMO		15 (15%)	139 (29%)	154 (26%)	
VA/military		1 (1%)	3 (1%)	4 (1%)	
Medicaid		5 (5%)	6 (1%)	11 (2%)	
Other		1 (1%)	5 (1%)	6 (1%)	
None		2 (2%)	9 (2%)	11 (2%)	
Employment	579				0.068
Full time		14 (14%)	117 (24%)	131 (23%)	
Part time		7 (7%)	39 (8%)	46 (8%)	

	N	Pelvic Radiation (n=102)	No Pelvic Radiation (n=485)	Combined (n=587)	P-value
Retired		74 (74%)	289 (60%)	363 (63%)	
Unemployed		5 (5%)	34 (7%)	39 (7%)	
Site	587				<0.001
Utah		3 (3%)	11 (2%)	14 (2%)	
Atlanta		5 (5%)	42 (9%)	47 (8%)	
LA		8 (8%)	135 (28%)	143 (24%)	
Louisiana		77 (75%)	148 (31%)	225 (38%)	
NJ		5 (5%)	127 (26%)	132 (22%)	
CaPSURE		4 (4%)	22 (5%)	26 (4%)	
TUMOR AND TREATMENT CHARACTERISTICS					
PSA at diagnosis, corrected, median (IQR)	587	7 (5–12)	6 (5–9)	6 (5–9)	0.118
Clinical tumor stage	586				0.006
T1		63 (62%)	363 (75%)	426 (73%)	
T2		39 (38%)	121 (25%)	160 (27%)	
Biopsy Gleason score	585				<0.001
6 or less		9 (9%)	195 (40%)	204 (35%)	
3 + 4		29 (28%)	171 (35%)	200 (34%)	
4 + 3		22 (22%)	63 (13%)	85 (15%)	
8,9,10		42 (41%)	54 (11%)	96 (16%)	
Damico risk group	585				<0.001
Low Risk		7 (7%)	163 (34%)	170 (29%)	
Intermediate Risk		36 (35%)	234 (48%)	270 (46%)	
High Risk		59 (58%)	86 (18%)	145 (25%)	
Use of ADT within 1 year of diagnosis	582				<0.001
No		26 (25%)	285 (59%)	311 (53%)	
Yes		76 (75%)	195 (41%)	271 (47%)	
Use of IMRT	587				<0.001
Yes		101 (99%)	387 (80%)	488 (83%)	
No		1 (1%)	98 (20%)	99 (17%)	
Use of IGRT	557				0.13
Yes		92 (90%)	384 (84%)	476 (85%)	
No		10 (10%)	71 (16%)	81 (15%)	
Radiation dose, Gy, median (IQR)	582	78 (77.4–79.2)	78 (76–79.2)	78 (76–79.2)	0.56
Radiation dose ≥75Gy	582				0.42
Yes		92 (90%)	419 (87%)	511 (88%)	
No		10 (10%)	61 (13%)	71 (12%)	

Abbreviations: IQR, interquartile range; TIBI, Total Illness Burden Index for Prostate Cancer; HMO, Health maintenance organization; VA, Veterans Affairs; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; ADT, androgen deprivation therapy

Table 2.

Association between pelvic radiation and disease-specific-related patient-reported functional outcomes.

Time	N	Pelvic Radiation, median (quartiles)	No Pelvic Radiation, median (quartiles)	Combined, median (quartiles)	Crude P-value[a]	Multivariable adjusted model[b] Pelvic Radiation vs. No Pelvic Radiation	
						Effect estimate (95% CI)	P-value
EPIC-26 urinary incontinence domain score							
Baseline	560	93 (73, 100)	100 (79, 100)	100 (79, 100)	0.04	n/a	
6 month	570	92 (67, 100)	100 (77, 100)	100 (73, 100)	0.08	0.55 (−3.83 to 4.93)	0.81
1 year	522	92 (71, 100)	100 (79, 100)	100 (75, 100)	0.28	1.78 (−1.85 to 5.42)	0.34
3 year	458	100 (75, 100)	94 (75, 100)	94 (75, 100)	0.95	4.12 (−0.32 to 8.57)	0.07
5 year	402	100 (73, 100)	100 (75, 100)	100 (73, 100)	0.99	3.78 (−1.80 to 9.36)	0.18
EPIC-26 urinary irritative domain score							
Baseline	560	88 (69, 94)	88 (75, 94)	88 (75, 94)	0.83	n/a	
6 month	564	88 (75, 94)	88 (75, 94)	88 (75, 94)	0.32	0.59 (−2.70 to 3.87)	0.73
1 year	540	88 (81, 98)	88 (77, 94)	88 (80, 94)	0.82	1.74 (−0.86 to 4.34)	0.19
3 year	458	88 (81, 100)	88 (81, 100)	88 (81, 100)	0.26	3.20 (0.01 to 6.39)	0.05
5 year	403	94 (81, 100)	88 (81, 100)	88 (81, 100)	0.99	1.41 (−2.50 to 5.32)	0.48
EPIC-26 bowel function score							
Baseline	572	100 (88, 100)	100 (92, 100)	100 (92, 100)	0.24	n/a	
6 month	570	100 (79, 100)	96 (83, 100)	96 (83, 100)	0.68	0.94 (−2.60 to 4.49)	0.60
1 year	549	96 (83, 100)	96 (83, 100)	96 (83, 100)	0.78	2.02 (−0.75 to 4.79)	0.15
3 year	469	96 (84, 100)	96 (83, 100)	96 (83, 100)	0.54	3.07 (−0.38 to 6.52)	0.081
5 year	409	96 (83, 100)	96 (88, 100)	96 (88, 100)	0.65	0.76 (−3.38 to 4.90)	0.72
EPIC-26 sexual function score							
Baseline	548	48 (12, 80)	58 (22, 80)	58 (18, 80)	0.09	n/a	
6 month	535	5 (0, 38)	35 (0, 68)	27 (0, 67)	<0.001	−1.78 (−7.60 to 4.03)	0.55
1 year	529	7 (0, 58)	38 (10, 65)	33 (7, 65)	<0.001	−1.71 (−7.59 to 4.16)	0.57
3 year	448	8 (0, 57)	38 (10, 70)	33 (7, 70)	<0.001	−0.23 (−7.63 to 7.16)	0.95
5 year	384	16 (0, 52)	32 (7, 66)	28 (5, 65)	0.01	2.50 (−5.84 to 10.83)	0.56

Time	N	Pelvic Radiation, median (quartiles)	No Pelvic Radiation, median (quartiles)	Combined, median (quartiles)	Crude P-value[a]	Multivariable adjusted model[b]	
						Pelvic Radiation vs. No Pelvic Radiation	
						Effect estimate (95% CI)	P-value
EPIC-26 hormonal domain score							
Baseline	553	90 (75, 100)	90 (80, 100)	90 (80, 100)	0.06	n/a	
6 month	555	80 (65, 90)	90 (75, 100)	85 (75, 100)	<0.001	−0.36 (−4.03 to 3.32)	0.85
1 year	534	85 (70, 95)	90 (75, 100)	90 (75, 100)	0.06	1.41 (−1.82 to 4.65)	0.39
3 year	455	90 (75, 95)	95 (80, 100)	94 (80, 100)	0.12	4.74 (1.22 to 8.27)	0.01
5 year	398	90 (80, 95)	95 (80, 100)	95 (80, 100)	0.16	4.18 (0.40 to 7.97)	0.03

[a] Crude P-values are calculated by Wilcoxon test.

[b] All regression models are adjusted for baseline domain score, time since treatment, biopsy Gleason score, PSA at diagnosis (corrected) and propensity scores.

Table 3.

Association between pelvic radiation and general health-related patient-reported functional outcomes.

Time	N	Pelvic Radiation, median (quartiles)	No Pelvic Radiation, median (quartiles)	Combined, median (quartiles)	Crude P-value[a]	Multivariable adjusted model[b] Pelvic Radiation vs. No Pelvic Radiation	
						Effect estimate (95% CI)	P-value
SF36 physical functioning score							
Baseline	564	85 (50, 95)	90 (70, 100)	90 (65, 100)	0.04	n/a	
6 month	572	75 (45, 94)	85 (65, 95)	85 (60, 95)	0.003	2.44 (−2.31 to 7.18)	0.31
1 year	550	85 (50, 95)	90 (67, 100)	87 (65, 100)	0.003	2.03 (−2.49 to 6.54)	0.38
3 year	470	75 (45, 90)	85 (60, 95)	85 (55, 95)	0.003	−0.43 (−6.15 to 5.29)	0.88
5 year	415	70 (32, 95)	85 (60, 95)	85 (55, 95)	0.006	−3.74 (−10.92 to 3.43)	0.31
SF36 emotional well being score							
Baseline	574	84 (68, 92)	88 (72, 92)	84 (72, 92)	0.76	n/a	
6 month	571	84 (75, 92)	84 (71, 92)	84 (72, 92)	0.61	3.01 (0.19 to 5.83)	0.04
1 year	548	84 (68, 92)	84 (72, 92)	84 (72, 92)	0.90	2.30 (−0.31 to 4.91)	0.08
3 year	467	84 (76, 92)	88 (72, 92)	88 (72, 92)	0.71	1.40 (−2.19 to 4.99)	0.44
5 year	414	88 (72, 92)	88 (72, 92)	88 (72, 92)	0.90	2.48 (−1.40 to 6.36)	0.21
SF36 energy and fatigue score							
Baseline	574	70 (55, 85)	75 (55, 85)	75 (55, 85)	0.50	n/a	
6 month	571	65 (50, 80)	70 (50, 80)	70 (50, 80)	0.25	2.23 (−1.71 to 6.17)	0.27
1 year	548	65 (53, 75)	70 (50, 80)	70 (50, 80)	0.31	1.85 (−1.42 to 5.11)	0.27
3 year	467	70 (55, 80)	70 (55, 80)	70 (55, 80)	0.28	1.80 (−2.11 to 5.70)	0.37
5 year	414	65 (52, 80)	70 (50, 80)	70 (50, 80)	0.48	3.28 (−1.40 to 7.96)	0.17

[a] Crude P-values are calculated by Wilcoxon test.

[b] All regression models are adjusted for baseline domain score, time since treatment, biopsy Gleason score, PSA at diagnosis (corrected) and propensity scores.