Original Article

Five-Year Outcomes From a Prospective Comparative Effectiveness Study Evaluating External-Beam Radiotherapy With or Without Low-Dose-Rate Brachytherapy Boost for Localized Prostate Cancer

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BACKGROUND: To inform patients who are in the process of selecting prostate cancer treatment, the authors compared disease-specific function after external-beam radiotherapy (EBRT) alone versus EBRT plus a low-dose-rate (LDR) brachytherapy boost (EBRT-LDR). **METHODS:** For this prospective study, men who had localized prostate cancer in 2011 and 2012 were enrolled. Assessments at baseline, 0.5, 1, 3, and 5 years included the patient-reported Expanded Prostate Index Composite, the 36-item Medical Outcomes Study Short-Form Health Survey, and treatment-related regret. Regression models were adjusted for baseline function and for patient and treatment characteristics. The minimum clinically important difference in scores on the Expanded Prostate Index Composite 26-item instrument was from 5 to 7 for urinary irritation and from 4 to 6 for bowel function. **RESULTS:** Six-hundred ninety-five men met inclusion criteria and received either EBRT (n = 583) or EBRT-LDR (n = 112). Patients in the EBRT-LDR group were younger (median age, 66 years [interquartile range [IQR], 60-71 years] vs 69 years [IQR, 64-74 years]; $P < .001$), were less likely to receive pelvic radiotherapy (10% vs 18%; $P = .040$), and had higher baseline 36-item Medical Outcomes Study Short-Form Health Survey physical function scores (median score, 95 [IQR, 86-100] vs 90 [IQR, 70-100]; $P < .001$). Over a 3-year period, compared with EBRT, EBRT-LDR was associated with worse urinary irritative scores (adjusted mean difference at 3 years, −5.4; 95% CI, −9.3, −1.6) and bowel function scores (−4.1; 95% CI, −7.6, −0.5). The differences were no longer clinically meaningful at 5 years (difference in urinary irritative scores: −4.5; 95% CI, −8.4, −0.5; difference in bowel function scores: −2.1; 95% CI, −5.7, −1.4). However, men who received EBRT-LDR were more likely to report moderate or big problems with urinary function bother (adjusted odds ratio, 3.5; 95% CI, 1.5-8.2) and frequent urination (adjusted odds ratio, 2.6; 95% CI, 1.2-5.6) through 5 years. There were no differences in survival or treatment-related regret between treatment groups. **CONCLUSIONS:** Compared with EBRT alone, EBRT-LDR was associated with clinically meaningful worse urinary irritative and bowel function over 3 years after treatment and more urinary bother at 5 years. ***Cancer* 2021;127:1912-1925**. © *2021 American Cancer Society*.

LAY SUMMARY:

- In men with prostate cancer who received external-beam radiation therapy (EBRT) with or without a brachytherapy boost (EBRT-LDR), EBRT-LDR was associated with clinically worse urinary irritation and bowel function through 3 years but resolved after 5 years.
- Men who received EBRT-LDR continued to report moderate-to-big problems with urinary function bother and frequent urination through 5 years.
- There was no difference in treatment-related regret or survival between patients who received EBRT and those who received EBRT-LDR.
- These intermediate-term estimates of function may facilitate counseling for men who are selecting treatment.

KEYWORDS: dose escalation, external-beam radiotherapy with low-dose brachytherapy boost (EBRT-LDR), health-related quality of life, prostate cancer quality of life, quality of life (QoL).

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INTRODUCTION

Seminal studies over the past 20 years confirmed the benefit of dose-escalation in external-beam radiotherapy (EBRT) to improve oncologic outcomes in patients with localized prostate adenocarcinoma.[1-3] However, EBRT dose escalation beyond certain thresholds is not feasible given the narrow therapeutic ratio from added toxicity.[4] The addition of a low dose-rate (LDR) brachytherapy boost to EBRT (EBRT-LDR) is an alternative and more conformal dose-escalation technique that can maximize the biologically equivalent dose to improve oncologic outcomes for patients with intermediate-risk and high-risk disease.[4-6] Among these patients with unfavorable risk, EBRT-LDR has the potential to improve disease-specific survival and overall survival (OS) compared with either EBRT alone or radical prostatectomy based on observational studies.[6,7] The Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) study (ClinicalTrials.gov identifier NCT00175396) remains the only randomized controlled trial that compared EBRT-LDR with EBRT alone using modern doses. Although that study demonstrated improved biochemical progression-free survival in those who received EBRT-LDR, it came at the trade-off of increased acute and late genitourinary morbidity and worse health-related quality of life.[5,8,9] However, it is important to note that the trial did not use contemporary radiation techniques, overall lacked a prespecified statistical plan for toxicity, and tracked a limited number of patient-reported outcomes (PROs), including some nonvalidated scales.[8,9]

PROs, particularly functional outcomes, are an important measure because they open the opportunity for dialogue between patients and physicians, allow for an assessment of the risk-to-benefit ratio in treatment decision making, and improve patient satisfaction.[10-12] Beyond single-institution and retrospective reports, there are limited intermediate-term to long-term prospective studies that compare EBRT-LDR versus EBRT.[13-16] Given the suggestion of a survival benefit with EBRT-LDR over EBRT in some studies and the paucity of data regarding possible increased toxicity with EBRT-LDR, we sought to evaluate PROs among men undergoing EBRT alone and EBRT-LDR for localized prostate cancer among those enrolled on the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study.[13-16]

MATERIALS AND METHODS

Study Population

CEASAR is a prospective, multisite, observational comparative effectiveness study that evaluates treatment outcomes and toxicities for a contemporary cohort of men treated for localized prostate cancer (ClinicalTrials.gov identifier NCT01326286).[17] Men were enrolled from 2011 to 2012 if they were aged <80 and had a pathologic diagnosis of localized prostate adenocarcinoma within 6 months before enrollment and a prostate-specific antigen (PSA) level <50 ng/dL. Men were enrolled 5 five Surveillance, Epidemiology, and End Results registry areas (Louisiana, Utah, Atlanta, Los Angeles, and New Jersey), and the cohort was augmented with the addition of patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database.[18,19] Institutional review board approval was obtained at each site.

Outcome Measures

Study participants completed baseline, 6-month, 1-year, 3-year, and 5-year questionnaires. The CEASAR trial directly captured demographic data and PROs. For the purposes of the current report, the most relevant PRO surveys included the 26-item Expanded Prostate Cancer Index Composite (EPIC), the 36-item Medical Outcomes Study Short-Form Health Survey (SF-36), and a 5-item treatment regret scale. EPIC is a validated survey that captures functional domains specific to prostate cancer treatment adverse effects (ie, urinary, bowel, sexual, and hormone).[20] SF-36 is a validated survey that measures health-related quality-of-life domains (ie, physical function, emotional well-being, and energy/fatigue).[21] Patient treatment-related regret was assessed using the validated Clark 5-item scale.[22] Additional surveys included the Total Illness Burden Index for Prostate Cancer (TIBI-CaP), the Participatory Decision-Making Scale, the Provider-Dependent Health Care Orientation Scale (PDHCOS), the Center for Epidemiologic Studies Depression Scale, and the Medical Outcomes Study Social Support Scale.[23-27] Electronic medical records were abstracted to detail tumor characteristics, PSA levels, and treatment history.

Defining Clinically and Statistically Meaningful Differences

We adapted the minimal clinically important difference (MCID), which was determined previously for each SF-36 and EPIC domain, using a distribution-based and anchor-based approach.[28,29] The MCID for EPIC was 5 to 7 for urinary irritation, 6 to 9 for urinary incontinence, 4 to 6 for bowel function, 10 to 12 for sexual function, and 4 to 6 hormonal function. The MCID for the SF-36 was 7 for physical function, 6 for emotional well-being, and 9 for energy/fatigue.

Statistical Analysis

Patients' demographic and clinical characteristics were summarized as medians and interquartile ranges (IQRs) (continuous) or as frequencies and percentages (categorical) by radiation group (EBRT vs EBRT-LDR). Differences between radiation groups were assessed using Wilcoxon rank-sum or Pearson chi-square tests. For the primary outcome (EPIC and SF-36 domain scores), median scores with IQRs were used to describe each radiation group. To evaluate differences between radiation groups, multivariable longitudinal linear regression was used, and the adjusted mean differences in scores with 95% CIs were reported as the effect measurements. For the secondary outcomes (a priori selected patient rating of individual problems), frequencies and adjusted odds ratios (aORs) with 95% CIs estimated from multivariable longitudinal logistic regression models were reported. All multivariable models were adjusted for age (continuous, restricted-cubic-splines), race, the TIBI-CaP score, D'Amico risk classification, androgen-deprivation therapy (ADT), pelvic radiation therapy, PDHCOS (continuous, linear), the Participatory Decision-Making Scale (continuous, linear), the Medical Outcomes Study Social Support Scale (continuous, linear), the Center for Epidemiologic Studies Depression Scale (continuous, linear), time from treatment (continuous, restricted-cubic-splines), site of treatment, baseline SF-36 physical function score (continuous, linear), and other corresponding baseline domain scores (continuous, restricted cubic splines). To account for the potential correlations among multiple records collected from the same individual at different time points, the Huber-White method was used to estimate the robust variance-covariance matrix.[30,31] To account for missing values for covariates, the multiple-imputation chained-equations method was used in all regression models, and no outcome variables were imputed.[32] For the secondary outcomes OS and prostate cancer-specific survival (PCSS), the Kaplan-Meier method was used for estimation, and the log-rank test was used to compare groups. No multivariable analysis was attempted because there were limited data on these outcomes. Two-sided P values $<.05$ were considered statistically significant. All analyses were conducted using R version 3.6 (R Foundation for Statistical Computing).[33]

RESULTS

Participant and Clinical Characteristics

Among 3277 men who met CEASAR inclusion criteria, 695 were included in the final analysis, including 112 in the EBRT-LDR group and 583 in the EBRT group (see Supporting Fig. 1). The 6-month, 1-year, 3-year, and 5-year response rates were 95.8%, 93.2%, 81.4%, and 71.2%, respectively (see Supporting Fig. 1). The overall median follow-up for vital status was 73 months (IQR, 63-78 months). Patients in the 2 radiation groups had similar OS ($P = .20$) and PCSS ($P = .60$). At 5 years, the OS rates were 95.2% versus 92.8%, and the PCSS rates were 99.0% versus 99.6% for the EBRT-LDR and EBRT groups, respectively (see Supporting Table 1).

Baseline participant and clinical characteristics are summarized in Table 1. Participants in the EBRT-LDR group, compared with the EBRT group, were younger (median age, 66 years [IQR, 60-71 years] vs 69 years [IQR, 64-74, respectively]; $P < .001$) and were more likely to accrue at certain geographic sites (site 2: 77% vs 8%; $P < .001$). Men in the EBRT-LDR group, compared with the EBRT group, were less likely to receive radiotherapy to the pelvis (10% vs 18%; $P = 0.040$), to have a high illness burden (TIBI-CaP score ≥ 5: 28% vs 42%; $P = .032$), to be passive decision-makers (PDHCOS median score, 17 [IQR, 6-35] vs 29 [IQR, 9-46]; $P = .002$), or to receive ADT in the first year after enrollment (16% vs 46%; $P < .001$). A subgroup analysis of patients who had favorable disease and those who had unfavorable disease identified similar trends (see Supporting Table 2).

Men who received EBRT-LDR were prescribed a median EBRT radiation dose of 45 Gray (Gy) (IQR, 45.0-52.5 Gy) to the prostate; an LDR boost was prescribed as Iodine-125 (I-125) to a median dose of 90 Gy (IQR, 80.0-110.0 Gy) in 86 men and as Palladium-103 to a median dose of 100 Gy (IQR, 92.5-100 Gy) in 16 men. Participants who received EBRT alone received a median radiation dose of 78 Gy (IQR, 76.0-79.2 Gy).

Urinary Irritative Symptoms

Baseline unadjusted urinary irritative function was similar between treatment groups (Fig. 1, Table 2). A clinically significant decline in urinary irritative function (MCID, 5-7 points) was reported by men undergoing EBRT-LDR from a median of 91 points at baseline to 75 points at 6 months (followed by gradual improvement to 81 points at 1 year, 88 points at 3 years, and 88 points at 5 years). When controlling baseline domain scores and other covariates, treatment with EBRT-LDR (Fig. 2, Table 2) was associated with clinically meaningful worse urinary irritative function through 3 years (adjusted mean difference, −5.4; 95% CI, −9.3, −1.6; $P = .006$). The 5-year difference in urinary irritative function was statistically significant but did not meet the threshold for clinical

TABLE 1. Baseline Participant and Clinical Characteristics

Characteristic	No. (%)			P[a]
	EBRT-LDR, n = 112	EBRT, n = 583	Combined, n = 695	
Age at diagnosis: Median [IQR], y	66 [60-71]	69 [64-74]	69 [63-73]	<.001
Race				
White	82 (74)	413 (71)	495 (71)	.24
Black	23 (21)	104 (18)	127 (18)	
Hispanic	3 (3)	37 (6)	40 (6)	
Asian	1 (1)	22 (4)	23 (3)	
Other	2 (2)	6 (1)	8 (1)	
Education				
<High school	6 (6)	87 (16)	93 (14)	.16
High school graduate	21 (21)	116 (21)	137 (21)	
Some college	26 (26)	129 (23)	155 (23)	
College graduate	23 (23)	114 (20)	137 (21)	
Graduate/professional school	24 (24)	115 (20)	139 (21)	
Marital status				
Not married	23 (23)	142 (25)	165 (25)	.58
Married	78 (77)	418 (75)	496 (75)	
Total Illness Burden Index for Prostate Cancer[b]				
0-2	24 (24)	96 (17)	120 (18)	.032
3-4	49 (48)	232 (41)	281 (42)	
≥5	29 (28)	236 (42)	265 (40)	
D'Amico risk grouping[c]				
Low risk	35 (31)	170 (29)	205 (30)	.91
Intermediate risk	50 (45)	265 (46)	315 (45)	
High risk	27 (24)	146 (25)	173 (25)	
PSA at diagnosis, corrected, ng/mL				
<4	17 (15)	75 (13)	92 (13)	.036
≥4 to <10	85 (76)	388 (67)	473 (68)	
≥10 to <20	8 (7)	87 (15)	95 (14)	
≥20 to <50	2 (2)	33 (6)	35 (5)	
Clinical tumor classification				
T1	86 (77)	426 (73)	512 (74)	.43
T2	26 (23)	156 (27)	182 (26)	
Gleason score on biopsy				
≤6	38 (34)	198 (34)	236 (34)	.68
3 + 4	40 (36)	200 (34)	240 (35)	
4 + 3	12 (11)	85 (15)	97 (14)	
≥8	22 (20)	98 (17)	120 (17)	
Accrual site				
Site 1	1 (1)	14 (2)	15 (2)	<.001
Site 2	86 (77)	48 (8)	134 (19)	
Site 3	2 (2)	140 (24)	142 (20)	
Site 4	15 (13)	222 (38)	237 (34)	
Site 5	3 (3)	134 (23)	137 (20)	
Site 6	5 (4)	25 (4)	30 (4)	
Any ADT in first year of enrollment				
Yes	18 (16)	266 (46)	284 (41)	<.001
No	93 (84)	314 (54)	407 (59)	
Received pelvic radiation				
Yes	10 (10)	100 (18)	110 (16)	.040
No	95 (90)	469 (82)	564 (84)	
Received IMRT				
Yes	89 (85)	472 (83)	561 (83)	.58
No	16 (15)	100 (17)	116 (17)	
Received IGRT				
Yes	77 (79)	464 (86)	541 (85)	.097
No	20 (21)	76 (14)	96 (15)	
EBRT dose per fraction, Gy				
≤2	91 (99)	524 (95)	623 (95)	.16
2-3	1 (1)	9 (2)	10 (2)	
>3	0 (0)	20 (4)	20 (3)	
Participatory decision-making scale: Median [IQR][d]	79 [71-89]	79 [64-89]	79 [64-89]	.13

TABLE 1. *Continued*

Characteristic	No. (%)			P^a
	EBRT-LDR, n = 112	EBRT, n = 583	Combined, n = 695	
Provider-dependent health care orientation scale: Median [IQR][e]	17 [6-35]	29 [9-46]	25 [8-46]	.002
Social support scale: median [IQR][f]	95 [75-100]	95 [70-100]	95 [70-100]	.73
Depression scale, median [IQR][g]	11 [4-22]	15 [4-30]	15 [4-30]	.11

Abbreviations: ADT, androgen-deprivation therapy; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; EBRT, external-beam radiotherapy; Gy, gray; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; LDR, low-dose brachytherapy; PSA, prostate-specific antigen.

[a]*P* values were determined by assessing the EBRT group versus the EBRT-LDR group using either a Wilcoxon test for continuous variables or the Pearson chi-square test for categorical variables.

[b]This index measures patient illness and comorbidity burden on a scale from 0 to 23, with higher scores reflecting greater severity and number of comorbidities.

[c]For D'Amico risk grouping, low risk indicates Gleason score <6, and PSA <10 ng/mL, and clinical T1c-T2a tumor; intermediate risk, Gleason score 7 or PSA 10 to 20 ng/mL or clinical T2b tumor; high risk, Gleason score 8 or PSA >20 ng/mL or clinical T2c-T3 tumor.

[d]This scale measures patient decision-making style on a scale from 0 to 100 using the Provider-Dependent Health Care Orientation Scale, with higher scores reflecting increased patient choice, control, and responsibility.

[e]Measures patient decision-making passivity on a scale from 0 to 100 using the Participatory Decision-Making Scale, with higher scores reflecting increased passivity.

[f]This scale measures the degree of social support on a scale from 0 to 100 using the 5-item Medical Outcomes Study Social Support Scale, with higher scores reflecting greater support.

[g]This scale measures patient depression on a scale from 0 to 100 using the Epidemiologic Studies Depression Scale, with higher scores reflecting more severe depressive symptoms.

significance (adjusted mean difference, −4.5; 95% CI, −8.4, −0.5; $P = .026$).

Treatment with EBRT-LDR was associated with reporting of moderate or big problems (Table 2) with urinary function bother through 5 years (aOR, 3.5; 95% CI, 1.5-8.2; $P = .004$), frequent urination through 5 years (aOR, 2.6; 95% CI, 1.2-5.6; $P = .017$), and urinary burning sensation through 3 years (aOR, 9.3; 95% CI, 2.8-30.5; $P < .001$) followed by gradual resolution at 5 years (aOR, 4.1; 95% CI, 0.9-18.8; $P = .072$).

Urinary Incontinence

Baseline unadjusted urinary incontinence function was similar between treatment groups (Fig. 1, Table 2). There was no clinically significant difference in urinary incontinence (MCID, 6-9 points) between treatment groups through 5 years (Fig. 2, Table 2). There were no differences between treatment groups in reporting of moderate or big urinary leakage or daily incontinence pad use symptoms through 5 years (Table 2).

Bowel Function

Baseline unadjusted bowel function was similar between treatment groups (Fig. 1, Table 2). A clinically significant decline in bowel function (MCID, 4-6 points) was reported by men undergoing EBRT-LDR from a median of 100 points at baseline to 92 points at 6 months (followed by gradual improvement to 92 points at 1 year, 96 points at 3 years, and 92 points at 5 years). When controlling baseline domain scores and other covariates, treatment with EBRT-LDR (Fig. 2, Table 2) was associated with clinically meaningful worse bowel function through 3 years (adjusted mean difference, −4.1; 95% CI, −7.6, −0.5; $P = .027$). There was no clinically significant difference in bowel function between treatment groups through 5 years (adjusted mean difference, −2.1; 95% CI, −5.7, 1.4; $P = .241$).

Treatment with EBRT-LDR was associated with reporting of moderate or big problems (Table 2) of bloody stools at 1 year (aOR, 3; 95% CI, 1.2-7.6; $P = .02$), which normalized through 3 to 5 years. There were no differences between treatment groups in reporting of moderate or big bowel function bother or bowel urgency through 5 years.

Sexual Function

Baseline unadjusted sexual function was similar between treatment groups (Fig. 1, Table 2). There were clinically meaningful declines in sexual function (MCID, 10-12 points) in both treatment groups at 5 years, with the median domain score falling from 65 points at baseline to 38 points for men who received EBRT-LDR and from 58 to 28 points for men who received EBRT alone (Table 2). However there was no clinically significant difference in sexual function between treatment groups through 5 years (Fig. 2, Table 2). There were no treatment group differences in the reporting of moderate or big sexual function bother or insufficient erection quality through 5 years (Table 2).

Hormone Function

Baseline unadjusted hormonal function was similar between treatment groups (Fig. 1, Table 2). There

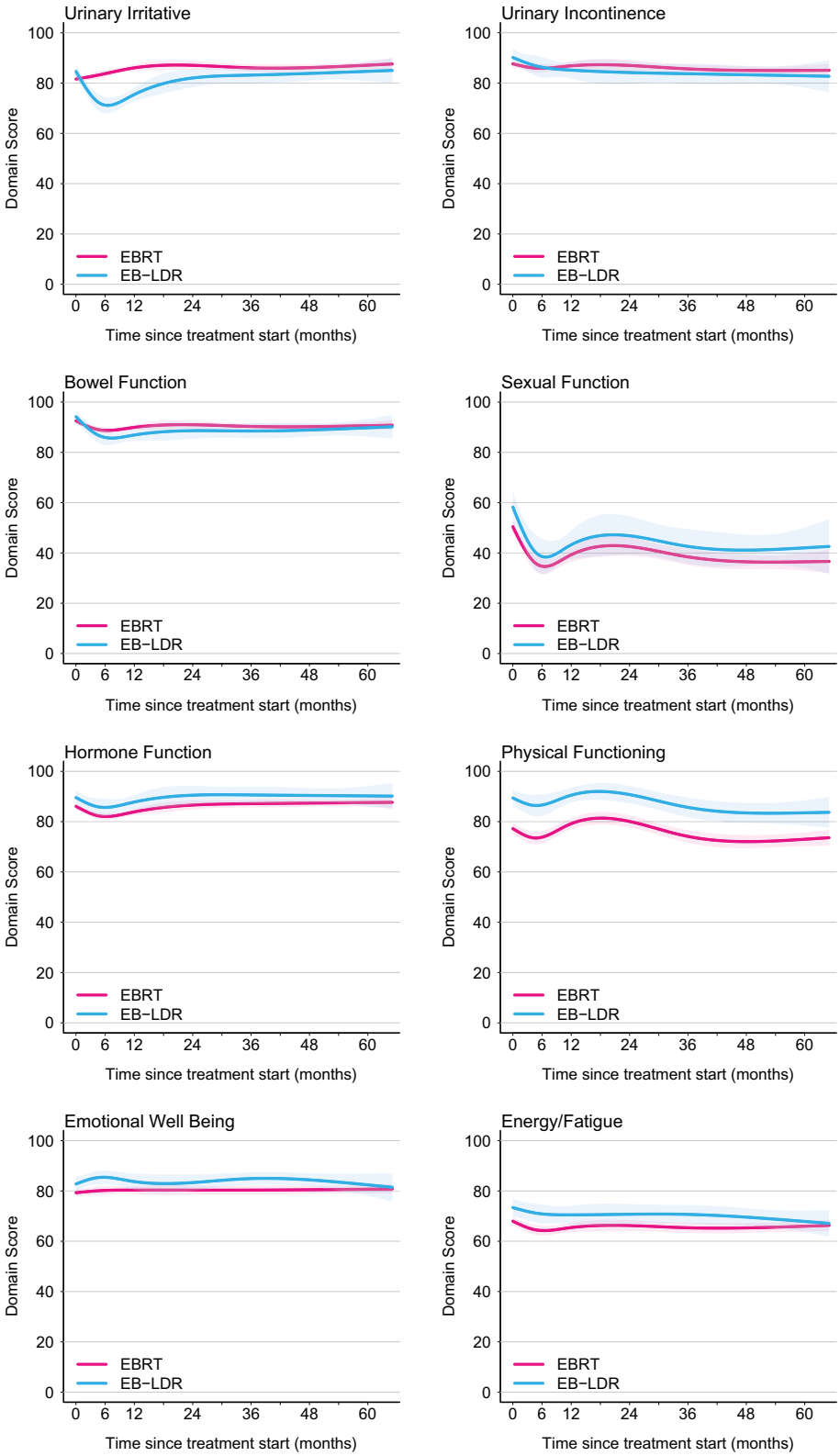
Urinary Irritative
Urinary Incontinence
Bowel Function
Sexual Function
Hormone Function
Physical Functioning
Emotional Well Being
Energy/Fatigue
Domain Score
Time since treatment start (months)
EBRT
EB−LDR
0
20
40
60
80
100
0 6 12 24 36 48 60

Figure 1. Unadjusted Expanded Prostate Cancer Index Composite scores and 36-item Medical Outcomes Study Short-Form Health Survey (SF-36) domain scores are illustrated comparing patients who received external-beam radiotherapy alone (EBRT) with those who received EBRT plus low-dose-rate brachytherapy (EB-LDR) over 5 years. Unadjusted domain scores using the 26-item Expanded Prostate Cancer Index Composite and the 36-item Short Form were tracked at baseline, 6 months, 1 year, 3 years, and 5 years. Domain scores range from 0 to 100, with higher scores indicating better function. Expanded Prostate Cancer Index Composite domains include urinary irritative function, urinary incontinence, bowel function, sexual function, and hormone function. Short-Form domains include physical function, emotional well-being, and energy/fatigue. Participants in the EB-LDR group (solid cyan line) were compared with those in the EBRT group (solid magenta line), and 95% CIs were calculated (shaded region).

were clinically meaningful declines in hormonal function (MCID, 4-6 points) in both treatment groups at 6 months, with improvement to baseline function at later time points (Table 2). However, there was no clinically significant difference in hormone function between treatment groups through 5 years (Fig. 2, Table 2).

Health-Related Quality of Life

Baseline unadjusted median physical function and energy/fatigue scores were higher in the EBRT-LDR group versus the EBRT-alone group (median, 95 [IQR, 86-100] vs 90 [IQR, 70-100]; $P < .001$) and (median, 80 [IQR, 70-85] vs 70 [IQR, 55-85; $P = .010$), respectively; and baseline emotional well-being was similar between treatment groups (Fig. 1, Table 2). When controlling baseline domain scores and other covariates (Fig. 3, Table 2), participants in the EBRT-LDR group had statistically better physical function at 6 months (adjusted mean difference, +4.1; 95% CI, 0.2-8.0; $P = .041$) and at 3 years (adjusted mean difference, +4.3; 95% CI, 0.1-8.4; $P = .042$), but this was not identified as clinically significant (MCID, 7 points). There was no clinically significant difference in energy/fatigue (MCID, 9 points) or emotional well-being (MCID, 6 points) between treatment groups through 5 years (Fig. 3, Table 2).

Patient-Reported Treatment-Related Regret

At the 5-year follow-up assessment, <10% of patients in either group expressed *quite a bit* or *very much* regret over treatment choice on any of the 5-item questions, and there were no differences between groups (see Supporting Table 3).

DISCUSSION

Among a modern prospective cohort of men with localized prostate cancer, we observed a distinct adverse effect profile after treatment with EBRT-LDR and EBRT alone. Specifically, treatment with EBRT-LDR, compared with EBRT alone, was associated with clinically meaningful worse urinary irritative function and bowel function through 3 years after treatment. Although these functional differences were no longer clinically meaningful at 5 years, men who received EBRT-LDR were still more likely to report moderate or big problems with urinary function and frequent urination through 5 years. Despite differences in patient-reported functional outcomes, there was no difference in patient-reported treatment-related regret between the 2 groups.

Although some of the functional outcomes of EBRT-LDR versus EBRT have been examined in the ASCENDE-RT trial, there are several crucial differences in the current CEASAR study. The ASCENDE-RT trial randomized men to receive either 3-dimensional conformal EBRT plus ADT or EBRT with I-125 LDR boost plus ADT; however, there was no requirement for EBRT image guidance. In contrast, the majority of men in the CEASAR study received more advanced, modern treatment with intensity-modulated EBRT and daily image guidance, I-125 or Palladium-103 LDR boost, and risk-based ADT. All of these treatment factors can affect the adverse effect profile described in the current study but may also be more representative of the treatments patients receive in the real world. Moreover, the ASCENDE-RT trial did not report on ethnic/racial accrual demographics for a trial set in British Columbia, a region with a predominantly Caucasian (75%) and Asian (22%) population.[34] In contrast, the CEASAR cohort included 29% non-White men and is more representative of the ethnic/racial diversity in the United States; however, we did not investigate the interactions between race and treatment groups in this analysis. Finally, the ASCENDE-RT trial did not specify a plan for toxicity analysis and relied on the SF-36 version 2 health-related quality of life questionnaire with an appended, nonvalidated scale for urinary/bowel/sexual function.[8,9] In contrast, for the current study, we used multiple validated questionnaires that provided a more detailed account of the patient experience after treatment.

The greatest functional impact observed in the current study was on urination, specifically urinary irritative function, which was clinically meaningfully worse at the 6-month, 1-year, and 3-year follow-up assessments in the

TABLE 2. Unadjusted and Adjusted Patient-Reported Outcomes on the Expanded Prostate Cancer Index Composite Domain Scores and Short-Form Domain Scores Stratified by Treatment Group and Time Point

				Adjusted Linear Model: Effect Size = Point Difference Between Groups		
	Unadjusted Domain Score: Median [IQR]			EBRT-LDR vs EBRT		
Time	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
EPIC urinary function domains[a]						
Urinary irritative						
Baseline	91 [75-95]	88 [75-94]	.062	—	—	—
6 mo	75 [56-88]	88 [75-94]	.001	−14.7[b]	−18.7, −10.7	<.001
1 y	81 [66-88]	88 [81-94]	.001	−12.5[b]	−16.8, −8.1	<.001
3 y	88 [75-100]	88 [81-100]	.51	−5.4[b]	−9.3, −1.6	.006
5 y	88 [75-94]	88 [81-100]	.23	−4.5	−8.4, −0.5	.026
Urinary incontinence						
Baseline	100 [85-100]	100 [79-100])	.32	—	—	—
6 mo	94 [73-100]	100 [75-100]	.60	−3.0	−6.9, 0.9	.14
1 y	92 [73-100]	100 [77-100]	.32	−4.6	−8.7, −0.6	.025
3 y	94 [73-100]	94 [75-100]	.74	−4.3	−9.1, 0.5	.082
5 y	92 [73-100]	100 [75-100]	.34	−3.8	−9.9, 2.2	.21

				Adjusted Logistic Model: Effect Size = aOR of Moderate or Big Problem		
	Unadjusted Frequency: Moderate or Big Problem: No. (%)			EBRT-LDR vs EBRT		
Time	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
EPIC urinary function individual items[a]						
Urinary function bother						
Baseline	7 (6)	69 (12)	.080	—	—	—
6 mo	22 (22)	72 (13)	.016	3.4	1.7-6.8	<.001
1 y	15 (15)	51 (10)	.14	3.1	1.7-5.8	<.001
3 y	12 (13)	46 (10)	.40	2.8	1.2-6.5	.013
5 y	12 (15)	42 (10)	.19	3.5	1.5-8.2	.004
Frequent urination						
Baseline	20 (18)	124 (22)	.42	—	—	—
6 mo	32 (32)	103 (18)	.002	3.3	1.8-5.8	<.001
1 y	29 (28)	78 (14)	<.001	3.2	1.9-5.4	<.001
3 y	18 (19)	68 (14)	.25	2.9	1.5, 5.6	.002
5 y	16 (21)	56 (13)	.11	2.6	1.2-5.6	.017
Burning on urination						
Baseline	4 (4)	24 (4)	.80	—	—	—
6 mo	22 (22)	28 (5)	<.001	6.8	2.8-16.6	<.001
1 y	17 (16)	15 (3)	<.001	8.6	3.7-19.8	<.001
3 y	8 (9)	10 (2)	.001	9.3	2.8-30.5	<.001
5 y	3 (4)	4 (1)	.051	4.1	0.9-18.8	.072
Urinary leakage						
Baseline	4 (4)	24 (4)	.79	—	—	—
6 mo	3 (3)	31 (6)	.29	0.7	0.2-2.1	.49
1 y	4 (4)	31 (6)	.44	1.0	0.4-2.5	.92
3 y	6 (6)	23 (5)	.57	2.3	0.7-7.2	.15
5 y	6 (8)	27 (7)	.70	1.8	0.5-6.2	.38
Daily incontinence pad use, >1 pad use						
Baseline	4 (4)	24 (4)	.79	—	—	—
6 mo	3 (3)	31 (6)	.29	1.3	0.5-3.2	.60
1 y	4 (4)	31 (6)	.44	1.8	0.9-3.6	.10
3 y	6 (6)	23 (5)	.57	2.2	1.0-5.2	.059
5 y	6 (8)	27 (7)	.70	0.8	0.3-2.3	.68

				Adjusted Linear Model; Effect Size = Point Difference Between Groups		
	Unadjusted Domain Score: Median [IQR]			EBRT-LDR vs EBRT		
Time	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
EPIC bowel function domain[a]						
Baseline	100 [92-100]	100 [92-100]	.11	—	—	—

TABLE 2. *Continued*

Time	Unadjusted Domain Score: Median [IQR]			Adjusted Linear Model; Effect Size = Point Difference Between Groups		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
6 mo	92 [79-100]	96 [83-100]	.020	−4.0[b]	−7.8, −0.1	.042
1 y	92 [79-100]	96 [83-100]	.16	−6.5[b]	−9.9, −3.1	<.001
3 y	96 [83-100]	96 [83-100]	.62	−4.1[b]	−7.6, −0.5	.027
5 y	92 [83-100]	96 [88-100]	.14	−2.1	−5.7, 1.4	.24

Time	Unadjusted Frequency Moderate or Big Problem: No. (%)			Adjusted Logistic Model: Effect Size = aOR of Moderate or Big Problem		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
Bowel function individual items[c]						
Bloody stools						
Baseline	0 (0)	4 (1)	.38	—	—	—
6 mo	1 (1)	8 (1)	.73	0.5	0.0-10.3	.64
1 y	2 (2)	11 (2)	.94	3.0	1.2-7.6	.02
3 y	0 (0)	8 (2)	.20	0.0	0.0-0.2	.008
5 y	0 (0)	4 (1)	.39	0.0	0.0-0.0	.003
Bowel function bother						
Baseline	3 (3)	21 (4)	.63	—	—	—
6 mo	6 (6)	45 (8)	.45	0.5	0.2-1.5	0.24
1 y	4 (4)	41 (8)	.17	0.8	0.4-1.8	0.59
3 y	7 (7)	28 (6)	.60	1.5	0.6-3.7	0.42
5 y	3 (4)	21 (5)	.65	0.9	0.2-3.3	0.83
Bowel urgency						
Baseline	3 (3)	21 (4)	.63	—	—	—
6 mo	10 (10)	44 (8)	.48	1.4	0.5-3.8	.46
1 y	8 (8)	39 (7)	.86	1.9	0.8-4.3	.14
3 y	9 (10)	33 (7)	.40	2.3	0.9-6.1	.094
5 y	5 (6)	32 (8)	.69	1.2	0.3-3.9	.81

Time	Unadjusted Domain Score: Median [IQR]			Adjusted Linear Model; Effect Size = Point Difference Between Groups		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
EPIC sexual function domain[a]						
Sexual function						
Baseline	65 [33-85]	58 [18-80]	.060	—	—	—
6 mo	38 [6-70]	28 [0-68]	.10	−2.1	−8.6, 4.4	.53
1 y	40 [7-70]	33 [7-65]	.36	−0.5	−6.2, 5.2	.86
3 y	37 [7-70]	33 [6-70]	.37	−1.3	−7.5, 4.9	.67
5 y	38 [7-75]	28 [5-65]	.19	2.2	−4.5, 9.0	.51

Time	Unadjusted Frequency Moderate or Big Problem: No. (%)			Adjusted Logistic Model; Effect Size = aOR		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
Sexual function individual items[c]						
Sexual function bother: Moderate or big problem						
Baseline	35 (34)	177 (32)	.75	—	—	—
6 mo	39 (39)	206 (38)	.86	1.3	0.7-2.3	.40
1 y	44 (43)	201 (39)	.40	1.5	0.9-2.5	.091
3 y	36 (40)	156 (35)	.38	1.6	0.9-2.8	.098
5 y	26 (34)	154 (39)	.41	0.8	0.4-1.6	.61

TABLE 2. *Continued*

Time	Unadjusted Frequency Moderate or Big Problem: No. (%)			Adjusted Logistic Model; Effect Size = aOR		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
Erection insufficient for penetration						
Baseline	52 (50)	313 (57)	.18	—	—	—
6 mo	66 (65)	390 (72)	.15	1.0	0.6-1.9	.89
1 y	69 (67)	378 (72)	.29	1.2	0.7-2.1	.48
3 y	62 (68)	320 (71)	.57	1.2	0.6-2.3	.61
5 y	48 (62)	289 (74)	.046	0.6	0.3-1.2	.13

Time	Unadjusted Domain Score: Median [IQR]			Adjusted Linear Model: Effect Size = Point Difference Between Groups		
				EBRT-LDR vs EBRT		
	EBRT-LDR, N = 112	EBRT, N = 583	*P*	Effect	95% CI	*P*
EPIC hormone function domain[a]						
Hormone function						
Baseline	95 [85-100]	90 [80-100]	.12	—	—	—
6 mo	90 [80-100]	85 [75-100]	.019	−1.2	−4.6, 2.1	.48
1 y	90 [80-100]	90 [75-100]	.080	−0.4	−3.9, 3.1	.82
3 y	95 [85-100]	90 [80-100]	.029	−0.6	−4.1, 2.9	.74
5 y	95 [85-100]	95 [80-100]	.18	−0.6	−4.1, 2.8	.72
SF-36 physical function domain[a]						
Physical function						
Baseline	95 [86-100]	90 [70-100)	<.001	—	—	—
6 mo	95 [88-100]	85 [60-95)	<.001	4.1	0.2, 8.0	.041
1 y	100 [90-100]	90 [65-100)	<.001	2.1	−1.7, 5.9	.28
3 y	95 [85-100]	85 [55-95)	<.001	4.3	[0.1, 8.4	.042
5 y	90 [75-95]	85 [55-95)	.002	4.7	−0.5, 9.8	.076
SF-36 emotional well-being domain[a]						
Emotional well-being						
Baseline	86 [80-92]	84 [70-92]	.25	—	—	—
6 mo	92 [80-96]	84 [72-92]	.004	0.5	−2.7, 3.6	.77
1 y	88 [76-92]	84 [72-92]	.15	−1.8	−6.0, 2.4	.40
3 y	88 [76-92]	88 [72-92]	.15	−0.5	−3.9, 2.8	.76
5 y	88 [76-92]	87 [72-92]	.23	−2.6	−7.9, 2.8	.35
SF energy and fatigue domain[a]						
Energy and fatigue						
Baseline	80 [70-85]	70 [55-85]	.010	—	—	—
6 mo	75 [65-85]	70 [50-80]	.003	0.8	−3.2, 4.8	.69
1 y	75 [60-80]	70 [50-80]	.029	1.3	−3.0, 5.5	.56
3 y	75 [60-80]	70 [55-80]	.066	1.2	−2.5, 4.8	.53
5 y	70 [60-80]	70 [50-80]	.43	−0.4	−5.1, 4.3	.86

Abbreviations: aOR, adjusted odds ratio; EBRT, external-beam radiotherapy; EPIC, 26-item Expanded Prostate Cancer Index Composite; IQR, interquartile range; LDR, low-dose brachytherapy; SF-36, the 36-item Medical Outcomes Study Short-Form Health Survey.

[a]These values represent a clinically meaningful difference, defined as meeting statistical significance and clinical significance. Clinical significance is defined as the difference between groups exceeding the minimum clinically important difference. The EPIC minimum clinically important difference was defined as 5 to 7 points for urinary irritative, 6 to 9 points for urinary incontinence, 4 to 6 points for bowel function, 10 to 12 points for sexual function, and 4 to 6 points for hormonal function. The minimum clinically important point difference for the SF-36 was defined as 7 points for physical well-being, 6 points for emotional well-being, and 9 points for energy/fatigue.

[b]Domain scores for EPIC and SF-36 are represented as unadjusted values in the left column, on scales from 0 to 100, with higher scores representing better function. Unadjusted scores are represented as median values with IQRs (25th percentile to 75th percentile). Values in right column values are based on a multivariable regression model with the effect size representing the adjusted mean point difference using EBRT as the reference group. Negative effect size values reflect worse patient-reported outcomes in the EBRT-LDR group, whereas positive values reflect better patient-reported outcomes in the EBRT-LDR group. The multivariable linear regression model was adjusted for age, race, comorbidities, disease risk classification, receipt of androgen-deprivation therapy, receipt of pelvic radiation therapy, depression scores, decision-making style scores, social support scores, time from treatment, geographic site of treatment, and corresponding baseline scores.

[c]Clinically important individual items were scored on a Likert scale and dichotomized for group comparison in the left column. Unadjusted numbers of patients who report a moderate or big problem are represented as frequencies. The right column values are based on a multivariable regression model, with the effect size representing an aOR of reporting a moderate or big problem using EBRT as the reference group. An effect size >1.0 indicates that the patient-reported outcome occurs more frequently in the EBRT-LDR group. The multivariable logistic regression model was adjusted for age, race, comorbidities, disease risk classification, receipt of androgen-deprivation therapy, receipt of pelvic radiation therapy, depression scores, decision-making style scores, social support scores, time from treatment, geographic site of treatment, and corresponding baseline scores.

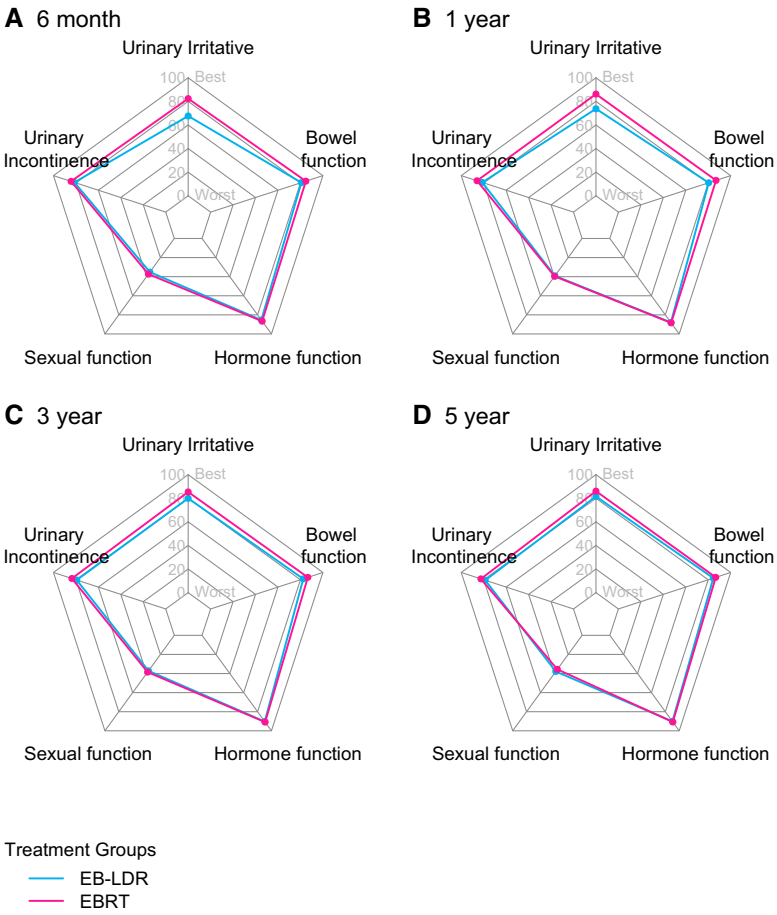

Figure 2. Adjusted Expanded Prostate Cancer Index Composite domain scores are compared between patients who received external-beam radiotherapy alone (EBRT) and those who received EBRT plus low-dose-rate brachytherapy (EB-LDR) over 5 years. (A-D) Radar plots of adjusted domain scores from the 26-item Expanded Prostate Cancer Index Composite were generated by comparing baseline values with the values at (A) 6 months, (B) 1 year, (C) 3 years, and (D) 5 years in the EB-LDR group (solid cyan line) and the EBRT-alone group (solid magenta line). The Expanded Prostate Cancer Index domains and the minimum clinically important difference in scores for each domain were: urinary irritative function, 5 to 7 points; urinary incontinence, 6 to 9 points; bowel function, 4 to 6 points; sexual function, 10 to 12 points; and hormone function, 4 to 6 points. The center of each figure represents worst function (score = 0), and the outermost line represents best function (score = 100). The multivariable linear regression model was adjusted for age, race, comorbidities, disease risk classification, receipt of androgen-deprivation therapy, receipt of pelvic radiation therapy, depression scores, decision-making style scores, social support scores, time from treatment, geographic site of treatment, Medical Outcomes Study Short-Form Health Survey physical function score, and other corresponding domain scores at baseline.

EBRT-LDR group. Although these changes were no longer clinically meaningful at the 5-year mark, men in the EBRT-LDR group were still more likely to report moderate or big problems with urinary function and frequent urination. Comparatively, the ASCENDE-RT EBRT-LDR group demonstrated a significant decline in urinary function at the 3.5-year, 4-year, and 6-year follow-up assessments. However, the ASCENDE-RT urinary function scale relied on a nonvalidated questionnaire skewed toward the assessment of incontinence (eg, questions on urinary control, incontinence pad use, problems with urinary leakage, and frequency of urinary leakage) as opposed to urinary irritative function. Unlike the ASCENDE-RT study, the current study did not find a clinically meaningful difference in urinary incontinence at any time point, and participants did not report a significant worsening with urinary leakage or daily incontinence pad use.

Aside from urinary function, bowel function was also clinically meaningfully worse in the CEASAR EBRT-LDR group at the 6-month, 1-year, and 3-year follow-up assessments. These changes were no longer clinically meaningful at the 5-year mark, and men in the EBRT-LDR group did not report a difference in moderate or big problems with bowel function, bowel urgency, or bloody

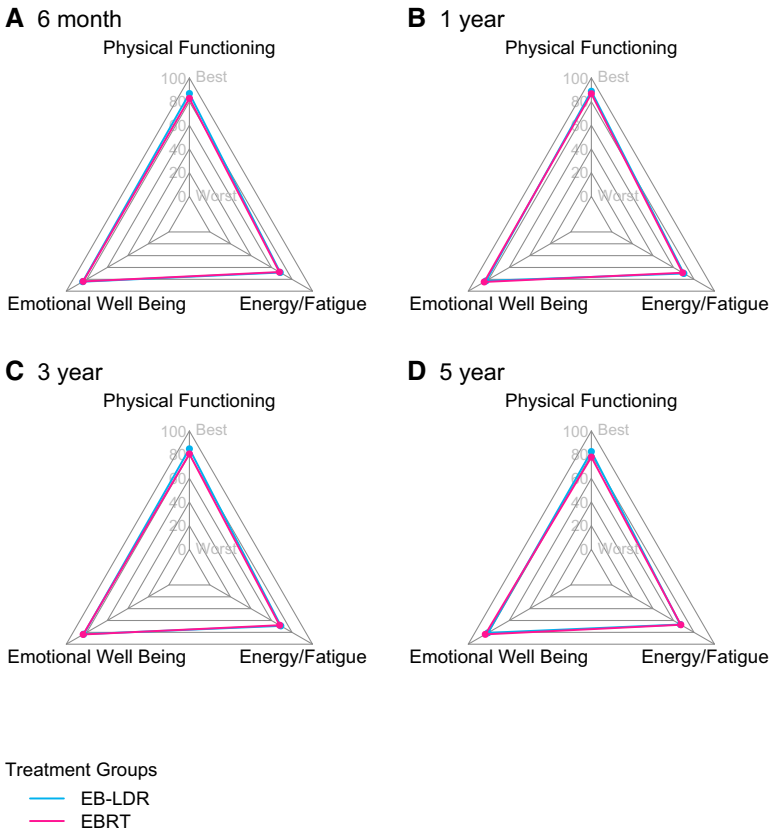

Figure 3. Adjusted scores on domains from the Medical Outcomes Survey Short Form Health Survey (SF-36) are compared between patients who received external-beam radiotherapy alone (EBRT) and those who received EBRT plus low-dose-rate brachytherapy (EB-LDR) over 5 years. (A-D) Radar plots of adjusted domain scores from the SF-36 were generated by comparing baseline values with the values at (A) 6 months, (B) 1 year, (C) 3 years, and (D) 5 years in the EB-LDR group (solid cyan line) and the EBRT-alone group (solid magenta line). The SF-36 domains and the minimum clinically important differences in scores for each domain were: physical function, 7 points; emotional well-being, 6 points; and energy/fatigue, 9 points. The center of each figure represents worst function (score = 0), and the outermost line represents best function (score = 100). The multivariable linear regression model was adjusted for age, race, comorbidities, disease risk classification, receipt of androgen-deprivation therapy, receipt of pelvic radiation therapy, depression scores, decision-making style scores, social support scores, time from treatment, geographic site of treatment, and corresponding baseline domain scores.

stools at any time point. Similarly, the ASCENDE-RT EBRT-LDR group demonstrated a significant decline in bowel function at the 1-year mark followed by a gradual recovery period at the 3-year, 5-year, and 6-year follow-up assessments.

Finally, although, in the current study, we noted clinically meaningful declines in sexual function and hormone function in both groups, there was no difference in sexual function or hormone function when comparing the EBRT-LDR group with the EBRT group. This is in contrast to the ASCENDE-RT trial, which reported an EBRT-LDR association with worse sexual function at the 1-year, 2-year, and 2.5-year follow-up assessments. Unlike ASCENDE-RT, which mandated 1 year of ADT use, participants in the EBRT-LDR group from the current study were less likely to receive ADT than men in the EBRT-alone group. ADT was administered upon risk-based assessment at the discretion of each clinician and was accounted for in our multivariable model when comparing treatment groups.

Finally, the disease-related outcomes are encouraging. The 5-year OS and PCSS rates in the CEASAR EBRT-LDR group (95% and 99%, respectively) versus the EBRT-alone group (93% and 100%, respectively) compare favorably with the ASCENDE-RT EBRT-LDR group (91% and 97%, respectively) versus the EBRT-alone group (89% and 98%, respectively). However, additional follow-up is necessary given the underlying biology of prostate cancer progression and data from ASCENDE-RT, which indicate that disease-outcome curves begin to separate around the 5-year mark.

Several limitations should be noted when interpreting these results. First, prospective observational studies

are at risk for treatment selection and reporting bias. To account for this, we used a rigorous multivariable regression model that adjusts PROs. Second, missing survey data could be a source of bias; this was accounted for by using a multiple imputation method. Third, this study solely focuses on the use of LDR for brachytherapy boosts, and the results may not reflect toxicity or outcome patterns for high-dose-rate brachytherapy boosts. Fourth, the current population-based cohort relied on EBRT-LDR and EBRT treatment without prespecified restrictions or quality measures for dose, fractionation, or other technique elements. Consequently, the median I-125 boost dose was lower than the recommended consensus guideline dose or the doses used in the ASCENDE-RT trial, which could affect the observed toxicity profile.[35] However, both the consensus guidelines and ASCENDE-RT data were published after completion of patient accrual in the CEASAR study, and the prescribed doses reflect a real-world setting scenario in which clinical judgement was used to deliver adequate doses that do not appear to have diminished disease-related outcomes. Fifth, this study did not take into account baseline, treatment, or posttreatment prostate medications (eg, α blockers), which could have affected functional outcomes. Sixth, recall of function may influence reported baseline function for men who completed the baseline questionnaire after starting treatment. However, we previously reported that the absolute differences in baseline scores between men enrolled in the CEASAR study who completed the baseline survey before versus after starting treatment were very small (range, 1-3 points), and the Prostate Cancer Outcome Study validation study demonstrated most men accurately recall prediagnostic function 6 months after prostate cancer diagnosis.[36,37] Finally, this study did not account for the use of biodegradable rectal spacers, preoperative magnetic resonance imaging, or other technical advancements for LDR boost.[38,39] As such, the addition of biodegradable rectal spacers may lead to decreases in bowel toxicity, and preoperative magnetic resonance image planning allows better urethral delineation, which may translate to improved urinary toxicity.

In conclusion, in this prospective cohort of men with localized prostate cancer who received modern EBRT-LDR and EBRT techniques, EBRT-LDR was associated with clinically meaningful worse urinary irritative and bowel function through 3 years but, the differences were no longer clinically meaningful at 5 years. These findings may facilitate the counseling of men who are selecting treatment.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

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