HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2023 December 01.

Published in final edited form as:

J Urol. 2022 December ; 208(6): 1226–1239. doi:10.1097/JU.0000000000002902.

Patient-Reported Outcomes after External Beam Radiotherapy with Low Dose-Rate Brachytherapy Boost versus Radical Prostatectomy for Localized Prostate Cancer: Five-Year Results from a Prospective Comparative Effectiveness Study

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Ethical approval: All procedures performed in the study were in accordance with the ethical standards of the local research committee and the 1964 Helsinki Declaration and its later amendments.

Informed consent: Informed consent was obtained from patients at the initiation of the study.

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Abstract

Background: Data comparing radical prostatectomy (RP) and external beam radiation therapy with low-dose rate brachytherapy boost (EBRT-LDR) are lacking. To better guide shared decision-making regarding treatment, we compared patient reported outcomes (PROs) through 5 years following RP or EBRT-LDR for localized prostate cancer.

Methods: From 2011–2012, men aged < 80 years with localized prostate adenocarcinoma were enrolled and followed longitudinally. PROs included the Expanded Prostate Index Composite. Regression models adjusted for baseline scores and covariates were constructed.

Results: The study population included 112 men treated with EBRT-LDR and 1553 treated with RP. Compared to RP, EBRT-LDR was associated with clinically meaningful worse urinary irritative/obstructive (adjusted mean score difference [95% confidence interval]: −5.0 [−8.7, −1.3]; P=0.008 at 5 years) and better urinary incontinence function (13.3 [7.7, 18.9]; $P<0.001$ at 5 years) through 5 years. Urinary function bother was similar between groups ($P>0.4$ at all timepoints). Treatment with EBRT-LDR was associated with worse bowel function (−4.0 [−6.9, −1.1]; $P=0.006$ at 5 years) through 5 years compared to RP. Treatment with EBRT-LDR was associated with better sexual function at 1 year (12.0 [6.5, 17.5]; $P<0.001$ at 1 year) compared to RP, but there was insufficient evidence to reject the supposition that no difference was seen at 3 or 5 years.

Conclusion: Compared to RP, EBRT-LDR was associated with clinically meaningful worse urinary irritative/obstructive and bowel functions but better urinary incontinence function through 5 years after treatment. These patient-reported functional outcomes may clarify treatment expectations and help inform treatment choices for localized prostate cancer.

Keywords (MeSH)

patient reported outcome measures; radical prostatectomy; low dose rate brachytherapy

Introduction

Radical prostatectomy (RP) is the most commonly used treatment in the United States for intermediate-risk and high-risk localized prostate cancer.[1] Since the publication of the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) randomized trial, there has been increasing interest in dose-escalated radiotherapy combining external beam radiation therapy (EBRT), low dose-rate (LDR) brachytherapy boost, and androgen deprivation therapy (ADT).[2]

Prospective studies comparing RP and EBRT with brachytherapy boost (BT) are lacking and retrospective studies provide conflicting evidence regarding impacts on prostate cancer-specific survival (PCSS) and overall survival (OS).[3–8] In the absence of high-quality evidence regarding survival differences between the treatments, assessments of functional outcomes and health-related quality-of-life (HRQoL) are crucial for patient selection and education. Longitudinal data on patient-reported outcomes (PROs) better enable patients to make evidenced-based and well-informed treatment decisions that are concordant with their values and preferences.[9] Comparisons of functional outcomes or HRQoL between patients treated with RP or EBRT-LDR have not been reported.[3, 4, 6] To address the existing gaps in knowledge, we evaluated a prospective cohort of patients treated with contemporary surgical and radiation therapy techniques to compare PROs—including function, treatment regret, and QoL—between RP and EBRT-LDR over 5 years of follow up.

Materials & Methods

Study population

Men with localized prostate cancer were enrolled in Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR), a multi-site prospective study (NCT01326286).[10] Enrollment occurred from 2011–2012 among men younger than 80 years of age with a prostate-specific antigen (PSA) of <50 ng/dL, and diagnosis of a pathologically-confirmed localized prostate adenocarcinoma within 6 months of study participation. Enrollment occurred at five SEER registry areas and was augmented by the addition of patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database.[11] Institutional review board approval was obtained at each study site, and all participants provided informed consent. Medical records were abstracted for tumor characteristics, PSA levels, and treatment history.

Outcome measures

CEASAR captured patient demographic data and PROs through surveys at baseline, 6 months, and 1, 3, and 5 years. Surveys included the 26-item Expanded Prostate Cancer Index Composite (EPIC) which captures functional domains specific to prostate cancer treatment adverse effects; the 36-item Short Form Health Survey (SF36) which captures

HRQoL domains; and the Clark 5-item treatment-related regret scale.[12–14] Additional questionnaires included the Total Illness Burden Index for Prostate Cancer (TIBI-CaP), Participatory Decision-Making Scale (PDMS), Provider-Dependent Health Care Orientation Scale (PDHCOS), Center for Epidemiologic Studies Depression Scale (CES-D), and the Medical Outcomes Study Social Support Scale (MOS).[15–19]

Minimal clinically important differences

The minimal clinically important differences (MCIDs) in points for EPIC domains (5–7 urinary irritation; 6–9 urinary incontinence; 4–6 bowel function; and 10–12 sexual function) and SF36 domains (7 physical function; 6 emotional well-being; and 9 energy/fatigue) were adapted from previous publications that used an anchor-based and distribution-based approach[7, 20]

Statistical analysis

Demographic and clinical characteristics were summarized with median and quartiles for continuous variables, or frequency and percentage for categorical variables. Treatment group (i.e., EBRT-LDR vs. RP) differences were summarized with Wilcoxon rank-sum or Pearson chi-squared tests. The primary outcome (i.e., EPIC and SF36 domain scores) was summarized with median values and quartiles for each group. In order to determine differences between groups, multivariable longitudinal linear regressions were used and reported as adjusted mean score differences with 95% confidence intervals (CIs). The secondary outcomes were selected *a priori* among patient rating of individual problems and examined using longitudinal logistic regression models with results expressed as adjusted odds ratios (aORs) and the corresponding 95% CIs. All multivariable models adjusted for age (continuous, restricted-cubic-splines), race, TIBI-CaP, D'Amico risk classification, androgen deprivation therapy (ADT) within 1 year after treatment, PDHCOS (continuous, linear), PDMS (continuous, linear), MOS (continuous, linear), CES-D (continuous, linear), time from treatment (continuous, restricted-cubic-splines), site of treatment, baseline SF-36 physical function score (continuous, linear) if outcome is EPIC-26, and other corresponding baseline domain scores (continuous, restricted-cubic-splines). The Huber–White method was used to estimate the robust variance-covariance matrix to account for missing values for covariates.[21, 22] The multiple-imputation chained-equations method was utilized in all regression models to account for missing values for covariates; no outcome variables were imputed.[23] Two-sided *P*-values less than 0.05 were considered statistically significant. All analyses were conducted using R version-4.0. The findings, especially for secondary analyses, should be interpreted as exploratory rather than confirmatory considering the large number of estimates that are reported.

Results

Participants and clinical characteristics

The analysis dataset included 1645 men: 112 in the EBRT-LDR group and 1553 in the RP group. Response rates at 6 months, 1, 3, and 5 years were 95%, 93%, 85%, and 77%, respectively (Supplementary Figure 1). The median follow-up for vital status was 73 months [63, 79]. Baseline characteristics of study participants are summarized in Table 1. EBRT-

LDR patients were older, more likely to be Black, more commonly had high-risk disease and were more likely to have received ADT in the first year after treatment. A subgroup analysis of patients with favorable and unfavorable disease characteristics demonstrated similar differences (Supplementary Table 1).

Most men (91%) treated with RP underwent nerve-sparing procedures, most of which were bilateral (79%). Men who received EBRT-LDR were prescribed a median EBRT dose of 45.0 Gy [45.0, 52.5] to the prostate; LDR boost was prescribed as Iodine-125 (I-125) to a median dose of 90.0 Gy [80.0, 110.0] in 86 men and Palladium-103 (Pd-103) to a median dose of 100.0Gy [92.5, 100.0] in 16 men.

Urinary irritative/obstructive

Baseline urinary irritative/obstructive function did not differ between groups. A clinically meaningful *decline* in urinary irritative/obstructive function (MCID 5–7 points) was reported by men undergoing EBRT-LDR, from a baseline median of 91 points to 75 at 6 months and 81 at 1 year, followed by improvement to 88 at 3 years and 5 years). A clinically meaningful *improvement* in urinary irritative/obstructive function was reported by men undergoing RP, from a baseline median of 88 points to 94 at all subsequent follow-ups (Figure 1, Table 2).

When controlling for baseline scores and other covariates, treatment with EBRT-LDR was associated with clinically meaningful *worse* urinary irritative function compared to treatment with RP through 5 years. Men in the EBRT-LDR group were *more likely* to report moderate-or-big problems with frequent urination symptoms through 3 years followed by resolution at 5 years; and moderate-or-big problems with burning with urination symptoms through 3 years followed by resolution at 5 years. There was insufficient evidence to reject the supposition that there was no difference in urinary function bother (Figure 2, Supplementary Table 2).

Urinary incontinence

Baseline urinary incontinence function did not differ between groups. A clinically meaningful *decline* in urinary incontinence function (MCID 6–9 points) was reported by men undergoing EBRT-LDR, from a baseline median of 100 points to a median of 92 at 5 years. A clinically meaningful *decline* in urinary incontinence function was reported by men undergoing RP, from a baseline median of 100 points to 73 at 5 years (Figure 1, Table 2).

When controlling for baseline scores and other covariates, treatment with EBRT-LDR was associated with clinically meaningful *better* urinary incontinence function compared to treatment with RP through 5 years. Treatment with EBRT-LDR was *inversely* associated with problems with moderate-or-big urinary leakage symptoms through 1 year followed by resolution at 3 years. Men who underwent EBRT-LDR were *less likely* to report using one-or-more pads through 5 years (Figure 2, Supplementary Table 2).

Bowel function

Baseline bowel function did not differ between groups (Figure 1, Table 2). A clinically meaningful *decline* in bowel function (MCID 4–6 points) was reported by men undergoing

EBRT-LDR, from a baseline median of 100 points to 92 at 5 years. A clinically meaningful change was not observed for men undergoing RP.

When controlling for baseline scores and other covariates, treatment with EBRT-LDR (Figure 2, Supplementary Table 2) was associated with clinically meaningful *worse* bowel function compared to treatment with RP through 5 years. Treatment with EBRT-LDR was *more likely* to be associated with problems with moderate-or-big bloody stool symptoms through 1 year followed by resolution at 3 years and problems with moderate-or-big bowel urgency symptoms through 3 years followed by resolution at 5 years. Despite these associations, the absolute rate of moderate-or-big problems with bloody stools was ≤2% for both treatment groups through 5 years, and the absolute rate of moderate-to-big bowel urgency symptoms was 6% for patients treated with EBRT-LDR and 3% for patients treated with RP at 5 years. No statistically significant difference was observed in bowel function bother.

Sexual function

Baseline sexual function (Figure 1, Table 2) was *lower* in the EBRT-LDR vs. RP group (65 [33, 85] vs. 78 [38, 95]; P=0.016). A clinically meaningful *decline* in sexual function (MCID 10–12) was reported by men undergoing EBRT-LDR, from a baseline median of 65 points to 38 at 5 years. A clinically meaningful *decline* in sexual function was reported by men undergoing RP, from a baseline median of 78 points to 35 at 5 years.

When controlling for baseline scores and other covariates, treatment with EBRT-LDR was associated with clinically meaningful *better* sexual function compared with treatment with RP through 1 year followed by resolution at 3 years which was statistically, but not clinically, significant. Treatment with EBRT-LDR was *less likely* to result in problems with moderate-or-big sexual bother through 1 year followed by resolution at 3 years; or lead to insufficient erections through 5 years (Figure 2, Supplementary Table 2).

Hormonal function

Baseline hormone function did not differ between groups (Figure 1, Table 2). A clinically meaningful *decline* in hormone function (MCID 4–6) was reported by men undergoing EBRT-LDR, from a baseline median of 95 points to 90 at 6 months and 1 year, followed by improvement to 95 at years 3 and 5. A clinically meaningful change in hormone function was not reported by men undergoing RP. When controlling for baseline scores and other covariates, there was no clinically meaningful difference in hormone function through 5 years (Figure 2, Supplementary Table 2).

Health-related quality-of-life

Baseline SF36 emotional well-being (Figure 1, Supplementary Table 2) was *higher* in the EBRT-LDR vs. RP group. Otherwise, there were no baseline differences in SF36 physical function or energy/fatigue. When controlling for baseline scores and other covariates, there were no clinically meaningful differences between treatment groups in physical function (MCID 7), emotional well-being (MCID 6), or energy/fatigue (MCID 9) through 5 years (Figure 3, Supplementary Table 2).

Patient-reported treatment-related regret

There was no significant difference in treatment-related regret between RP and EBRT-LDR (Supplementary Table 3).

Discussion

In this prospective cohort study of men with localized prostate cancer, we observed that patients treated with EBRT-LDR and RP continued to have distinct adverse event profiles through 5 years of treatment. Specifically, EBRT-LDR was associated with clinically meaningful worse urinary irritative/obstructive and bowel function and RP was associated with clinically meaningful worse urinary incontinence function. Importantly, though these differences were statistically significant and clinically meaningful, their magnitudes substantially attenuated by 5 years. Compared with RP, EBRT-LDR was also associated with better sexual function at 1 year but no statistically significant difference was seen at 3 or 5 years. There were no clinically meaningful differences in physical function, emotional well-being, energy/fatigue, or treatment-related regret through 5 years.

Studies comparing HRQoL for patients receiving RP vs. EBRT + BT boost are limited. One study examined functional outcomes for patients undergoing RP vs. EBRT + high-dose rate (HDR) boost and found no significant differences between treatment groups for any HRQoL variables.[24] No comparisons of functional outcomes between RP and EBRT-LDR have been published and no randomized trials directly comparing these modalities are ongoing. However, studies comparing EBRT + BT boost to EBRT alone may help put our findings in context. The ASCENDE-RT trial, which compared dose escalated EBRT ± LDR boost for intermediate- and high-risk disease, utilized the SF36v2 survey to assess HRQoL. At 6-year follow up, patients who received EBRT-LDR plus ADT were more likely to experience physician-reported grade ≥3 genitourinary toxicity and worse declines in patient-reported urinary function and physical function vs. those who received EBRT plus ADT.[25] These results mirror the comparisons of EBRT-LDR with RP in the current study, which show persistence of urinary irritative/obstructive symptoms through 5 years for patients receiving EBRT-LDR. Parry et al. reported on patient-reported functional outcomes following EBRT ± HDR boost based on English cancer registry data linked to a survey sent to patients. The study showed that, vs. EBRT alone, EBRT + HDR boost resulted in worse urinary irritation/obstruction scores (adjusted difference −6.1 [−8.8, −3.4]) as assessed by EPIC. Given that surveys were administered at non-uniform times and that only a minority of surveys (33%) had follow up ≥ 18 months, a longitudinal relationship between irritative/obstructive symptoms and treatment with EBRT + HDR is difficult to determine from this study. Additionally, the generalizability of these findings to EBRT-LDR is uncertain.[26] In the present analysis, the largest difference in irritative/obstructive symptoms between EBRT-LDR and RP was observed at 6 months and this difference lessened over time but remained both statistically and clinically significant in favor of RP through 5 years. Notably, urinary function and bowel function *bother* were similar between the two groups at 5 years. Several studies have compared PROs for patients treated with RP vs. EBRT monotherapy, BT monotherapy, or active surveillance and have shown worse erectile dysfunction and

urinary incontinence for RP vs. other treatments, as well as equivalent or worse bowel symptoms for patients treated with EBRT or BT monotherapy vs. other treatments.[27, 28]

This study has several limitations. First, comparisons of RP and EBRT-LDR in prostate cancer may be affected by confounding by external factors. While we attempted to account for differences between groups in a multivariable regression model, confounding likely extends beyond attributes evaluated or captured in this study. Second, missing survey data may also contribute to bias, especially if the data are not missing at random; although we attempted to account for this using multiple imputation methods for independent variables. Third, this population-based cohort included patients treated with EBRT-LDR without standardization of dose, fractionation, or technique. The median I-125 dose in this cohort was lower than consensus guideline doses and those used in the ASCENDE-RT trial, which may have attenuated the toxicities seen.[2] Fourth, data regarding the brachytherapy technique, including the use of rectal spacers, planning technique, seed placement approach, and dosimetric parameters to the target volumes and organs at risk were not prospectively captured in this database, making it challenging to contextualize the toxicity seen in the EBRT-LDR group. Additionally, this study did not enroll patients who received HDR brachytherapy, which is associated in other contexts with more favorable QoL and toxicity outcomes than LDR.[29] Similarly, patients treated with LDR monotherapy, used by some even for high-risk disease[30], were not included. As such, these results are not generalizable to EBRT-HDR or LDR monotherapy treatment, both of which may be associated with superior QoL outcomes than those described for EBRT-LDR. Fifth, 77% of all EBRT-LDR patients were enrolled at a single center, potentially limiting the generalizability of these results. While physician-level data were not collected, it is possible that these patients were treated by relatively few brachytherapists, potentially further limiting generalizability. Sixth, many patients with low-risk disease received interventions in the current study. While treatment of low-risk disease was a more common practice at the time of study enrollment, this may limit generalizability given that current guidelines favor active surveillance for these patients. Seventh, unmatched baseline characteristics or differential non-response bias between the cohorts may have led us to fail to identify a true advantage in sexual function associated with EBRT-LDR vs. RP; though sexual function scores were similar at 5 years, baseline sexual function was higher and the decline was greater in the RP cohort (RP: 78 at baseline, 35 at 5 years; EBRT-LDR: 65 at baseline, 38 at 5 years). Finally, this study considers data through 5 years following treatment, which is expected to capture the majority of functional change a patient may experience; however, it is possible that the data may insufficiently capture late effects. Ten-year data are forthcoming.

In conclusion, in this prospective cohort of men with localized prostate cancer, EBRT-LDR was associated with clinically meaningful worse bowel and worse urinary irritative/obstructive function and RP was associated with worse urinary incontinence function through 5 years. Despite these differences, however, urinary function bother was similar between groups. These findings may clarify treatment expectations and help men make informed treatment choices for their localized prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This study was supported by the Agency for Healthcare Research and Quality (1R01HS019356, 1R01HS022640), the Patient-Centered Outcomes Research Institute (CE-12-11-4667) and the National Cancer Institute (R01CA230352). This work was also supported in part by the Cancer Center Support Grant (NCI Grant P30 CA016672). Data management was facilitated by Vanderbilt University's Research Electronic Data Capture (REDCap) system, which is supported by the Vanderbilt Institute for Clinical and Translational Research grant (UL1TR000445 from National Center for Advancing Translational Sciences). Additional support was provided by the Utah Cancer Registry, which is funded by the National Cancer Institute's SEER Program, Contract No. HHSN261201800016I, the US Centers for Disease Control and Prevention's National Program of Cancer Registries, Cooperative Agreement No. NU58DP006320, with additional support from the University of Utah and Huntsman Cancer Foundation.

Availability of Data and Material:

Due to the nature of this research, participants of this study did not agree for their individual data to be shared publicly, so supporting data is not available.

Abbreviations and acronyms

ADT	androgen deprivation therapy
ASCENDE-RT	Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy
BT	brachytherapy
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
CEASAR	Comparative Effectiveness Analysis of Surgery and Radiation
CES-D	Center for Epidemiologic Studies Depression Scale
EBRT	external beam radiation therapy
EPIC	Expanded Prostate Cancer Index Composite
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
HDR	high dose rate
HRQoL	health-related quality of life
I-125	iodine-125
LDR	low dose rate
MCID	minimal clinically important difference

MOS	Medical Outcomes Study Social Support Scale
NCDB	National Cancer Data Base
OS	overall survival
PCSS	prostate cancer-specific survival
Pd-103	palladium-103
PDHCOS	Provider-Dependent Health Care Orientation Scale
PDMS	Participatory Decision-Making Scale
PRO	patient-reported outcomes
PSA	prostate specific antigen
QoL	quality of life
RP	radical prostatectomy
SEER	Surveillance, Epidemiology, and End Results
SF36	36-item Short Form Health Survey
TIBI-CaP	Total Illness Burden Index for Prostate Cancer

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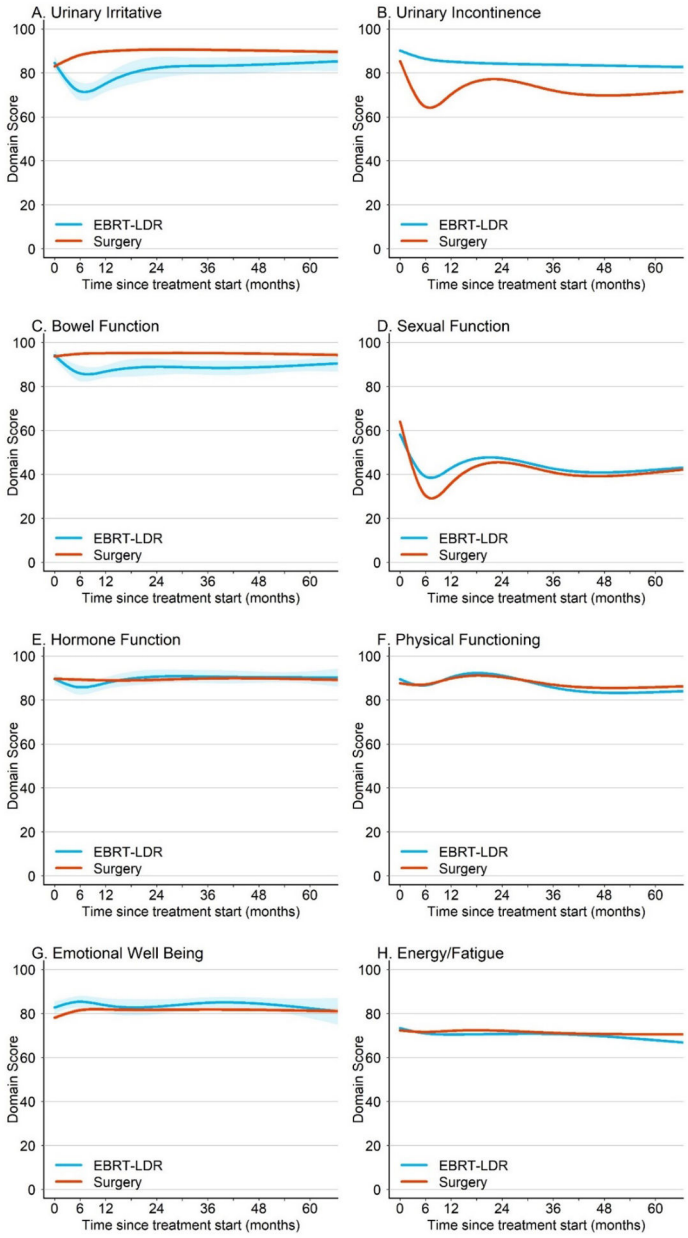

Figure 1:

Unadjusted Expanded Prostate Cancer Index Composite and Short Form Domain Scores Comparing EBRT-LDR vs. RP Through Five Years

Unadjusted domain scores (ranging from 0–100 with higher scores reflecting better function) were tracked at baseline, 6 months, 1 year, 3 years, and 5 years for EPIC and SF36 surveys. Panels (A) through (E) reflect the EPIC domains such as urinary irritation, urinary incontinence, bowel function, sexual function, and hormone function. Panels (F) through (H) reflect the SF36 domains such as physical function, emotional well-being, and energy/fatigue.

All EPIC domains were well-balanced at baseline with the exception of sexual function which was lower in the EBRT-LDR group vs. RP group (65 points [quartiles: 33, 85] vs.

78 points [38, 95]; *P*=0.016). All SF36 domains were well-balanced at baseline with the exception of emotional well-being which was higher in the EBRT-LDR group vs. RP group (86 points [80, 92] vs. 84 points [68, 92]; *P*=0.009).

Abbreviations: External beam radiotherapy plus low-dose brachytherapy (EBRT-LDR); radical prostatectomy (RP); 26-item Expanded Prostate Cancer Index Composite (EPIC); 36-item Short Form (SF36).

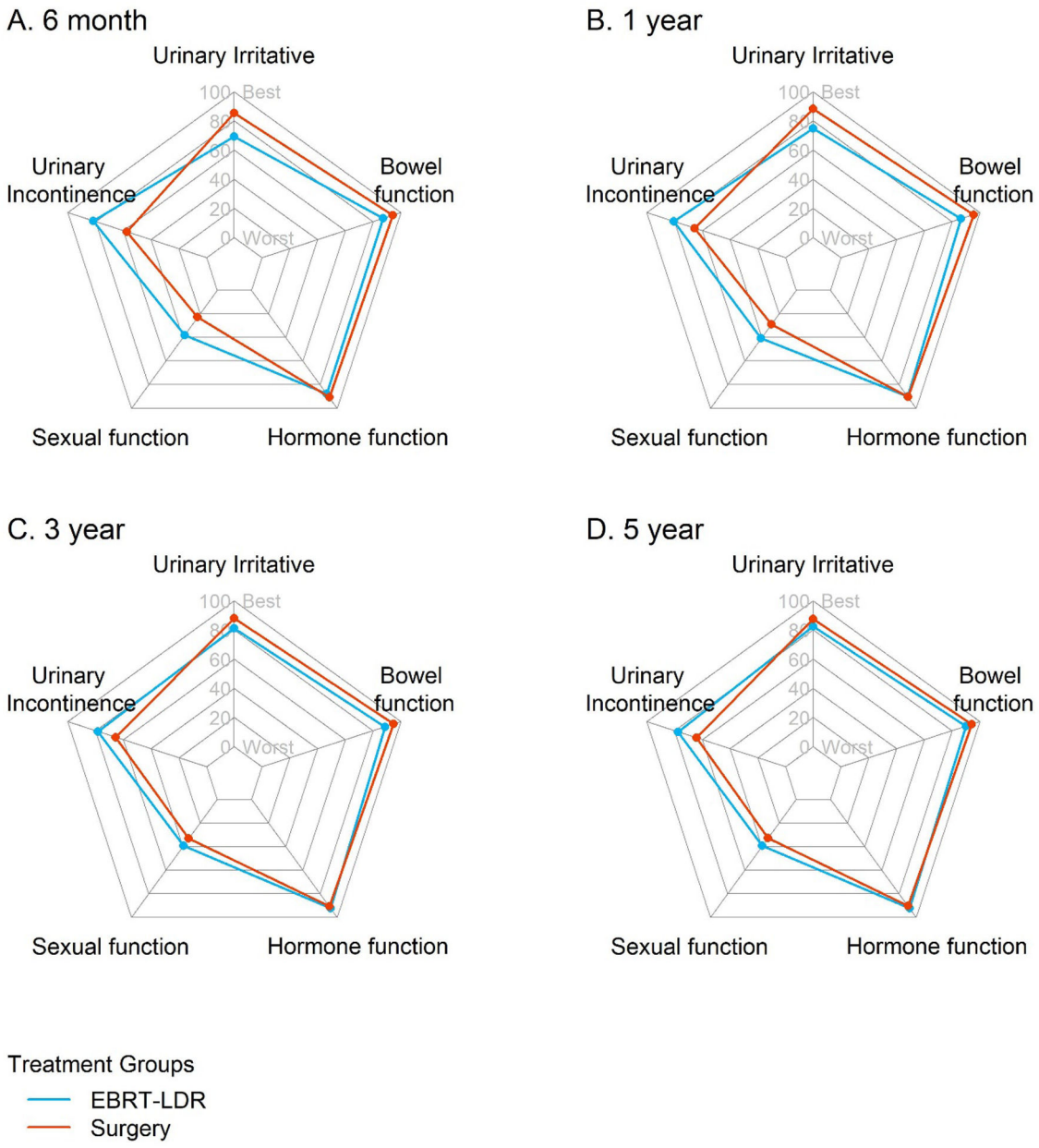

Figure 2:

Adjusted Expanded Prostate Cancer Index Composite Domain Scores Comparing EBRT-LDR vs. RP Through Five Years

Adjusted domain scores for EPIC function (ranging from 0–100 with higher scores reflecting better function) were represented through radar plots by comparing baseline to (A) 6 months, (B) 1 year, (C) 3 years, and (D) 5 years in the EBRT-LDR group (blue line) vs. RP group (red line). The EPIC minimum clinically important difference scores were 5–7 points for urinary irritative/obstructive function, 6–9 points for urinary incontinence, 4–6 points for bowel function, 10–12 points for sexual function, and 4–6 points for hormone function. The outermost part of the radar plot represents best function (score of 100) and the center represents worst function (score of 0). The adjusted domain scores were generated by

applying a multivariable linear regression model that accounts for baseline scores and other covariates.

EBRT-LDR, when compared to RP, was associated with a clinically meaningful decline in urinary irritative/obstructive function (−5-point difference [95% CI −8.7, −1.3]; P=0.008) and bowel function (−4-point difference [95% CI −6.9, −1.1]; P=0.006) through 5 years. RP, when compared to EBRT-LDR, was associated with a clinically meaningful decline in urinary incontinence (−13.3-point difference [95% CI −7.7, −18.9]; P<0.001) through 5 years and sexual function (−12-point difference [95% −6.5, −17.5]; P<0.001) through 1 year.

Abbreviations: External beam radiotherapy plus low-dose brachytherapy (EBRT-LDR); radical prostatectomy (RP); 26-item Expanded Prostate Cancer Index Composite (EPIC); 36-item Short Form (SF36); 95% confidence interval (95% CI).

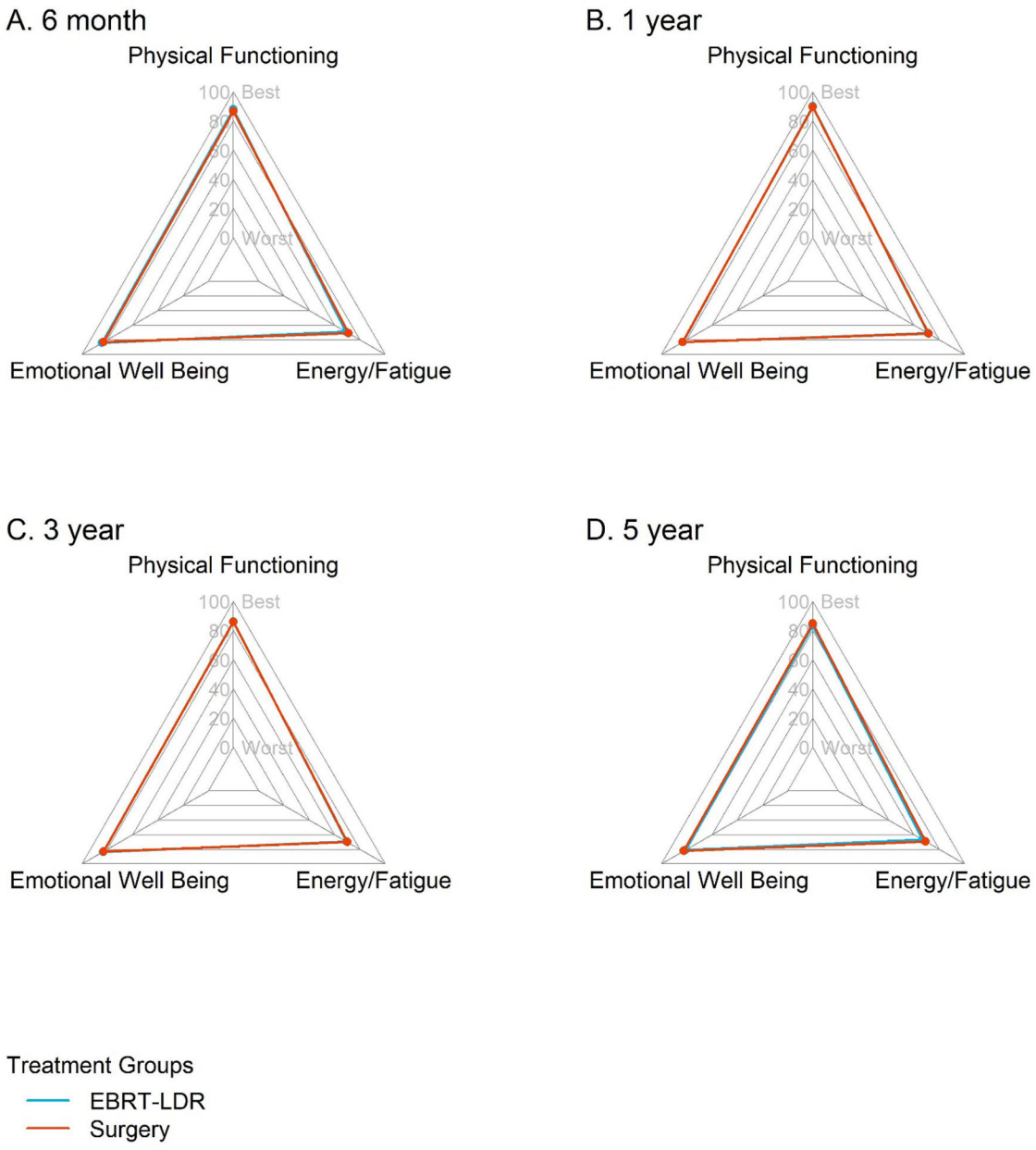

Figure 3:

Adjusted Short Form Domain Scores Comparing EBRT-LDR vs. Radical Prostatectomy Through Five Years

Adjusted domain scores for SF36 function (ranging from 0–100 with higher scores reflecting better function) were represented through radar plots by comparing baseline to (A) 6 months, (B) 1 year, (C) 3 years, and (D) 5 years in the EBRT-LDR group (blue line) vs. RP group (red line). The SF36 minimum clinically important difference scores were 7 points for physical function, 6 points for emotional well-being, and 9 points for energy/fatigue. The outermost part of the radar plot represents best function (score of 100) and the center represents worst function (score of 0). The adjusted domain scores were generated by applying a multivariable linear regression model that accounts for baseline scores and other

covariates. There were no clinically meaningful changes in SF36 function between the two groups through 5 years.

Abbreviations: External beam radiotherapy plus low-dose brachytherapy (EBRT-LDR); radical prostatectomy (RP); 36-item Short Form (SF36).

Table 1:

Baseline Participant and Treatment Clinical Characteristics

		EBRT-LDR (n=112)	RP (n=1533)	Combined (n=1645)	*P*-value*
Age at diagnosis, median (Q_1, Q_3)		66 (60, 71)	62 (57, 66)	62 (57, 67)	<0.001
Race	White	82 (74%)	1136 (75%)	1218 (75%)	0.026
	Black	23 (21%)	190 (12%)	213 (13%)	
	Hispanic	3 (3%)	125 (8%)	128 (8%)	
	Asian	1 (1%)	46 (3%)	47 (3%)	
	Other	2 (2%)	23 (2%)	25 (2%)	
Education	Less than high school	6 (6%)	131 (9%)	137 (9%)	0.78
	High school graduate	21 (21%)	302 (21%)	323 (21%)	
	Some college	26 (26%)	316 (22%)	342 (22%)	
	College graduate	23 (23%)	345 (24%)	368 (24%)	
	Graduate/professional school	24 (24%)	351 (24%)	375 (24%)	
Marital status	Not married	23 (23%)	246 (17%)	269 (17%)	0.14
	Married	78 (77%)	1196 (83%)	1274 (83%)	
Total Illness Burden Index for Prostate Cancer[a]	0–2	24 (24%)	483 (33%)	507 (33%)	0.12
	3–4	49 (48%)	625 (43%)	674 (43%)	
	≥5	29 (28%)	344 (24%)	373 (24%)	
D'Amico risk grouping[b]	Low Risk	35 (31%)	640 (42%)	675 (41%)	0.039
	Intermediate Risk	50 (45%)	637 (42%)	687 (42%)	
	High Risk	27 (24%)	254 (17%)	281 (17%)	
PSA at diagnosis, corrected	<4	17 (15%)	301 (20%)	318 (19%)	0.50
	≥4 to <10	85 (76%)	1058 (69%)	1143 (69%)	
	≥10 to <20	8 (7%)	134 (9%)	142 (9%)	
	≥20 to <50	2 (2%)	40 (3%)	42 (3%)	
Clinical tumor stage	T1	86 (77%)	1147 (75%)	1233 (75%)	0.67
	T2	26 (23%)	383 (25%)	409 (25%)	
Gleason score on biopsy	≤6	38 (34%)	750 (49%)	788 (48%)	0.001
	3 + 4	40 (36%)	460 (30%)	500 (30%)	
	4 + 3	12 (11%)	170 (11%)	182 (11%)	
	≥8	22 (20%)	149 (10%)	171 (10%)	
Accrual site	Site 1	1 (1%)	128 (8%)	129 (8%)	<0.001
	Site 2	86 (77%)	196 (13%)	282 (17%)	
	Site 3	2 (2%)	447 (29%)	449 (27%)	
	Site 4	15 (13%)	395 (26%)	410 (25%)	
	Site 5	3 (3%)	245 (16%)	248 (15%)	
	Site 6	5 (4%)	122 (8%)	127 (8%)	

		EBRT-LDR (n=112)	RP (n=1533)	Combined (n=1645)	*P*-value*
Any ADT in first year after treatment	Yes	18 (16%)	75 (5%)	93 (6%)	<0.001
	No	93 (84%)	1442 (95%)	1535 (94%)	
Participatory decision-making scale, median (Q_1, Q_3)[c]		79 (71, 89)	86 (71, 93)	86 (71, 93)	0.22
Provider-dependent health care orientation scale, median (Q_1, Q_3)[d]		17 (6, 35)	21 (8, 38)	21 (8, 38)	0.60
Social support scale, median (Q_1, Q_3)[e]		95 (75, 100)	95 (75, 100)	95 (75, 100)	0.52
Depression scale, median (Q_1, Q_3)[f]		11 (4, 22)	15 (4, 30)	15 (4, 30)	0.093
Surgery type	None	N/A	95 (9%)	N/A	N/A
	Unilateral nerve-sparing	N/A	128 (12%)	N/A	N/A
	Bilateral nerve-sparing	N/A	859 (79%)	N/A	N/A
Received pelvic radiation	Yes	10 (10%)	N/A	N/A	N/A
	No	95 (90%)	N/A	N/A	N/A
Received IMRT	Yes	89 (85%)	N/A	N/A	N/A
	No	16 (15%)	N/A	N/A	N/A
Received IGRT	Yes	77 (79%)	N/A	N/A	N/A
	No	20 (21%)	N/A	N/A	N/A
EBRT dose per fraction	≤2 Gy	91 (99%)	N/A	N/A	N/A
	2–3 Gy	1 (1%)	N/A	N/A	N/A
	>3 Gy	0	N/A	N/A	N/A
Median EBRT radiation dose (Q_1, Q_3), Gy		45 (45, 52.5)	N/A	N/A	N/A
Number receiving I-125 (%)		86 (84%)	N/A	N/A	N/A
Median I-125 dose (Q_1, Q_3), Gy		91 (80, 110)	N/A	N/A	N/A
Number receiving Pd-103 (%)		16 (16%)	N/A	N/A	N/A
Median Pd-103 dose (Q_1, Q_3), Gy		100 (92, 100)	N/A	N/A	N/A

*Assessed EBRT-LDR vs. RP group using either a Wilcoxon test for continuous variables or Pearson *Chi*-squared test for categorical variables.

[a]Measures patient illness and co-morbidity burden, with higher scores reflecting greater severity and number of co-morbidities.

[b]Classified by D'Amico risk grouping: Low risk defined as Gleason score <6 and PSA <10 ng/mL and clinical stage T1c-T2a; intermediate risk defined as Gleason score 7 or PSA 10–20 ng/mL or clinical stage T2b; high risk defined as Gleason score 8 or PSA >20 ng/mL or clinical stage T2c-T3.

[c]Measures patient decision-making style (scale 0–100) using the Provider-Dependent Health Care Orientation Scale, with higher scores reflecting increased patient choice, control, and responsibility.

[d]Measures patient decision-making passivity (scale 0–100) using the Participatory Decision-Making Scale, with higher scores reflecting increased passivity.

[e]Measures degree of social support (scale 0–100) using the Medical Outcomes Study Social Support Scale, with higher scores reflecting greater support.

[f]Measures patient depression (scale 0–100) using the Epidemiologic Studies Depression Scale, with higher scores reflecting more severe depressive symptoms.

Abbreviations: External beam radiotherapy plus low-dose brachytherapy (EBRT-LDR); radical prostatectomy (RP); prostate-specific antigen (PSA); androgen deprivation therapy (ADT); intensity modulated radiotherapy (IMRT); image-guided radiotherapy (IGRT); Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), 1st and 3rd quartiles (Q_1 , Q_3).

Table 2:

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

Time	EBRT-LDR (N=112)	RP (N=1533)	*P*-value[a]	EBRT-LDR vs. RP Effect	[95% CI]	*P*-value
EPIC Urinary Function Domains[a]						
Urinary irritative/obstructive	Unadjusted median (Q_1, Q_3) domain score			Adjusted linear model; effect size = point difference between groups		
Baseline	91 (75, 95)	88 (75, 100)	0.446	-	-	-
6 months	75 (56, 88)	94 (81, 100)	0.001	−16.3*	[−19.9, −12.7]	<0.001
1 year	81 (66, 88)	94 (81, 100)	0.001	−13.4*	[−17.6, −9.2]	<0.001
3 years	88 (75, 100)	94 (88, 100)	0.001	−6.9*	[−10.6, −3.2]	<0.001
5 years	88 (75, 94)	94 (88, 100)	0.001	−5.0*	[−8.7, −1.3]	0.008
Urinary Incontinence	Unadjusted median (Q_1, Q_3) domain score			Adjusted linear model; effect size = point difference between groups		
Baseline	100 (85, 100)	100 (79, 100)	0.481	-	-	-
6 months	94 (73, 100)	67 (46, 94)	0.001	24.2*	[20.1, 28.2]	<0.001
1 year	92 (73, 100)	75 (52, 100)	0.001	15.1*	[11.0, 19.2]	<0.001
3 years	94 (73, 100)	75 (54, 100)	0.001	12.8*	[8.0, 17.6]	<0.001
5 years	92 (73, 100)	73 (52, 100)	0.001	13.3*	[7.7, 18.9]	<0.001
EPIC Bowel Function Domain[a]						
Bowel Function	Unadjusted median (Q_1, Q_3) domain score			Adjusted linear model; effect size = point difference between groups		
Baseline	100 (92, 100)	100 (92, 100)	0.75	-	-	-
6 months	92 (79, 100)	100 (96, 100)	0.001	−7.1*	[−10.4, −3.9]	<0.001
1 year	92 (79, 100)	100 (96, 100)	0.001	−9.1*	[−11.9, −6.4]	<0.001
3 years	96 (83, 100)	100 (96, 100)	0.001	−6.3*	[−9.4, −3.1]	<0.001
5 years	92 (83, 100)	100 (96, 100)	0.001	−4.0*	[−6.9, −1.1]	0.006
EPIC Sexual Function Domain[a]						
Sexual function	Unadjusted median (Q_1, Q_3) domain score			Adjusted linear model; effect size = point difference between groups		

Time	EBRT-LDR	RP		EBRT-LDR vs. RP		
	(N=112)	(N=1533)	*P*-value[a]	Effect	[95% CI]	*P*-value
Baseline	65 (33, 85)	78 (38, 95)	0.016	-	-	-
6 months	38 (6, 70)	22 (5, 53)	0.011	15.2*	[9.1, 21.3]	<0.001
1 year	40 (7, 70)	28 (7, 65)	0.252	12.0*	[6.5, 17.5]	<0.001
3 years	37 (7, 70)	33 (10, 70)	0.721	6.0	[0.1, 12.0]	0.046
5 years	38 (7, 75)	35 (7, 73)	0.774	6.7	[−0.1, 13.4]	0.052
EPIC Hormone Function Domain[a]						
Hormone function	Unadjusted median (Q_1, Q_3) domain score			Adjusted linear model; effect size = point difference between groups		
Baseline	95 (85, 100)	95 (85, 100)	0.484	-	-	-
6 months	90 (80, 100)	95 (85, 100)	0.048	−3.0	[−5.7, −0.3]	0.028
1 year	90 (80, 100)	95 (81, 100)	0.085	−0.2	[−3.3, 2.8]	0.877
3 years	95 (85, 100)	95 (85, 100)	0.868	1.6	[−1.5, 4.7]	0.321
5 years	95 (85, 100)	95 (85, 100)	0.828	1.8	[−1.2, 4.8]	0.249

*Represents a clinically meaningful difference defined as meeting statistical significance and clinical significance. Clinical significance is defined as the difference between groups exceeding the MCID. EPIC MCID was defined as 5–7 points for urinary irritative/obstructive, 6–9 points for urinary incontinence, 4–6 points for bowel function, 10–12 points for sexual function, and 4–6 points for hormonal function.

[a]Domain scores for EPIC are represented as unadjusted values in the left column, scaled from 0 to 100 with higher scores representing better function. Unadjusted scores are represented as median values with interquartile range (25^{th} percentile, 75^{th} percentile). The right column values are based on a multivariable regression model with the effect size representing the adjusted mean point difference using surgery as the reference group. Effect size negative values reflect worse patient-reported outcomes in the EBRT-LDR group while 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, use of androgen deprivation therapy, use of pelvic radiation therapy, depression scores, decision-making style scores, social support scores, time from treatment, geographic site of treatment, and corresponding baseline scores.

Abbreviations: External beam radiotherapy plus low-dose brachytherapy (EBRT-LDR); radical prostatectomy (RP); 95% confidence interval (95% CI); adjusted odds ratio (aOR); 26-item Expanded Prostate Cancer Index Composite (EPIC); minimum clinically important difference (MCID); 1^{st} and 3^{rd} quartiles (Q_1, Q_3).