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Patient-reported Outcomes After External Beam Radiotherapy With Low Dose Rate Brachytherapy Boost vs Radical Prostatectomy for Localized Prostate Cancer: Five-year Results From a Prospective Comparative Effectiveness Study

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

Materials and Methods: From 2011-2012, men aged <80 years with localized prostate adenocarcinoma were enrolled and followed longitudinally. Patient reported outcomes 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 external beam radiation therapy with low dose rate brachytherapy boost and 1,553 treated with radical prostatectomy. Compared to radical prostatectomy, external beam radiation therapy with low dose rate brachytherapy boost was associated with clinically meaningful worse urinary irritative/obstructive (adjusted mean score difference [95% confidence interval]: 5.0 [−8.7, −1.3]; $P = .008$ at 5 years) and better urinary incontinence function (13.3 [7.7, 18.9]; $P < .001$ at 5 years) through 5 years. Urinary function bother was similar between groups ($P > .4$ at all timepoints). Treatment with external beam radiation therapy with low dose rate brachytherapy boost was associated with worse bowel function (−4.0 [−6.9, −1.1]; $P = .006$ at 5 years) through 5 years compared to radical prostatectomy. Treatment with external beam radiation therapy with low dose rate brachytherapy boost was associated with better sexual function at 1 year (12.0 [6.5, 17.5]; $P < .001$ at 1 year) compared to

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radical prostatectomy, but there was insufficient evidence to reject the supposition that no difference was seen at 3 or 5 years.

Conclusions: Compared to radical prostatectomy, external beam radiation therapy with low dose rate brachytherapy boost 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.

Key Words: patient reported outcome measures, prostatectomy, brachytherapy

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 (BT) boost, and androgen deprivation therapy (ADT).[2]

Prospective studies comparing RP and EBRT with BT are lacking, and retrospective studies provide conflicting evidence regarding impacts on prostate cancer-specific survival and overall survival.[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 quality of life (QoL)—between RP and EBRT-LDR over 5 years of follow-up.

MATERIALS AND 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 PSA of $<$50 ng/dL, and diagnosis of a pathologically confirmed localized prostate adenocarcinoma within 6 months of study participation. Enrollment occurred at 5 Surveillance, Epidemiology, and End Results 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 from Vanderbilt University Medical Center (coordinating center, IRB No. 110299) and from each participating site. 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

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Conflict of Interest: Brian De: Medical Survey Income: Sermo, Inc. Daniel A. Barocas: Advisory Board: Ambu, Lantheus, Pacific Edge. Christopher J. D. Wallis: Janssen Oncology, SESEN Bio, Precision Point Specialty LLC. Chad Tang: Bayer, Diffusion Pharmaceuticals, Wolters Kluwer.

Ethics Statement: Institutional Review Board approval was obtained from Vanderbilt University Medical Center (coordinating center, IRB No. 110299) and from each participating site.

Author Contributions: Brian De: Conceptualization, Data curation, writing—original draft, and writing—review and editing. Dario Pasalic: Conceptualization, data curation, writing—original draft, and writing—review and editing. Daniel A. Barocas: Conceptualization, data curation, funding acquisition, investigation, methodology, writing—original draft, and writing—review and editing. Li-Ching Huang: Data curation, formal analysis, writing—original draft, and writing—review and editing. Zhiguo Zhao: Data curation, formal analysis, writing—original draft, and writing—review and editing. Tatsuki Koyama: Data curation, formal analysis, writing—original draft, and writing—review and editing. Chad Tang: Writing—review and editing. Michael Goodman: Investigation, methodology, and writing—review and editing. Ann S. Hamilton: Investigation, methodology, and writing—review and editing. Xiao-Cheng Wu: Investigation, methodology, and writing—review and editing. Lisa E. Paddock: Investigation, methodology, and writing—review and editing. Antoinette M. Stroup: Investigation, methodology, and writing—review and editing. Matthew R. Cooperberg: Investigation, methodology, and writing—review and editing. Mia Hashibe: Investigation, methodology, and writing—review and editing. Brock B. O'Neil: Investigation, methodology, and writing—review and editing. Sherrie H. Kaplan: Investigation, methodology, and writing—review and editing. Sheldon Greenfield: Investigation, methodology, and writing—review and editing. David F. Penson: Conceptualization, data curation, funding acquisition, investigation, methodology, and writing—review and editing. Karen E. Hoffman: Conceptualization, data curation, writing—original draft, and writing—review and editing.

Data Availability: 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.

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 TIBI-CaP (Total Illness Burden Index for Prostate Cancer), PDMS (Participatory Decision-Making Scale), PDHCOS (Provider-Dependent Health Care Orientation Scale), CES-D (Center for Epidemiologic Studies Depression Scale), and the MOS (Medical Outcomes Study Social Support Scale).[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]

Demographic and clinical characteristics were summarized with median and quartiles for continuous variables, or frequency and percentage for categorical variables. Treatment group (ie, EBRT-LDR vs RP) differences were summarized with Wilcoxon rank-sum or Pearson chi-squared tests. The primary outcome (ie, 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 and the corresponding 95% CIs. All multivariable models adjusted for age (continuous, restricted-cubic-splines), race, TIBI-CaP, D'Amico risk classification, 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 .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 data set included 1,645 men: 112 in the EBRT-LDR group and 1.553 in the RP group. Response rates at 6 months, and 1, 3, and 5 years were 95%, 93%, 85%, and 77%, respectively (see supplementary Figure, https://www.jurology.com). 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, https://www.jurology.com).

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 to a median dose of 90.0 Gy (80.0, 110.0) in 86 men and palladium-103 to a median dose of 100.0 Gy (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 and 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 and supplementary Table 2, https://www.jurology.com).

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

Table 1. *Baseline Participant and Treatment Clinical Characteristics*

	EBRT-LDR (n = 112)	RP (n = 1,533)	*P* value[a]
Age at diagnosis, median (Q_1, Q_3), y	66 (60, 71)	62 (57, 66)	<.001
Race, No. (%)			
White	82 (74)	1,136 (75)	.026
Black	23 (21)	190 (12)	
Hispanic	3 (3)	125 (8)	
Asian	1 (1)	46 (3)	
Other	2 (2)	23 (2)	
Education, No. (%)			
Less than high school	6 (6)	131 (9)	.78
High school graduate	21 (21)	302 (21)	
Some college	26 (26)	316 (22)	
College graduate	23 (23)	345 (24)	
Graduate/professional school	24 (24)	351 (24)	
Marital status, No. (%)			
Not married	23 (23)	246 (17)	.14
Married	78 (77)	1,196 (83)	
Total Illness Burden Index for Prostate Cancer, No. (%)[b]			
0-2	24 (24)	483 (33)	.12
3-4	49 (48)	625 (43)	
≥5	29 (28)	344 (24)	
D'Amico risk grouping, No. (%)[c]			
Low Risk	35 (31)	640 (42)	.039
Intermediate Risk	50 (45)	637 (42)	
High Risk	27 (24)	254 (17)	
PSA at diagnosis, corrected, No. (%)			
<4	17 (15)	301 (20)	.50
≥4 to <10	85 (76)	1,058 (69)	
≥10 to <20	8 (7)	134 (9)	
≥20 to <50	2 (2)	40 (3)	
Clinical tumor stage, No. (%)			
T1	86 (77)	1,147 (75)	.67
T2	26 (23)	383 (25)	
Gleason score on biopsy, No. (%)			
≤6	38 (34)	750 (49)	.001
3+4	40 (36)	460 (30)	
4+3	12 (11)	170 (11)	
≥8	22 (20)	149 (10)	
Accrual site, No. (%)			
Site 1	1 (1)	128 (8)	< .001
Site 2	86 (77)	196 (13)	
Site 3	2 (2)	447 (29)	
Site 4	15 (13)	395 (26)	
Site 5	3 (3)	245 (16)	
Site 6	5 (4)	122 (8)	
Any ADT in first year after treatment, No. (%)			
Yes	18 (16)	75 (5)	< .001
No	93 (84)	1,442 (95)	
Participatory decision-making scale, median (Q_1, Q_3)[d]	79 (71, 89)	86 (71, 93)	.22
Provider-dependent health care orientation scale, median (Q_1, Q_3)[e]	17 (6, 35)	21 (8, 38)	.60
Social support scale, median (Q_1, Q_3)[f]	95 (75, 100)	95 (75, 100)	.52
Depression scale, median (Q_1, Q_3)[g]	11 (4, 22)	15 (4, 30)	.093
Surgery type, No. (%)			
No nerve-sparing	N/A	95 (9)	N/A
Unilateral nerve-sparing	N/A	128 (12)	N/A
Bilateral nerve-sparing	N/A	859 (79)	N/A
Received pelvic radiation, No. (%)			
Yes	10 (10)	N/A	N/A
No	95 (90)	N/A	N/A
Received IMRT, No. (%)			
Yes	89 (85)	N/A	N/A
No	16 (15)	N/A	N/A
Received IGRT, No. (%)			
Yes	77 (79)	N/A	N/A
No	20 (21)	N/A	N/A
EBRT dose per fraction, No. (%)			
≤2 Gy	91 (99)	N/A	N/A
>2-<3 Gy	1 (1)	N/A	N/A
≥3 Gy	0	N/A	N/A
Median EBRT radiation dose (Q_1, Q_3), Gy	45 (45, 52.5)	N/A	N/A
Receiving I-125, No. (%)	86 (84)	N/A	N/A

(continued)

Table 1. (*continued*)

	EBRT-LDR (n = 112)	RP (n = 1,533)	*P* value[a]
Median I-125 dose (Q_1, Q_3), Gy	91 (80, 110)	N/A	N/A
Receiving Pd-103, No. (%)	16 (16)	N/A	N/A
Median Pd-103 dose (Q_1, Q_3), Gy	100 (92, 100)	N/A	N/A

Abbreviations: ADT, androgen deprivation therapy; EBRT-LDR, external beam radiotherapy plus low-dose brachytherapy; Gy, Gray; IGRT, image-guided radiotherapy; IMRT, intensity modulated radiotherapy; N/A, not applicable; PSA, prostate-specific antigen; Q, quartile; RP, radical prostatectomy.
[a] Assessed EBRT-LDR vs RP group using either a Wilcoxon test for continuous variables or Pearson χ^2 test for categorical variables.
[b] Measures patient illness and comorbidity burden, with higher scores reflecting greater severity and number of comorbidities.
[c] 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.
[d] 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.
[e] Measures patient decision making passivity (scale 0-100) using the Participatory Decision-Making Scale, with higher scores reflecting increased passivity.
[f] Measures degree of social support (scale 0-100) using the Medical Outcomes Study Social Support Scale, with higher scores reflecting greater support.
[g] Measures patient depression (scale 0-100) using the Epidemiologic Studies Depression Scale, with higher scores reflecting more severe depressive symptoms.

reported by men undergoing RP, from a baseline median of 100 points to 73 at 5 years (Figure 1 and 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 1 or more pads through 5 years (Figure 2 and supplementary Table 2, https://www.jurology.com).

Bowel Function

Baseline bowel function did not differ between groups (Figure 1 and 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 was associated with clinically meaningful worse bowel function compared to treatment with RP through 5 years (Figure 2 and supplementary Table 2, https://www.jurology.com). 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 was lower in the EBRT-LDR vs RP group (65 [33, 85] vs 78 [38, 95]; $P = .016$; Figure 1 and Table 2). 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 and supplementary Table 2, https://www.jurology.com).

Hormonal Function

Baseline hormone function did not differ between groups (Figure 1 and 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 and supplementary Table 2, https://www.jurology.com).

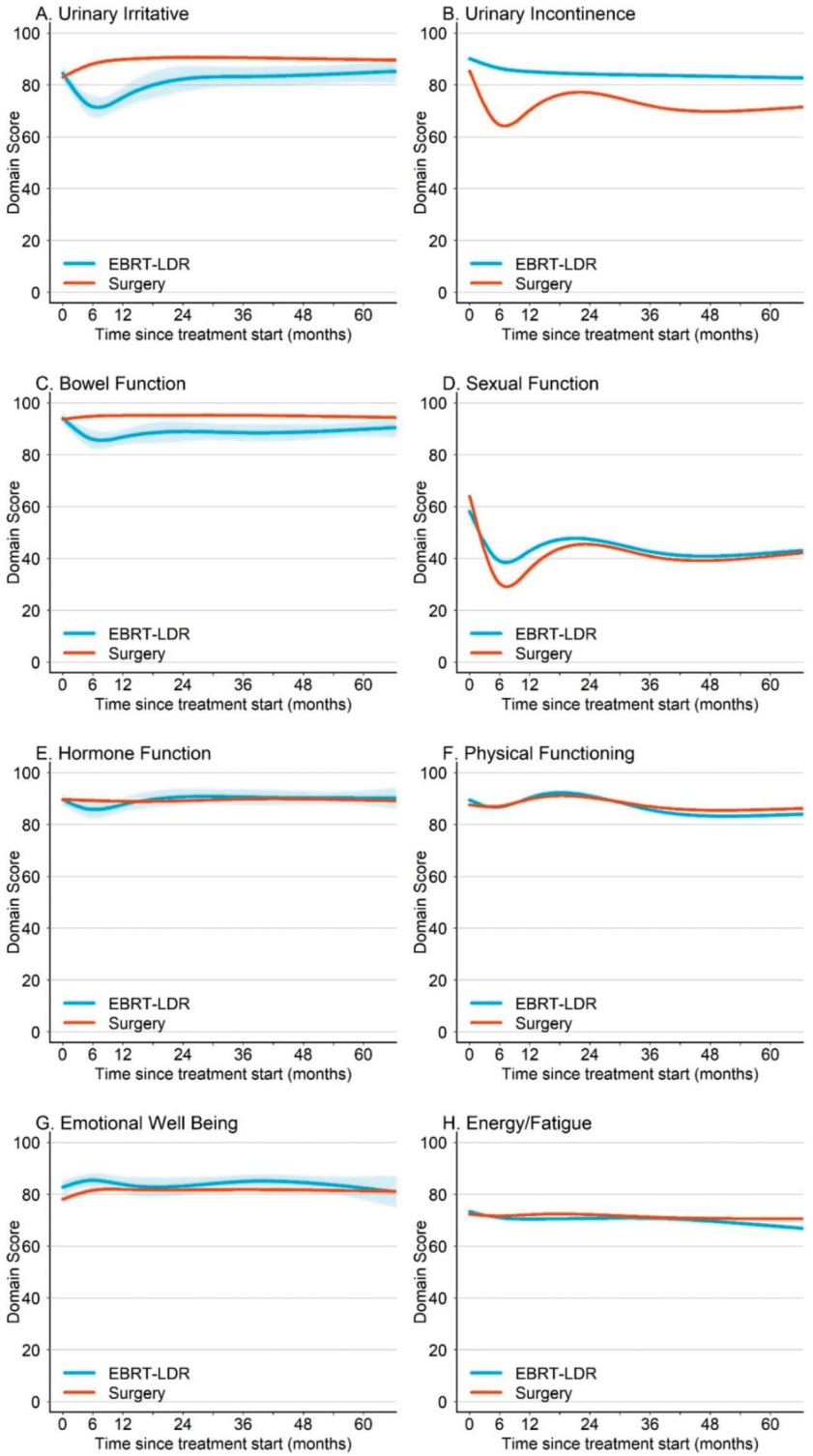

Figure 1. Unadjusted 26-item Expanded Prostate Cancer Index Composite and 36-item Short Form domain scores comparing external beam radiotherapy plus low-dose brachytherapy (EBRT-LDR) vs radical prostatectomy through 5 years. Unadjusted domain scores (ranging from 0-100 with higher scores reflecting better function) were tracked at baseline, 6 months, 1 year, 3 years, and 5 years for 26-item Expanded Prostate Cancer Index Composite and 36-item Short Form surveys. A-E, 26-item Expanded Prostate Cancer Index Composite domains urinary irritation (*A*), urinary incontinence (*B*), bowel function (*C*), sexual function (*D*), and hormone function (*E*). F-H, 36-item Short Form domains such as physical function (*F*), emotional well-being (*G*), and energy/fatigue (*H*). All 26-item Expanded Prostate Cancer Index Composite domains were well-balanced at baseline with the exception of sexual function, which was lower in the EBRT-LDR group vs radical prostatectomy group (65 points [quartiles: 33, 85] vs 78 points [38, 95]; $P = .016$). All 36-item Short Form domains were well-balanced at baseline with the exception of emotional well-being, which was higher in the EBRT-LDR group vs radical prostatectomy group (86 points [80, 92] vs 84 points [68, 92]; $P = .009$).

Table 2. *Unadjusted and Adjusted Patient-reported Outcomes on the Expanded Prostate Cancer Index Composite Domain Scores Stratified by Treatment Group and Time Point*

	EBRT-LDR	RP	EBRT-LDR vs RP		
	(N = 112)	(N = 1,533)	Effect	(95% CI)	
Time	Unadjusted median (Q_1, Q_3) domain score		Adjusted linear model[a]		*P* value
		EPIC Urinary Function Domains[b]			
Urinary irritative/obstructive					
Baseline	91 (75, 95)	88 (75, 100)	-	-	-
6 mo	75 (56, 88)	94 (81, 100)	−16.3[c]	(−19.9, −12.7)	< .001
1 y	81 (66, 88)	94 (81, 100)	−13.4[c]	(−17.6, −9.2)	< .001
3 y	88 (75, 100)	94 (88, 100)	−6.9[c]	(−10.6, −3.2)	< .001
5 y	88 (75, 94)	94 (88, 100)	−5.0[c]	(−8.7, −1.3)	.008
Urinary incontinence					
Baseline	100 (85, 100)	100 (79, 100)	-	-	-
6 mo	94 (73, 100)	67 (46, 94)	24.2[c]	(20.1, 28.2)	< .001
1 y	92 (73, 100)	75 (52, 100)	15.1[c]	(11.0, 19.2)	< .001
3 y	94 (73, 100)	75 (54, 100)	12.8[c]	(8.0, 17.6)	< .001
5 y	92 (73, 100)	73 (52, 100)	13.3[c]	(7.7, 18.9)	< .001
		EPIC Bowel Function Domain[b]			
Bowel function					
Baseline	100 (92, 100)	100 (92, 100)	-	-	-
6 mo	92 (79, 100)	100 (96, 100)	−7.1[c]	(−10.4, −3.9)	< .001
1 y	92 (79, 100)	100 (96, 100)	−9.1[c]	(−11.9, −6.4)	< .001
3 y	96 (83, 100)	100 (96, 100)	−6.3[c]	(−9.4, −3.1)	< .001
5 y	92 (83, 100)	100 (96, 100)	−4.0[c]	(−6.9, −1.1)	.006
		EPIC Sexual Function Domain[b]			
Sexual function					
Baseline	65 (33, 85)	78 (38, 95)	-	-	-
6 mo	38 (6, 70)	22 (5, 53)	15.2[c]	(9.1, 21.3)	< .001
1 y	40 (7, 70)	28 (7, 65)	12.0[c]	(6.5, 17.5)	< .001
3 y	37 (7, 70)	33 (10, 70)	6.0	(0.1, 12.0)	.046
5 y	38 (7, 75)	35 (7, 73)	6.7	(−0.1, 13.4)	.052
		EPIC Hormone Function Domain[b]			
Hormone function					
Baseline	95 (85, 100)	95 (85, 100)	-	-	-
6 mo	90 (80, 100)	95 (85, 100)	−3.0	(−5.7, −0.3)	.028
1 y	90 (80, 100)	95 (81, 100)	−0.2	(−3.3, 2.8)	.877
3 y	95 (85, 100)	95 (85, 100)	1.6	(−1.5, 4.7)	.321
5 y	95 (85, 100)	95 (85, 100)	1.8	(−1.2, 4.8)	.249

Abbreviations: CI, confidence interval; EBRT-LDR, external beam radiotherapy plus low-dose brachytherapy; EPIC, 26-Item Expanded Prostate Cancer Index Composite; Q, quartile; RP, radical prostatectomy.

[a] Effect size = point difference between groups.

[b] 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 (25th percentile, 75th 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.

[c] 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. EPIC minimum clinically important difference 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.

HRQoL

Baseline SF36 emotional well-being was higher in the EBRT-LDR vs RP group (Figure 1 and supplementary Table 2, https://www.jurology.com). 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 and supplementary Table 2, https://www.jurology.com).

Patient-reported Treatment-related Regret

There was no significant difference in treatment-related regret between RP and EBRT-LDR (supplementary Table 3, https://www.jurology.com).

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

Figure 2. Adjusted 26-item Expanded Prostate Cancer Index Composite domain scores comparing external beam radiotherapy plus low-dose brachytherapy (EBRT-LDR) vs radical prostatectomy through 5 years. Adjusted domain scores for 26-item Expanded Prostate Cancer Index Composite function (ranging from 0-100 with higher scores reflecting better function) were represented through radar plots by comparing baseline to 6 months (*A*), 1 year (*B*), 3 years (*C*), and 5 years (*D*) in the EBRT-LDR group (blue line) vs radical prostatectomy group (red line). The 26-item Expanded Prostate Cancer Index Composite 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 radical prostatectomy, was associated with a clinically meaningful decline in urinary irritative/obstructive function (−5-point difference [95% CI −8.7, −1.3]; $P = .008$) and bowel function (−4-point difference [95% CI −6.9, −1.1]; $P = .006$) through 5 years. Radical prostatectomy, 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]; $P < .001$) through 5 years and sexual function (−12-point difference [95% −6.5, -17.5]; $P < .001$) through 1 year.

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

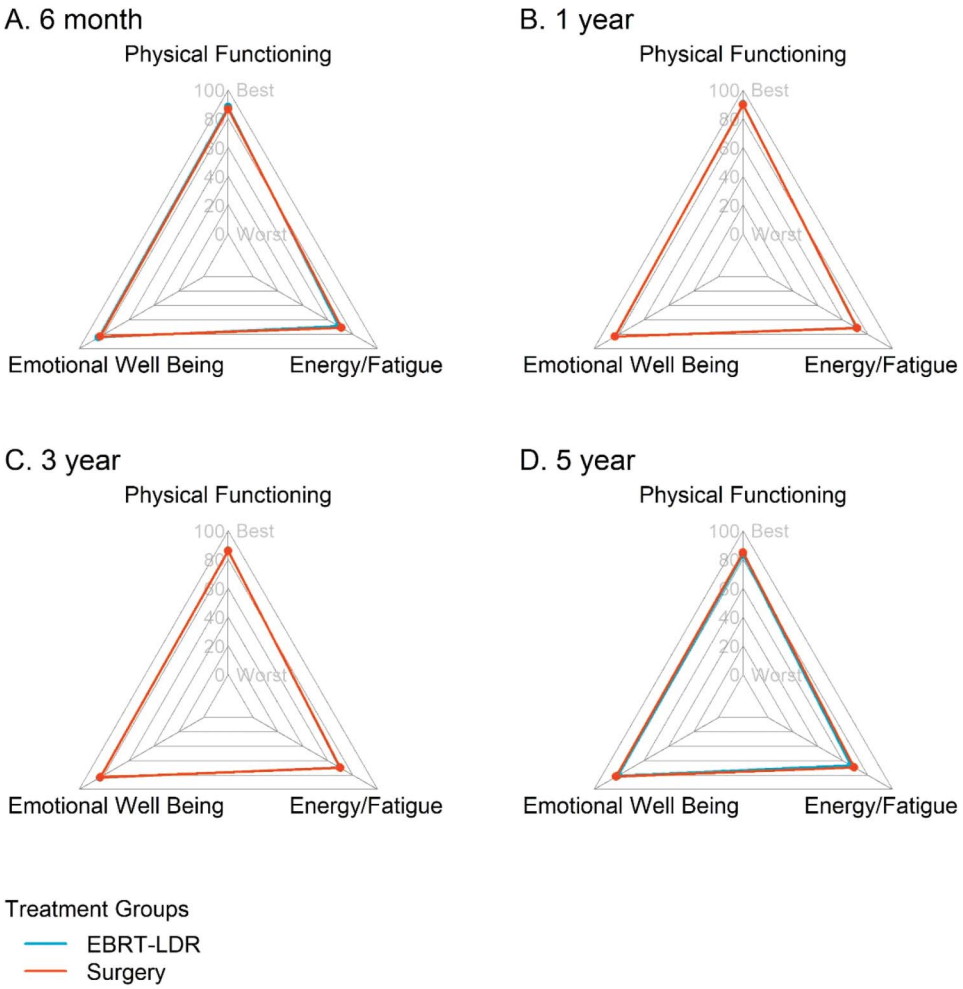

Figure 3. Adjusted 36-item Short Form domain scores comparing external beam radiotherapy plus low-dose brachytherapy (EBRT-LDR) vs radical prostatectomy through 5 years. Adjusted domain scores for 36-item Short Form function (ranging from 0-100 with higher scores reflecting better function) were represented through radar plots by comparing baseline to 6 months (*A*), 1 year (*B*), 3 years (*C*), and 5 years (*D*) in the EBRT-LDR group (blue line) vs radical prostatectomy group (red line). The 36-item Short Form 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 36-item Short Form function between the 2 groups through 5 years.

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.[26] 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 nonuniform 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 2 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 iodine-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 BT 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 BT, 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 nonresponse 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.

CONCLUSIONS

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.

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EDITORIAL COMMENTS

The gold standard of evidence in medicine is the multicenter, randomized, prospective clinical trial. A major effort to compare prostatectomy vs brachytherapy in this way over 20 years ago, the SPIRIT trial, closed prematurely due to low accrual. We were unable convince men to randomize to dissimilar treatment modalities, despite a robust education program. Thus, we are left with imperfect means of comparing surgical and brachytherapy treatment of clinically localized prostate cancer.

This study by De et al is a multicenter, prospective, nonrandomized study evaluating quality of life following prostatectomy or external beam radiation with a low dose brachytherapy boost. There are several weaknesses of this study, which the authors summarize nicely in the discussion section. Yet, given the inability to randomize between these techniques, this is probably the best we can do in terms of studying this question. Reassuringly, this study confirms many of the findings of Sanda et al, albeit with longer follow-up.[1] Irritative and obstructive symptoms are more pronounced with radiation. Urinary flow improves with surgery, but at the expense of increased incontinence. Erectile function is probably the most difficult question to assess in this study, given the difference in age and baseline sexual function. What is clear is that while the timing of erectile dysfunction with the 2 treatments differs, in the end there is no free lunch and there is a significant risk of erectile dysfunction with either

treatment. In the past 10 years there have been no major changes in either of these treatment modalities, although many of the patients treated in this study would currently be placed on active surveillance. So, the conclusions in this study remain valid.

Ultimately, patients deserve an unbiased discussion of the benefits and risks of each treatment modality. This paper clearly adds to the literature in this field.

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1. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358(12):1250-1261.

In this study by De and colleagues, the authors present 5-year patient-reported outcomes (PROs) from a multi-institutional prospectively collected database to compare external beam radiotherapy (EBRT) plus low dose rate brachytherapy boost (LDR) vs radical prostatectomy (RP) for localized prostate cancer. Because there is debate on the relative efficacy of these 2 treatments, data comparing PROs is a valuable contribution to the literature and useful for shared decision making.

The authors report that EBRT-LDR was associated with better incontinence function and better sexual function at 1 year, but this difference in sexual function attenuated by 3 years. EBRT-LDR was associated with worse urinary irritative/obstructive and worse bowel function compared to RP, though there were no differences in urinary or bowel function bother scores. Overall, these results are largely in line with the PROTECT trial findings with respect to PROs comparing RP to single-modality radiation (brachytherapy or EBRT, but not both).[1]

While there are no prospective trials reporting RP vs EBRT-LDR, the ASCENDE-RT trial randomized EBRT vs EBRT-LDR and reported improved biochemical control for the brachytherapy boost, but with more grade 3 genitourinary adverse events.[2] EBRT-LDR represents intensified therapy vs EBRT alone, with a *Journal of the American Medical Association* study reporting that EBRT+LDR had improved prostate cancer-specific mortality and lower rates of distant metastases vs EBRT alone or RP alone for Gleason 9-10 disease.[3] Patient selection is key, with EBRT-LDR appropriate only for unfavorable intermediate and high-risk disease per National Comprehensive Cancer Network guidelines.

The study has important limitations, including concerns about selection bias, unmeasured confounders, and generalizability. EBRT-LDR patients were median 4 years older and more likely to have high-risk disease. The EBRT-LDR cohort was much smaller (10:1), and 77% of the EBRT-LDR patients were treated at 1 center, raising concerns about generalizability. It should also be noted that the study findings do not apply to EBRT plus high dose rate brachytherapy, with studies of high dose rate brachytherapy generally showing better quality of life outcomes than LDR.

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This study compares patient reported outcomes in 1,533 men with prostate cancer who underwent radical prostatectomy vs 112 men treated with external beam radiation (EBRT) with low dose rate brachytherapy boost (LDR). This prospective comparative analysis reported worse urinary and bowel

symptoms but better continence and sexual function with EBRT-LDR. Although this is a worthy contribution, there are several important limitations of study.

The men who underwent EBRT-LDR were significantly older than those of the radical prostatectomy group ($P < .001$). Age is an independent risk factor for development for many of the patient reported outcomes studied. Furthermore, a higher percentage of high-risk patients (24% vs 17%) and a correspondingly lower percentage of low risk patients (31% vs 42%) were treated with EBRT-LDR.

Based on RTOG 0232 (not cited by the authors), comparing EBRT+LDR vs LDR alone, a more appropriate course of treatment for 34% to 70% of the radiotherapy cohort would have been LDR alone. This randomized phase 3 trial demonstrated comparable biochemical control but decreased morbidity with LDR alone.[1] Thus, had more of the radiotherapy patients in their study received a more modern, evidenced-based treatment, radiotherapy would have had a more favorable toxicity profile.

Several misleading and somewhat biased statements were made in this paper. For example, although better sexual function was noted in the EBRT-LDR group at 1 year ($P < .001$), the abstract reads "there was insufficient evidence to reject the supposition that no difference was seen at 3 or 5 years." Given the small number of patients treated with radiotherapy, such a statement is misleading. Based on ProtecT (also a randomized trial not cited), the differences in sexual potency after radiation compared to surgery were stable and sustained, suggesting that a similar result would be more likely than not had this study been larger.[2]

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REPLY BY AUTHORS

We appreciate the thoughtful commentary by Drs Ellis, Waters, Baumann, Sabol, and Roach. Practice patterns have changed in the intervening decade since study initiation; treatments utilized reflect selection at enrollment, not current practices. While appropriate patient selection remains vital, the presence of low-/intermediate-risk patients in the external beam radiotherapy (EBRT) plus low dose rate (LDR) brachytherapy cohort is a strength, since there would be greater confounding if exclusively high-risk patients received EBRT-LDR. Thus, the comparison of radical prostatectomy with EBRT-LDR—the focus of this study—remains valid. While there were age and baseline functional differences between cohorts, these were adjusted for in the analysis. Importantly, we compare outcomes only between radical prostatectomy and EBRT-LDR; other treatments such as EBRT with high dose rate brachytherapy, or LDR/ high dose rate monotherapy have distinct toxicity profiles.

Another limitation discussed is the comparison of sexual function at 5 years after treatment, at which point 70% of EBRT-LDR patients returned patient-reported outcome surveys. Following prostate cancer patients for 5 or more years can be challenging, and other studies have had comparable response rates.[1,2] While no difference in sexual function was seen at 3 or 5 years, we acknowledge that the absence of evidence is not evidence of absence—with a larger radiotherapy cohort and/or higher response rate, the difference at 1 year favoring EBRT-LDR may not have subsequently attenuated.

In the absence of randomized trials, our study provides the first high-quality, prospectively collected comparison of patient-reported outcomes for these treatments. Further investigation is nevertheless needed.

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