Clinical Investigation

Comparison of Patient-reported Outcomes After External Beam Radiation Therapy and Combined External Beam With Low-dose-rate Brachytherapy Boost in Men With Localized Prostate Cancer

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Summary

Men with localized prostate cancer treated with combined external beam therapy and low-dose-rate brachytherapy prostate boost who were enrolled in a prospective population-based study reported worse bowel function at 1 year and worse urinary irritative function through 3 years compared with men treated with external beam radiation therapy alone. These side effect profiles should be discussed with patients when considering combined external beam therapy and low-dose-rate brachytherapy prostate boost.

Purpose: To compare patient-reported disease-specific functional outcomes after external beam radiation therapy (EBRT) and EBRT combined with low-dose-rate brachytherapy prostate boost (EB-LDR) among men with localized prostate cancer.

Methods and Materials: The prospective, population-based Comparative Effectiveness Analysis of Surgery and Radiation study enrolled men with localized prostate cancer in 2011 to 2012. The 26-item Expanded Prostate Cancer Index Composite measured patient-reported disease-specific function at baseline and at 6, 12, and 36 months. Higher domain scores indicate better function. Minimal clinically important difference was defined as 6 for urinary incontinence, 5 for urinary irritative function, 4 for bowel function, 12 for sexual function, and 4 for hormonal function. Multivariable linear and logistic regression models were fit to estimate the effect of treatment on patient-reported outcomes.

Results: Five-hundred seventy-eight men received EBRT and 109 received EB-LDR. Median patient age was 69 years, and 70% had intermediate- or high-risk disease. Men in the EB-LDR group were younger ($P < .001$) and less likely to receive androgen deprivation therapy ($P < .001$). Baseline urinary, bowel, sexual, and hormonal function was similar between treatment groups ($P > .05$). On multivariable analyses, men receiving EB-LDR reported worse urinary irritative function at 6 months (adjusted mean difference [AMD] -14.4, $P < .001$), 12 months (AMD -12.9, $P < .001$), and 36 months (AMD -4.7, $P = .034$) than men receiving EBRT. At 12 months, men receiving EB-LDR reported worse bowel function (AMD -5.8, $P = .002$), but these differences were not seen at 36 months. There were no significant differences in sexual or hormone function between treatment groups.

Conclusions: Men treated with EB-LDR report worse bowel function at 1 year and worse urinary irritative function through 3 years compared with men treated with EBRT alone. These side effect profiles should be discussed with patients when considering EB-LDR versus EBRT treatment. © 2018 Elsevier Inc. All rights reserved.

Introduction

The results of randomized clinical trials (1-3) indicate that external beam radiation therapy (EBRT) with brachytherapy boost improves biochemical progression-free survival compared with EBRT alone for men with intermediate- and high-risk prostate cancer. National Comprehensive Cancer Network prostate cancer treatment guidelines recommend EBRT with brachytherapy boost as a treatment option for intermediate- and high-risk prostate cancer, and the American Society of Clinical Oncology/Cancer Care Ontario guidelines for brachytherapy for patients with prostate cancer recommend that brachytherapy boost be offered to eligible patients with intermediate- and high-risk disease (4, 5). In the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) Trial (1), the improvement in biochemical control after EBRT delivered with low-dose-rate (LDR) brachytherapy prostate boost (EB-LDR) came at the cost of increased physician-reported genitourinary toxicity. Other studies also suggest EBRT with brachytherapy boost increases physician-reported treatment toxicity (6, 7).

Patients' self-assessment of symptoms after prostate cancer radiation treatment can differ substantially from physician judgment (8-10), and comparative patient-reported functional outcomes after EB-LDR are lacking.

Therefore, we compared patient-reported urinary, bowel, and sexual function after EB-LDR and EBRT treatment among men enrolled in the prospective population-based Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study.

Methods and Materials

Study cohort

From January 2011 to February 2012, the CEASAR study enrolled men younger than 80 years of age with clinically localized prostate cancer, no evidence of nodal involvement or metastasis, and PSA ≤50 ng/mL. Patients were recruited from 5 Surveillance, Epidemiology and End Results registries (Atlanta, Los Angeles, Louisiana, New Jersey, and Utah) and a registry of patients with prostate cancer (Cancer of the Prostate Strategic Urologic Research Endeavor) (11). Details of the study design and objectives of the CEASAR study were described previously (12). The comparative effectiveness outcomes for men treated with EBRT, prostatectomy, and surveillance were previously published (13). This study was approved by the institutional review board at each participating location.

Surveys and data sources

Surveys were completed at baseline (time of study enrollment) and 6, 12, and 36 months after enrollment. The validated 26-item Expanded Prostate Index Composite (EPIC-26) was used to evaluate patient-reported disease-specific function. Summary scores were calculated for urinary irritative, urinary incontinence, bowel, sexual, and hormonal domains. Functional domain scores ranged from 0 to 100, with 100 representing better function. The urinary irritation domain measures dysuria, urgency, and urinary frequency. The urinary incontinence domain evaluates the degree of urinary leakage. The bowel function domain evaluates bowel frequency, urgency, bleeding, and pain. The sexual function domain focuses on the quality and frequency of erections. The hormonal domain focuses on symptoms such as low energy, gynecomastia, hot flashes, and weight gain. Surveys captured patient-reported race, age, income, education, marital status, and insurance. Validated instruments assessing patient-reported general health and function, emotional health, cancer-related anxiety, and illness management style were previously described (12). The Total Illness Burden Index for Prostate Cancer measured comorbidity, with higher scores corresponding to greater severity (14). The participatory decision-making scale (15, 16) measured the degree of shared decision making, and the provider-dependent health care orientation scale measured the degree of passivity or dependency (17).

Tumor characteristics, treatment, and treatment date were determined from medical chart abstraction that occurred 1 year after enrollment (12). For patients without available chart information, questionnaires and data from cancer registries determined treatment. Patients who underwent a radical prostatectomy were excluded from the study.

Analytic cohort

A total of 687 men met the inclusion criteria; were treated with EBRT or EB-LDR; and completed a baseline and 6-, 12-, or 36-month survey. Ninety-six percent completed the 6-month survey, 93% completed the 12-month survey, and 82% completed the 3-year survey. Small numbers of additional patients were excluded because data were insufficient (>20% of domain items missing a response) to calculate a summary score. The final sample size for each domain was 671 bowel, 659 urinary irritative, 659 urinary incontinence, 648 hormonal, and 642 sexual.

Statistical analysis

Patients' clinical and sociodemographic characteristics were summarized by radiation type (EB-LDR vs EBRT). Differences between the 2 groups were assessed with the Wilcoxon rank sum test (continuous variables) or the χ^2 test (categorical variables).

The primary outcomes were the following 5 functional EPIC-26 domain scores (18): urinary irritative, urinary incontinence, bowel, sexual, and hormone. The secondary outcomes included a priori selected individual items regarding problems with these functions. To evaluate the effects of radiation type on outcomes, multivariable linear regression models and logistic regression models were used for primary and secondary outcomes, respectively. Restricted cubic splines of time since treatment were used to detect changes in the association with the outcomes. The robust covariance matrix estimates by the Huber-White method (19, 20) were used to account for the potential correlation among multiple records pertaining to the same individual at different time points.

In all multivariable models we included age (continuous variable with restricted cubic splines), race (white, black, Hispanic, Asian, or other), Total Illness Burden Index for Prostate Cancer comorbidity score (0-2, 3-5, 6-8, or 9-15), D'Amico risk criteria (low, intermediate, or high), use of androgen deprivation therapy (yes or no), use of pelvic radiation (yes or no), baseline physical functioning (continuous, linear), social support scores (continuous, linear), depression scores (continuous, linear), participatory decision-making scale (continuous, linear), time since treatment (continuous, restricted cubic splines), site of radiation therapy (Louisiana, Utah, Atlanta, Los Angeles, New Jersey, or Cancer of the Prostate Strategic Urologic Research Endeavor), and corresponding baseline domain scores (continuous, restricted cubic splines) as the predictor variables. Planned subgroup analyses were carried out for each function domain separately. The baseline function scores were used to define the high and low baseline function subgroups (cutoff values of 90 and 100 were used for the sexual domain and other domains, respectively). For the primary endpoints, we report the adjusted mean difference (AMD) scores with 95% confidence intervals that were estimated from the multivariable models. For the secondary endpoint, odds ratios (ORs) were estimated and are reported with 95% confidence intervals. The multiple imputation method (21) was used in all regression models for missing predictor variable values. Statistical significance was considered to be .05 for all 2-sided P values. The minimal clinically important difference (MCID) (22) was determined by previously published and validated domain score thresholds: 5 points for urinary irritative function, 6 points for urinary incontinence function, 4 points for bowel function, 12 points for sexual function, and 4 points for hormonal function.

The Kaplan-Meier technique with log-rank tests was used to estimate the probability of overall and prostate cancer–specific survival. All analyses were conducted using R version 3.3.

Results

Clinical and patient characteristics

Five-hundred seventy-eight men received EBRT, and 109 received EB-LDR. Median patient age was 69 years, and

Table 1   Clinical and sociodemographic characteristics and baseline patient-reported function

	EB-LDR (N = 109)	EBRT (N = 578)	Combined (N = 687)	*P*-value
Patient characteristics				
Age at diagnosis, y				<.001
Median (Q1, Q3)	66.0 (60.0, 71.0)	69.0 (64.0, 73.8)	69.0 (63.0, 73.0)	
Race				.246
White	79 (73%)	408 (71%)	487 (71%)	
Black	23 (21%)	104 (18%)	127 (19%)	
Hispanic	3 (3%)	37 (6%)	40 (6%)	
Asian	1 (1%)	22 (4%)	23 (3%)	
Other	2 (2%)	6 (1%)	8 (1%)	
Education				.190
Less than high school	6 (6%)	86 (15%)	92 (14%)	
High school graduate	21 (21%)	115 (21%)	136 (21%)	
Some college	25 (26%)	128 (23%)	153 (23%)	
College graduate	23 (23%)	113 (20%)	136 (21%)	
Graduate/professional	23 (23%)	115 (21%)	138 (21%)	
Marital status				.626
Not married	23 (23%)	142 (26%)	165 (25%)	
Married	76 (77%)	414 (74%)	490 (75%)	
Total illness burden index				.028
0-2	24 (24%)	95 (17%)	119 (18%)	
3-4	48 (48%)	232 (41%)	280 (42%)	
≥5	28 (28%)	233 (42%)	261 (40%)	
Tumor and treatment characteristics				
D'Amico risk group				
Low risk	34 (31%)	168 (29%)	202 (29%)	.913
Intermediate risk	48 (44%)	262 (45%)	310 (45%)	
High risk	27 (25%)	146 (25%)	173 (25%)	
Prostate specific antigen, ng/mL				.046
<4	17 (16%)	82 (14%)	99 (14%)	
≥4 to <10	82 (75%)	377 (65%)	459 (67%)	
≥10 to <20	8 (7%)	86 (15%)	94 (14%)	
≥20 to <50	2 (2%)	33 (6%)	35 (5%)	
Clinical tumor stage				.275
T1	85 (78%)	421 (73%)	506 (74%)	
T2	24 (22%)	156 (27%)	180 (26%)	
Biopsy Gleason score				.591
≤6	37 (34%)	196 (34%)	233 (34%)	
3 + 4	39 (36%)	198 (34%)	237 (35%)	
4 + 3	11 (10%)	84 (15%)	95 (14%)	
8, 9, 10	22 (20%)	98 (17%)	120 (18%)	
Received ADT				<.001
No	90 (83%)	313 (54%)	403 (59%)	
Yes	18 (17%)	263 (46%)	281 (41%)	
Received pelvic radiation				.040
No	93 (90%)	465 (82%)	558 (84%)	
Yes	10 (10%)	100 (18%)	110 (16%)	
Received IMRT				.500
No	15 (15%)	100 (18%)	115 (17%)	
Yes	88 (85%)	468 (82%)	556 (83%)	
Received IGRT				.090
No	20 (21%)	76 (14%)	96 (15%)	
Yes	76 (79%)	460 (86%)	536 (85%)	
Decision-making style				
Participatory decision-making scale				.135
Median (Q1, Q3)	78.6 (71.4, 89.3)	78.6 (64.3, 89.3)	78.6 (64.3, 89.3)	
Provider-dependent passivity				.003
Median (Q1, Q3)	16.7 (7.3, 37.5)	29.2 (9.2, 45.8)	25.0 (8.3, 45.8)	

Table 1   (*continued*)

	EB-LDR (N = 109)	EBRT (N = 578)	Combined (N = 687)	*P*-value
Baseline SF36 function				
SF36 general health scale				.019
0	0 (0%)	4 (1%)	4 (1%)	
20	0 (0%)	13 (2%)	13 (2%)	
40	10 (9%)	86 (15%)	96 (14%)	
60	35 (32%)	220 (38%)	255 (37%)	
80	40 (37%)	182 (32%)	222 (32%)	
100	24 (22%)	70 (12%)	94 (14%)	
SF36 physical function scale				<.001
Median (Q1, Q3)	95.0 (87.5, 100.0)	90.0 (70.0, 100.0)	90.0 (70.0, 100.0)	
SF36 mental function scale				.222
Median (Q1, Q3)	85.0 (80.0, 92.0)	84.0 (69.0, 92.0)	84.0 (72.0, 92.0)	
SF36 energy and vitality scale				.012
Median (Q1, Q3)	80.0 (70.0, 85.0)	70.0 (55.0, 85.0)	75.0 (60.0, 85.0)	
Baseline EPIC function				
Urinary irritative domain score				.055
Median (Q1, Q3)	93.8 (75.0, 100.0)	87.5 (75.0, 93.8)	87.5 (75.0, 93.8)	
Urinary incontinence domain score				.309
Median (Q1, Q3)	100.0 (83.9, 100.0)	100.0 (79.2, 100.0)	100.0 (79.2, 100.0)	
Bowel function score				.173
Median (Q1, Q3)	100.0 (91.7, 100.0)	100.0 (91.7, 100.0)	100.0 (91.7, 100.0)	
Sexual function score				.053
Median (Q1, Q3)	65.0 (33.3, 85.0)	58.3 (18.3, 80.0)	60.0 (21.7, 80.0)	
Hormonal domain score				.12
Median (Q1, Q3)	95.0 (85.0, 100.0)	90.0 (80.0, 100.0)	90.0 (80.0, 100.0)	

Abbreviations: ADT = androgen deprivation therapy; EB-LDR = EBRT and low-dose-rate brachytherapy prostate boost; EBRT = external beam radiation therapy; EPIC = Expanded Prostate Index Composite; IGRT = image guided radiation therapy; IMRT = intensity modulated radiation therapy; Q = quartile; SF36 = Short-Form 36.

70% had intermediate- or high-risk disease (Table 1). Patients who received EB-LDR were younger (*P* < .001); had higher general health scores (*P* = .019), baseline physical function scores (*P* < .001), and energy and vitality scores (*P* = .012); and were less likely to receive androgen deprivation therapy (ADT) (*P* < .001) compared with patients who received EBRT. Patients treated with EBRT and those treated with EB-LDR reported similar baseline urinary irritative, urinary incontinence, bowel, sexual, and hormonal domain function (Table 1).

Patients treated with EBRT and EB-LDR exhibited similar degrees of shared decision making (*P* = .135); however, patients undergoing EBRT reported higher levels of passivity in making their treatment decisions (*P* = .003).

Among men treated with EBRT alone, the median external beam dose was 78.0 Gy (interquartile range [IQR] 76.0-79.2), with 18% receiving pelvic radiation. Among men treated with EB-LDR, 77.1% received I125 implant at a median dose of 90.0 Gy (IQR 80-110), and 14.7% received Pd103 implant at a median dose of 100.0 Gy (IQR 92.5-100). Fifty percent had documentation of postimplant dosimetry. The median external beam dose in men who underwent EB-LDR was 45.0 Gy (IQR 45.0-52.5), and 10% received pelvic radiation.

Urinary irritative symptoms

Men who underwent EB-LDR reported an immediate decline in urinary irritative function that persisted through 6 months with some improvement by 12 months and additional improvement in function through 3 years (Fig. 1). Adjusting for baseline function and other predictor variables, men who received EB-LDR reported lower urinary irritative domain function scores at 6 months (AMD −14.4, 95% CI −19.1 to −9.7), 12 months (AMD −12.9, 95% CI −17.7 to −8.1), and 3 years (AMD −4.7, 95% CI −9.1 to −0.4) (Table 2). The 6- and 12-month differences were greater than the MCID of 5 points between groups, whereas the 3-year difference was close to but did not meet the MCID.

Comparative urinary irritative function was similar when men were stratified by baseline function. Men with low baseline function and men with high baseline function reported worse urinary irritative domain function at 1 year (AMD −14.2, 95% CI −19.9 to −8.5 and AMD −11.4, 95% CI −20.3 to −2.6, respectively), but significant differences were not observed at 3 years (Table E1; available online at www.redjournal.org). In a subset analysis limited to men with intermediate- and high-risk disease, men who
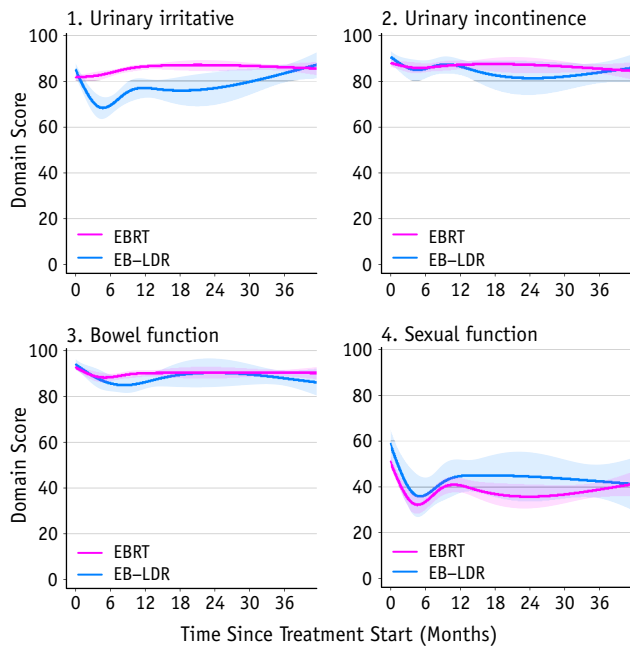
Fig. 1. Unadjusted mean disease-specific function over time reported by men managed with external beam radiation therapy (EBRT) and EBRT with low-dose-rate brachytherapy boost (EB-LDR). The lighter shading encompasses the 95% confidence interval.

received EB-LDR reported lower urinary irritative domain function at 6 months and 12 months that met the MCID (Table E2; available online at www.redjournal.org).

Before treatment, men in both groups reported similar rates of a moderate or big problem with urinary function (P = .10), urinary frequency (P = .50), and burning on urination (P = .80). Men who received EB-LDR were more likely to report a moderate or big problem with burning on urination at 6 months (adjusted odds ratio [AOR] 5.2; 95% CI 2.0-13.8), 1 year (AOR 16.9; 95% CI 5.5-51.4), and 3 years (AOR 6.5; 95% CI 1.9-21.8). At 1 year, 17% of the men who received EB-LDR reported a moderate or big problem with burning on urination compared with only 3% of men who received EBRT (Table 3). Men who received EB-LDR were also more likely to report a moderate or big problem with urinary frequency at 6 months (AOR 2.6; 95% CI 1.3-5.0) and 1 year (AOR 4.6; 95% CI 2.4-8.7), but there was no difference at 3 years. At 1 year, 28% of the men who underwent EB-LDR reported a moderate or big problem with urinary frequency, compared with only 14% of men who received EBRT.

Urinary incontinence

Urinary incontinence function after EBRT and EB-LDR is illustrated in Figure 1. Adjusting for baseline function and other predictor variables, men undergoing EBRT and EB-LDR reported similar urinary incontinence domain function at 6 months, 1 year, and 3 years (Table 2). When men were stratified by baseline function, men with high baseline function reported a greater difference in urinary incontinence function at 12 months that exceeded the MCID (AMD −7.4, 95% CI −13.1 to −1.7) (Table E1; available online at www.redjournal.org), but this difference was not maintained at 3 years (AMD −3.3, 95% CI −8.5 to 1.9).

Before treatment, men in both groups reported similar rates of a moderate or big problem with urinary leakage (P = .80) and similar rates of daily incontinence pad use

Table 2 Comparison of urinary, bowel, sexual, and hormonal domain scores between men treated with EB-LDR and EBRT

	EB-LDR vs EBRT*								
	6 month			1 year			3 year		
Functional domain	Mean score difference*	95% CI	P-value	Mean score difference†	95% CI	P-value	Mean score difference*	95% CI	P-value
Urinary irritative	−14.4	−19.1 to −9.7	<.001	−12.9	−17.7 to −8.1	<.001	−4.7	−9.1 to −0.4	.034
Urinary incontinence	−2.9	−7.1 to 1.4	.184	−4.4	−9.0 to 0.1	.056	−0.1	−4.8 to 4.6	.961
Bowel function	−4.2	−8.4 to −0.0	.048	−5.8	−9.5 to −2.1	.002	−3	−6.5 to 0.4	.087
Sexual function	−5.1	−11.9 to 1.7	.142	−3.3	−9.5 to 2.9	.3	−3.7	− 10.2 to 2.9	.275
Hormone function	−0.3	− 3.9 to 3.3	0.872	−0.6	−4.6 to 3.4	.756	−1.4	−5.7 to 2.8	.506

Abbreviations: AMD = adjusted mean difference; EBRT = external beam radiation therapy; EB-LDR = EBRT and low-dose-rate brachytherapy prostate boost.

* Reference group.

† Negative values indicate patient-reported function is worse in the EB-LDR group. Positive values indicate function is better in the EB-LDR group. Mean difference adjusted for baseline function, patient characteristics, health status, tumor characteristics, psychosocial measures, administration of pelvic radiation, use of androgen deprivation therapy, and study site.

Table 3   Comparison of responses to individual questions regarding problems with function

	Frequency of problem		ED-LDR vs EBRT*		
	EB-LDR	EBRT	OR[†]	95% CI	P-value
Urinary function					
Problem with urinary function[‡]					
Baseline	7%	12%			
6 mo	22%	13%	2.6	1.2-5.8	.015
1 y	15%	10%	3.6	1.6-8.1	.002
3 y	13%	10%	1.8	0.7-4.7	.204
Problem with pain or burning on urination[‡]					
Baseline	4%	4%			
6 mo	22%	5%	5.2	2.0-13.8	<.001
1 y	17%	3%	16.9	5.5-51.4	<.001
3 y	9%	2%	6.5	1.9-21.8	.002
Problem with needing to urinate frequently[‡]					
Baseline	19%	22%			
6 mo	31%	18%	2.6	1.3-5.0	.005
1 y	28%	14%	4.6	2.4-8.7	<.001
3 y	17%	14%	1.5	0.6-3.3	.357
Problem with urinary leakage[‡]					
Baseline	4%	4%			
6 mo	3%	6%	0.6	0.1-2.4	.4
1 y	4%	6%	1	0.4-3.0	.949
3 y	7%	5%	0.8	0.2-3.3	.741
Daily pad use					
Baseline	2%	3%			
6 mo	5%	6%	1.2	0.4-3.7	.708
1 y	8%	6%	2.6	1.1-6.2	.034
3 y	10%	8%	1.9	0.8-4.6	.158
Bowel function					
Problem with bowel function[‡]					
Baseline	3%	4%			
6 mo	6%	8%	0.6	0.2-2	.405
1 y	4%	8%	0.9	0.3-2.3	.812
3 y	8%	6%	1.2	0.4-3.8	.706
Problem with bowel urgency[‡]					
Baseline	3%	4%			
6 mo	10%	8%	1.5	0.5-4.5	.478
1 y	8%	7%	2.4	0.8-7.1	.125
3 y	10%	7%	1.1	0.3-4.3	.853
Sexual function					
Problem with sexual function[‡]					
Baseline	33%	32%			
6 mo	40%	38%	1.5	0.7-2.8	.273
1 y	43%	39%	1.6	0.8-2.9	.179
3 y	39%	35%	1.5	0.8-2.9	.242
Erections firm enough for intercourse[§]					
Baseline	49%	56%			
6 mo	66%	72%	0.9	0.5-1.6	.691
1 y	67%	72%	0.7	0.4-1.4	.296
3 y	67%	71%	0.7	0.4-1.5	.409

Abbreviations: CI = confidence interval; EBRT = external beam radiation therapy; EB-LDR = EBRT combined with low-dose-rate brachytherapy prostate boost; OR = odds ratio.

  * Reference group.
  [†] Odds ratios >1.0 indicate patient-reported problem occurs more frequently in the EB-LDR group. Estimates adjusted for baseline function, patient characteristics, health status, tumor characteristics, psychosocial measures, administration of pelvic radiation, use of androgen deprivation therapy and study site.
  [‡] Patient reported "moderate problem" or "big problem"
  [§] Patient reported no erections ("none") or "not firm enough for intercourse"

(P = .50, Table 3). Adjusting for baseline function and predictor variables, men who received EB-LDR were more likely to report daily incontinence pad use 12 months after treatment (OR 2.6; 95% CI 1.1-6.2); however, this difference was not seen at 3 years (OR 1.9; 95% CI 0.8-4.6). Men in both groups reported similar rates of a moderate or big problem with urinary leakage at 6 months, 12 months, and 3 years.

Bowel function

Bowel function after EBRT and EB-LDR is illustrated in Figure 1. Adjusting for baseline function and other predictor variables, including use of pelvic radiation, men undergoing EB-LDR reported lower bowel function scores at 6 months (AMD −4.2; 95% CI −8.4 to −0.0) and 12 months (AMD −5.8; 95% CI −9.5 to −2.1). These differences were greater than the MCID of 4 points (Table 2). The difference in bowel function resolved by 3 years (AMD −3.0, 95% CI −6.5 to 0.4). When men were stratified by baseline function, men with low baseline bowel function reported a greater difference in bowel function at 12 months (AMD −8.4; 95% CI −16.0 to −0.8) that was maintained through 3 years (AMD −9.8; 95% CI −17.3 to −2.2) (Table E1; available online at www. redjournal.org). In a subset analysis limited to men with intermediate- and high-risk disease, men who received EB-LDR reported lower bowel function, but this difference was not statistically significant (Table E2; available online at www.redjournal.org).

Before treatment, men in both groups reported similar rates of a moderate or big problem with bowel function (P = .70) and similar rates of a moderate or big problem with bowel urgency (P = .70). Adjusting for baseline function and other predictor variables, men in both groups reported similar rates of a moderate or big problem with bowel function and bowel urgency through 3 years (Table 3). There was no difference in the proportion of men who reported a moderate or big problem with bloody stools after undergoing EB-LDR (0%) or EBRT (2%) after 3 years (P = .205).

Sexual function

Men who underwent EBRT and EB-LDR reported an immediate decline in sexual function that persisted through 6 months with some improvement by 12 months and a stable decreased function relative to baseline through 36 months (Fig. 1). Adjusting for baseline function and other predictor variables, men undergoing EBRT and EB-LDR reported similar sexual domain function at 6 months, 12 months, and 3 years (Table 2). When men were stratified by baseline function, comparative sexual function was similar for those with low and high baseline function (Table E1; available online at www.redjournal. org). We performed a sensitivity analysis that excluded

ADT usage as a predictor variable for the multivariable model. When the ADT predictor variable was excluded, sexual function was also similar between treatment groups.

Adjusting for baseline function and other predictor variables, men in both groups reported similar rates of a moderate or big problem with sexual function and erections not firm enough for intercourse through 3 years (Table 3).

Hormonal function

Hormonal function after EBRT and EB-LDR was similar; both groups reported a decrease in hormonal function at 6 months with subsequent improvement (Fig. E1; available online at www.redjournal.org). Adjusting for baseline function and other predictor variables, men undergoing EBRT and EB-LDR reported similar hormonal domain function 6 months, 12 months, and 3 years after treatment (Table 2). Among the subgroup of patients with high-risk prostate cancer, there also was no significant difference in hormone function scores between treatment groups at 12 months (P = .656) and 3 years (P = .935). We performed a sensitivity analysis that excluded ADT usage as a predictor variable for the multivariable model. When the ADT predictor variable was excluded, hormonal function was also similar between treatment groups.

Survival outcomes

Among the intermediate- and high-risk patients, the 3-year overall survival was 97.0% (95% CI 93.0%-100.0%) for patients who received EB-LDR and 95.3% (95% CI 93.2%-97.4%) for patients who underwent EBRT. The log-rank test did not indicate a statistically significant difference between groups (P = .26). The 3-year prostate cancer−specific survival was 100% (95% CI 100%-100%) for patients who received EB-LDR and 99.5% (95% CI 98.8%-100.0%) for patients who received EBRT. The log-rank test did not indicate a statistically significant difference between groups (P = .56).

Discussion

In this prospective comparative effectiveness study, men with localized prostate cancer who received EB-LDR reported worse urinary function after treatment than men who received EBRT alone. The impact of EB-LDR on urinary irritative symptoms was evident 6 months after treatment and persisted through 3 years, with improvement in relative symptoms over time. Patients who underwent EB-LDR were more likely to report a moderate or big problem with urinary frequency through 12 months and a moderate or big problem with dysuria through 3 years compared with patients treated with EBRT. Men treated with EB-LDR also had worse bowel function at 6 months and 1 year, but this resolved by 3 years.

The early and sustained impact of EB-LDR on patient-reported urinary function compared with the impact of EBRT in our study is consistent with published reports of increased urinary complications after treatment with EB-LDR (23-25). The ASCENDE-RT randomized trial found that EB-LDR improved biochemical progression-free survival compared with EBRT with EBRT boost (1), but also increased the risk of physician-reported grade 3 genitourinary complications, urinary incontinence, and need for catheterization (6, 7). A study using the Surveillance, Epidemiology and End Results-Medicare database similarly found that men undergoing EB-LDR had more medical claims for grade 3 urinary adverse events compared with those receiving EBRT monotherapy (26).

The use of validated patient-reported outcomes in our study provides more detailed information on the symptoms patients experience after treatment. Specifically, urinary frequency and dysuria were more likely to be a problem for men treated with EB-LDR. Patient-reported outcomes are measures provided directly by the patient without interpretation by the clinician or researcher and are often more representative of the patient perspective on quality of life, effects of treatment, and relevant values for their goals of treatment (27-30). Patient self-assessment of symptoms is critical because patient perception of symptoms after prostate cancer radiation treatment can differ substantially from physician judgment (8-10).

The patients in our study reported EB-LDR had the greatest impact on urinary irritative function, with men undergoing EB-LDR more likely to be bothered by dysuria and frequency. Men treated with EB-LDR were also more likely to report daily incontinence pad use at 1 year; however, the difference in urinary incontinence function was only significant for those men who had high urinary incontinence function scores at baseline. The ASCENDE-RT trial reported a greater decline in patient-reported urinary function among patients receiving EB-LDR than in those treated with EBRT alone (7). However, the ASCENDE-RT patient questionnaire did not assess urinary irritative function. ASCENDE-RT used a nonvalidated scale, and nearly all of the urinary function questions assessed incontinence (frequency of urinary leakage, problem with urinary leakage, urinary control, incontinence pad use) with 1 question assessing overall urinary function. Our study provides more insight into urinary irritative function, and our population-based cohort reports less relative impact of EB-LDR on incontinence than was seen in ASCENDE-RT.

Patients who received EB-LDR in our study reported worse bowel function at 6 and 12 months compared with those who received EBRT, a decline that subsequently subsided. This is consistent with the greater decline in mean bowel function at 12 months reported by men who received EB-LDR in ASCENDE-RT; this decline also subsequently subsided. Of note, ASCENDE-RT found only a nonsignificant numerical increase in physician-reported gastrointestinal events, highlighting how patient-reported

function can provide insight beyond physician-reported toxicity. Although ASCENDE-RT stipulated that all patients receive pelvic nodal radiation, which influences bowel toxicity, only 18% of patients who received EBRT and 10% of those who received EB-LDR in our population-based study received pelvic radiation.

Although men who received EBRT with LDR in ASCENDE-RT reported a greater drop in sexual function at 1 and 2 years compared with men treated with EBRT (7), we found no difference in patient-reported sexual function between men treated with EB-LDR and EBRT through 3 years. Although ASCENDE-RT stipulated that all patients receive 12 months of ADT with treatment, men treated with EB-LDR in our study were less likely to receive ADT than were men treated with EBRT. We could not determine why men did or did not receive ADT; the nuance of clinical decision making is difficult to discern from medical chart abstraction. It is possible that ADT may have been administered to some men receiving EBRT to enhance cancer control when brachytherapy boost was not feasible or that ADT may have been administered to some men receiving EB-LDR for cytoreduction to facilitate brachytherapy boost. This variation in ADT use was adjusted for when comparing function between treatment groups.

Some limitations of this study are worth noting. First, as with all observational studies, confounding by indication is possible. To minimize bias, we adjusted for variables likely to predict treatment selection. Second, men treated for prostate cancer often have a long life expectancy, and we report function through only 3 years. This time frame does not capture delayed functional changes. The differences in urinary function seen at 3 years may continue to attenuate over time, and there may be functional changes from subsequent salvage therapy. Third, clinically meaningful differences in EPIC-26 domain scores are not well established. We used clinical judgment and published thresholds when interpreting the data (22). Our models predict average function, but the actual impact of treatment on function—and the perception of whether a functional change is meaningful—varies among patients. Fourth, 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 who completed the baseline survey before versus after starting treatment were very small (range, 1-3 points), and the Prostate Cancer Outcomes Study validation study demonstrated most men accurately recall prediagnostic function 6 months after prostate cancer diagnosis (31, 32). Fifth, although EB-LDR is not standard treatment for men with low-risk prostate cancer, we included these men in our analysis because the intent of the study was to compare the impact of treatment on patient-reported quality of life. However, urinary differences persisted when we excluded low-risk patients in a sensitivity analysis. Sixth, we did not have information on pretreatment prostate size and use of urinary modifying

medications, which could affect treatment morbidity; however, we did adjust for differences in baseline urinary function. Seventh, we were unable to determine the duration of ADT received because men may have received ADT after the time of medical chart abstraction. Finally, we report function at 6, 12, and 36 months, but acute toxicity during and immediately after treatment was not assessed.

This study uses a unique population-based cohort that reflects how EBRT and EB-LDR are delivered in the community with contemporary EBRT and LDR brachytherapy techniques. Therefore, delivery of radiation in this study cohort differed from delivery of radiation in clinical trials such as ASCENDE-RT in ways that may affect treatment toxicity. Notably, the median I-125 brachytherapy boost dose for the study cohort was lower than that delivered in ASCENDE-RT and lower than recommended by guidelines (5, 33). Lower prescription doses have been associated with decreased urinary morbidity after LDR brachytherapy. The lower boost dose in our study cohort suggests the possibility of lower-quality implants. Only half of the patients who underwent brachytherapy boost had documentation of postimplant dosimetry. We did not have information on technical aspects of the implants that may affect toxicity, such as urethral dose, bowel dose, or use of a hydrogel spacer. It has been hypothesized that the protocol-required generous inferior margin defining the brachytherapy treatment volume and the low inferior borders of the pelvic radiation fields increased the toxicity experienced by patients treated on ASCENDE-RT (7). Men treated on ASCENDE-RT were treated at 1 of 6 centers by brachytherapy experts. We were unable to determine the brachytherapy experience of treatment providers in our study cohort. It is possible some were low-volume providers, and limited brachytherapy experience has been associated with increased treatment toxicity. However, this effectiveness study demonstrates patient-reported function after EBRT with brachytherapy boost as administered in real-world practice.

Guidelines recommend EBRT with brachytherapy boost as a treatment option for men with intermediate- and high-risk disease (4, 5). Our finding of increased patient-reported toxicity after EB-LDR compared with EBRT needs to be considered in the context of the cancer control benefits of EB-LDR demonstrated in randomized trials.

Conclusions

In this prospective comparative effectiveness study of men treated for localized prostate cancer, men treated with EB-LDR reported worse bowel function at 1 year and worse urinary irritative function through 3 years compared with men treated with EBRT monotherapy. The biochemical control benefit from EB-LDR should be discussed in the context of the potential impact on urinary and bowel function.

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