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Clinical Investigation

Time Course and Accumulated Risk of Severe Urinary Adverse Events After High-Versus Low-Dose-Rate Prostate Brachytherapy With or Without External Beam Radiation Therapy

Jonathan D. Tward, MD, PhD,* Stephanie Jarosek, RN,† Haitao Chu, MD, PhD,† Cameron Thorpe, BS,* Dennis C. Shrieve, MD, PhD,* and Sean Elliott, MD, MS†

**Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; and †University of Minnesota, Minneapolis, Minnesota*

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Summary

Long-term toxicity comparative-effectiveness data for high-dose-rate (HDR) versus low-dose-rate (LDR) brachytherapy are lacking and are inconsistently reported. In this study, we include propensity-matched populations receiving HDR, LDR, HDR plus external beam radiation therapy, and LDR plus external beam radiation therapy and compare them with a control population to determine excess risk and number needed to harm for severe grade 3 urologic morbidity according to the Common Terminology

Purpose: Severe urinary adverse events (UAEs) include surgical treatment of urethral stricture, urinary incontinence, and radiation cystitis. We compared the incidence of grade 3 UAEs, according to the Common Terminology Criteria for Adverse Events, after low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy, as well as after LDR plus external beam radiation therapy (EBRT) and HDR plus EBRT.

Methods and Materials: Men aged >65 years with nonmetastatic prostate cancer were identified from the Surveillance, Epidemiology, and End Results−Medicare database who were treated with LDR (n = 12,801), HDR (n = 685), LDR plus EBRT (n = 8518), or HDR plus EBRT (n = 2392). The populations were balanced by propensity weighting, and the Kaplan-Meier incidence of severe UAEs was compared. Propensity-weighted Cox proportional hazards models were used to compare the adjusted hazard of UAEs. These UAEs were compared with those in a cohort of men not treated for prostate cancer.

Results: Median follow-up was 4.3 years. At 8 years, the propensity-weighted cumulative UAE incidence was highest after HDR plus EBRT (26.6% [95% confidence interval, 23.8%-29.7%]) and lowest after LDR (15.7% [95% confidence interval, 14.8%-16.6%]). The absolute excess risk over nontreated controls at 8 years was 1.9%, 3.8%, 8.4%, and 12.9% for LDR, HDR, LDR plus EBRT, and HDR plus EBRT, respectively. These represent numbers needed to harm of 53, 26, 12, and 8 persons, respectively. The additional risk of development of a UAE related to treatment for LDR, LDR plus EBRT, and HDR plus EBRT was greatest within the 2 years after

Reprint requests to: Jonathan D. Tward, MD, PhD, Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, 1950 Circle of Hope Dr, Salt Lake City, UT 84112. Tel: (801) 581-2396; E-mail: Jonathan.Tward@hci.utah.edu

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Criteria for Adverse Events. There is no statistical difference between LDR and HDR brachytherapy for late toxicity, and toxicity is acceptable compared with controls.

treatment and then continued to decline over time. Beyond 4 years, the risk of development of a new severe UAE matched the baseline risk of the control population for all treatments.

Conclusions: Toxicity differences were observed between LDR and HDR, but the differences did not meet statistical significance. However, combination radiation therapy (either HDR plus EBRT or LDR plus EBRT) increases the risk of severe UAEs compared with HDR alone or LDR alone. The highest increased risk of urinary toxicity occurs within the 2 years after therapy and then declines to an approximately 1% increase in incidence per year.

Introduction

Men with a diagnosis of localized prostate cancer have numerous management options, including active surveillance, expectant management, androgen-deprivation therapy, and curative-intent definitive therapy. Among patients who are offered curative-intent treatments, the vast majority are offered either radical prostatectomy or radiation therapy. However, current radiation therapy comprises a heterogeneous group of treatments and dosing including external beam–based therapies, high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy, and combinations of beam and brachytherapy, with or without androgen-deprivation therapy (1). There is no consensus as to the optimal treatment for localized prostate cancer, and urologists and radiation oncologists continue to debate the relative merits of therapies. Most men and their partners ultimately choose a therapy based on how well informed they are about the various options and their respective side effect profiles.

Our group has recently published a toxicity comparative-effectiveness analysis comparing urinary morbidity for surgical therapies versus various radiation therapies, as well as their combinations (2). Both HDR brachytherapy and LDR brachytherapy were combined as a single cohort for analysis. This did not allow the authors to discern differences between these radiobiologically different forms of brachytherapy. Both HDR brachytherapy and LDR brachytherapy have now been practiced as monotherapy for more than 2 decades (3-6), which allows us to compare the long-term toxicities of these modalities. The purpose of this study is to evaluate the risk of significant urinary adverse events (UAEs) in general, and bladder outlet obstruction (BOO) in particular, specifically in men undergoing either HDR or LDR, with or without external beam therapy. We also compare the risk of events in irradiated men with that in a control population from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, using propensity-weighted methods to adjust for selection bias. In addition, we evaluate how that risk changes over time.

Methods

This study was approved by the institutional review board. Our cohort is a subset of a cohort previously described. In brief, using the SEER cancer registry data linked with Medicare claims data, we identified men aged 66 years and older in whom nonmetastatic invasive prostate cancer had been diagnosed between 1998 and 2007 and who had received brachytherapy within 1 year of diagnosis. We observed the men using Medicare claims data until the end of 2009. We also identified 93,803 men without cancer from the 5% sample of Medicare beneficiaries residing in a SEER registry for a comparison group. Pseudo-treatment dates were assigned to controls to mirror the distribution of diagnosis dates in the cases.

Patients treated with brachytherapy were assigned to 1 of 4 mutually exclusive treatment groups: (*1*) LDR (n = 12,801); (*2*) HDR (n = 685); (*3*) LDR plus external beam radiation therapy (EBRT) (n = 8518); and (*4*) HDR plus EBRT (n = 2392). Patients with any claims for delivery of HDR in the year after diagnosis were assigned to the HDR treatment group, even in the rare cases in which claims for LDR were also found. In 99% of these rare cases, the single LDR Current Procedural Terminology code used was 77778 and was billed on the same day as the HDR procedure codes, indicating that this was not a salvage procedure. It is presumed the 77778 code was billed in error and that HDR was the primary modality.

Our outcome variable of interest was time to severe UAE, as defined by a diagnosis code and procedure on a single claim indicating that the patient had a urinary event significant enough to be managed with a procedure based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) (7). Diagnostic categories for defining any UAE included bladder spasm; cystitis; hematuria; urinary fistula; urinary incontinence; ureteral obstruction; and BOO, which includes urethral stricture and benign prostatic hypertrophy. The algorithm of diagnosis and procedural combinations used to describe any UAE has been previously published (2). Time to event was measured as the time from first treatment (or pseudo-treatment in the case of controls) until the patient had a UAE.

Given the observational nature of the study, treatment selection bias may have been present. To account for this, we used an inverse probability of treatment weighting (IPTW) scheme to balance the treatment groups (8, 9). In brief, we used patient age, year of treatment or pseudo-treatment, Charlson Comorbidity Index score (10), health maintenance organization enrollment, SEER registry of

residence, and socioeconomic characteristics (ZIP code, income, and education) to estimate each man's propensity to receive a diagnosis of prostate cancer using a generalized logit model; we then used those same characteristics in addition to clinical characteristics (tumor stage and grade and presence of baseline UAE [UAE in the 12 months prior to diagnosis]) to estimate the propensity of each case for receiving his treatment. A full description of the statistical method has been published previously (2). The IPTW was equal to the inverse of 1 minus the probability of a prostate cancer diagnosis for control subjects, and the product of the inverse of the probability of a cancer diagnosis and of receiving their treatment for cases, such that men who are less like others in their treatment groups have higher weights, balancing the covariates across treatment groups. Weights were truncated at the first and 99th percentile to reduce potential data sparsity (11).

Unweighted and weighted cumulative incidence curves were estimated using the Kaplan-Meier method. Patients were censored at further treatment (initiated after 12 months), enrollment in a health maintenance organization, death, or the end of the observation period (December 31, 2009). To further control for the residual confounding effect of age, comorbidity, and presence of baseline UAE on the time to UAE, we used a multivariate Cox proportional hazards model. When the proportional hazards assumptions were not met, an extended Cox model (12) was used to estimate time-dependent hazard ratios, partitioning time into variable length intervals. An analysis was undertaken to see how the age, Charlson Comorbidity Index score, and baseline UAEs affected the risk of development of a UAE after treatment (Table E1; available online at www.redjournal.org). Because these parameters did not interact with time, they retain the same values in our extended Cox model and the model still shows the increase one would expect in UAE by age and comorbidity, as well as the decrease one would expect without a UAE at baseline. Although some treatment cohorts had substantially more patients than others, the differential size did not affect our statistical methods. Our methods make no assumptions that require the size of the groups to be similar.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC). All reported P values are 2 tailed, and $P<.05$ was considered statistically significant.

Results

There were 118,199 persons included in the analysis: 93,803 served as controls, and 24,396 were treated with brachytherapy with or without EBRT. Unweighted demographic characteristics of the study population are listed in Table 1. After weighting, differences between the treatment groups for all demographic characteristics remained statistically significant, based on a χ^2 test; however, the IPTW procedure removed any clinical differences. Median follow-up was 4.3 years. In our control group, the incidence of a UAE was 13.8% (95% confidence interval [CI], 13.8%-14.2%) and that of a BOO was 11.8% (95% CI, 11.4%-12.2%) at 8 years. In the treatment groups, the propensity-weighted cumulative UAE incidence was highest after HDR plus EBRT (26.6% [95% CI, 23.8%-29.7%]) and lowest after LDR (15.7% [95% CI, 14.8%-16.6%]) at 8 years.

The absolute excess risk over controls of a UAE at 8 years was 1.9%, 3.8%, 8.4%, and 12.9% for LDR, HDR, LDR plus EBRT, and HDR plus EBRT, respectively. These translate into numbers needed to harm of 53, 26, 12, and 8 persons, respectively (Table 2, Fig. 1). For BOO, the absolute excess risk was 0.5%, 2.3%, 5.9%, and 9.4%, respectively, translating into numbers needed to harm of 200, 43, 17, and 11 persons, respectively.

The risk of development of severe UAEs changes over time. We created time-dependent regression models for different time cutpoints (defined as the hazard ratios of severe UAEs developing before vs after the time cutpoint relative to the risk in the control population). The additional risk of development of a UAE related to treatment for LDR, LDR plus EBRT, and HDR plus EBRT was greatest within the 2 years after treatment and continued to decline over time. For HDR monotherapy, the risk was greatest within the first 4 years and then declined. The risk of development of a severe UAE matched the baseline risk of the control population for all treatments at 4 years after therapy (Fig. 2). This effect is also graphically represented in Figure 1, where one can observe changes in the slopes of the treatment curves before 2 to 4 years, which then become roughly proportional to the slope of the control population thereafter. For BOO specifically, the additional risk patterns followed those of overall UAEs and are shown in Figure 3. Increasing age, Charlson Comorbidity Index score, and baseline adverse events all increased the risk of development of a UAE after therapy.

Discussion

A toxicity comparative-effectiveness study comparing surgical and radiation therapies, as well as their combinations, on the incidence of severe urologic adverse events was recently published (2). In that study, combinations of therapies resulted in higher incidences of UAEs than monotherapy. Unsurprisingly, prostate treatment was associated with a statistically significant increase in UAEs over a control population without prostate cancer. At 10 years, radical prostatectomy had significantly worse CTCAE-rated urologic toxicity than brachytherapy or EBRT monotherapy. In that study, however, both HDR brachytherapy and LDR (also known as "seed implant") brachytherapy were grouped together so that the authors could not distinguish differences between these techniques. Our study was performed to specifically evaluate for differences between the HDR and LDR techniques, alone and in combination with EBRT.

Table 1 Unweighted demographic characteristics of non-cancer control group and prostate cancer cohort stratified by treatment group

	Control	LDR	HDR	LDR plus EBRT	HDR plus EBRT	*P* value
Total	93,803 (79.40%)	12,801 (10.80%)	685 (0.60%)	8518 (7.20%)	2392 (2.00%)	
Age						
66-69 y	43,554 (46.4%)	3314 (25.9%)	177 (25.8%)	2181 (25.6%)	570 (23.8%)	.0004
70-74 y	29,822 (31.8%)	5157 (40.3%)	260 (38.0%)	3486 (40.9%)	888 (37.1%)	
75-79 y	12,993 (13.9%)	3382 (26.4%)	192 (28.0%)	2237 (26.3%)	735 (30.7%)	
≥80 y	7434 (7.9%)	948 (7.4%)	56 (8.2%)	614 (7.2%)	199 (8.3%)	
Race						
NH white	77,163 (82.3%)	11,325 (88.5%)	625 (91.2%)	7156 (84.0%)	2017 (84.3%)	<.0001
Black	6350 (6.8%)	867 (6.8%)	26 (3.8%)	864 (10.1%)	182 (7.6%)	
Hispanic	2534 (2.7%)	136 (1.1%)	-	146 (1.7%)	34 (1.4%)	
Asian or PI	4296 (4.6%)	263 (2.1%)	19 (2.8%)	191 (2.2%)	100 (4.2%)	
Other or unknown	3460 (3.7%)	210 (1.6%)	-	161 (1.9%)	59 (2.5%)	
Income						
Q1	25,582 (27.3%)	2712 (21.2%)	124 (18.1%)	1598 (18.8%)	406 (17.0%)	<.0001
Q2	23,759 (25.3%)	2773 (21.7%)	167 (24.4%)	1703 (20.0%)	488 (20.4%)	
Q3	22,236 (23.7%)	3385 (26.4%)	212 (30.9%)	2287 (26.8%)	711 (29.7%)	
Q4	22,226 (23.7%)	3931 (30.7%)	182 (26.6%)	2930 (34.4%)	787 (32.9%)	
Education						
Q1	26,025 (27.7%)	2831 (22.1%)	57 (8.3%)	2047 (24.0%)	311 (13.0%)	<.0001
Q2	23,633 (25.2%)	3072 (24.0%)	144 (21.0%)	2077 (24.4%)	443 (18.5%)	
Q3	23,069 (24.6%)	3321 (25.9%)	233 (34.0%)	2128 (25.0%)	718 (30.0%)	
Q4	21,076 (22.5%)	3577 (27.9%)	251 (36.6%)	2266 (26.6%)	920 (38.5%)	
Charlson Comorbidity Index score						
0	63,571 (67.8%)	8346 (65.2%)	431 (62.9%)	5293 (62.1%)	1506 (63.0%)	.0007
1	18,849 (20.1%)	3056 (23.9%)	176 (25.7%)	2195 (25.8%)	615 (25.7%)	
2	6764 (7.2%)	926 (7.2%)	60 (8.8%)	695 (8.2%)	170 (7.1%)	
≥3	4619 (4.9%)	473 (3.7%)	18 (2.6%)	335 (3.9%)	101 (4.2%)	
T category						
1		6708 (52.4%)	329 (48.0%)	3652 (42.9%)	773 (32.3%)	<.0001
2a		2110 (16.5%)	117 (17.1%)	1381 (16.2%)	384 (16.1%)	
2b		742 (5.8%)	-	1142 (13.4%)	310 (13.0%)	
2 NOS		2989 (23.3%)	184 (26.9%)	2058 (24.2%)	696 (29.1%)	
3		29 (0.2%)	-	179 (2.1%)	198 (8.3%)	
Unknown		223 (1.7%)	0 (0.0%)	106 (1.2%)	31 (1.3%)	
Grade						
1		348 (2.7%)	-	102 (1.2%)	42 (1.8%)	<.0001
2		10,381 (81.1%)	482 (70.4%)	4429 (52.0%)	1192 (49.8%)	
3		1764 (13.8%)	193 (28.2%)	3789 (44.5%)	1125 (47.0%)	
Unknown		308 (2.4%)	-	198 (2.3%)	33 (1.4%)	
Tx year						
1998	5481 (5.8%)	428 (3.3%)	-	356 (4.2%)	109 (4.6%)	<.0001
1999	5029 (5.4%)	515 (4.0%)	-	387 (4.5%)	168 (7.0%)	
2000	4887 (5.2%)	928 (7.2%)	22 (3.2%)	855 (10.0%)	231 (9.7%)	
2001	4877 (5.2%)	1416 (11.1%)	44 (6.4%)	1044 (12.3%)	280 (11.7%)	
2002	6147 (6.6%)	1634 (12.8%)	43 (6.3%)	1136 (13.3%)	292 (12.2%)	
2003	7606 (8.1%)	1670 (13.0%)	70 (10.2%)	960 (11.3%)	255 (10.7%)	
2004	8764 (9.3%)	1567 (12.2%)	103 (15.0%)	897 (10.5%)	253 (10.6%)	
2005	10,649 (11.4%)	1426 (11.1%)	112 (16.4%)	853 (10.0%)	246 (10.3%)	
2006	12,315 (13.1%)	1404 (11.0%)	116 (16.9%)	907 (10.6%)	223 (9.3%)	
2007	15,663 (16.7%)	1394 (10.9%)	122 (17.8%)	910 (10.7%)	254 (10.6%)	
2008	12,385 (13.2%)	419 (3.3%)	29 (4.2%)	213 (2.5%)	81 (3.4%)	
Registry						
San Francisco	3706 (4.0%)	397 (3.1%)	58 (8.5%)	196 (2.3%)	238 (9.9%)	<.0001
Connecticut	5369 (5.7%)	1124 (8.8%)	-	457 (5.4%)	-	
Detroit	6074 (6.5%)	918 (7.2%)	58 (8.5%)	770 (9.0%)	185 (7.7%)	
Hawaii	1635 (1.7%)	168 (1.3%)	-	170 (2.0%)	40 (1.7%)	
Iowa	5906 (6.3%)	721 (5.6%)	-	269 (3.2%)	-	

(*continued on next page*)

Table 1 (*continued*)

	Control	LDR	HDR	LDR plus EBRT	HDR plus EBRT	*P* value
New Mexico	2763 (2.9%)	182 (1.4%)	27 (3.9%)	71 (0.8%)	24 (1.0%)	
Seattle	5252 (5.6%)	1231 (9.6%)	-	552 (6.5%)	127 (5.3%)	
Utah	2804 (3.0%)	383 (3.0%)	392 (57.2%)	34 (0.4%)	786 (32.9%)	
Atlanta	3421 (3.6%)	688 (5.4%)	-	1286 (15.1%)	90 (3.8%)	
San Jose	2274 (2.4%)	396 (3.1%)	-	245 (2.9%)	25 (1.0%)	
Los Angeles	8225 (8.8%)	486 (3.8%)	29 (4.2%)	268 (3.1%)	208 (8.7%)	
Greater California	18,960 (20.2%)	1862 (14.5%)	33 (4.8%)	598 (7.0%)	222 (9.3%)	
Kentucky	7711 (8.2%)	1122 (8.8%)	-	485 (5.7%)	21 (0.9%)	
Louisiana	6178 (6.6%)	701 (5.5%)	-	422 (5.0%)	28 (1.2%)	
New Jersey	13,525 (14.4%)	2422 (18.9%)	52 (7.6%)	2695 (31.6%)	381 (15.9%)	
Baseline AE						
0	92,195 (98.3%)	11,797 (92.2%)	638 (93.1%)	7773 (91.3%)	2250 (94.1%)	<.0001
1	1608 (1.7%)	1004 (7.8%)	47 (6.9%)	745 (8.7%)	142 (5.9%)	

Abbreviations: AE = adverse event; EBRT = external beam radiation therapy; HDR = high dose rate; LDR = low dose rate; NH = non-Hispanic; NOS = not otherwise specified; PI = Pacific Islander; Q1, Q2, Q3, and Q4 = Quartiles 1, 2, 3, and 4. .

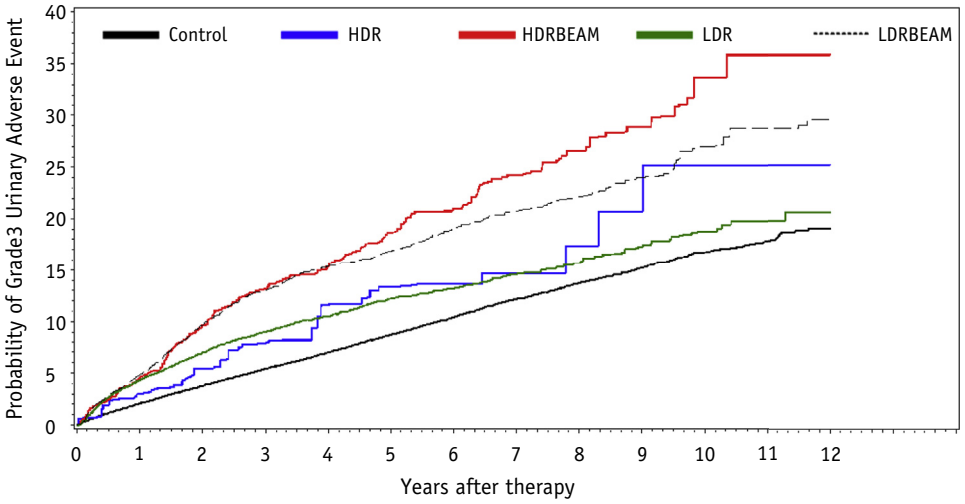
Comparative-effectiveness studies are important to aid providers and their patients in making informed decisions about the relative merits of these competing treatments. Few randomized trials have been completed comparing the various treatment modalities. Those that have been published tend to be criticized for either being underpowered or using techniques no longer considered modern-care standards, and so comparisons with modern practices are unclear. In general, men definitively treated for localized prostate cancer have a long life expectancy and can manifest side effects of surgical and radiation therapies many years after completing therapy.

The SEER-Medicare database is an excellent resource for large-scale, multi-cohort, real-world comparative-effectiveness studies because one can use procedural codes to glean the probability of toxicities over time based on treatments received by Medicare beneficiaries. Large population databases present an excellent opportunity to perform highly statistically powered comparisons for endpoints of interest when large-scale randomized trials or meta-analyses cannot otherwise be performed. However, given the possible inherent treatment selection biases present in retrospective analyses, drawing firm conclusions about comparative outcomes can be challenging. Propensity weighting can be used to statistically balance these biases, making any conclusions drawn from the comparisons more accurate (13). A limitation of propensity matching, however, is that it is only as good as the covariates in the model, so missing covariates of interest could make the interpretation of propensity-matched groups less

Table 2 Comparative toxicity rates in control group and patients receiving LDR monotherapy, HDR monotherapy, LDR plus EBRT, or HDR plus EBRT

	4 y					8 y				
	Control	LDR	HDR	LDR plus EBRT	HDR plus EBRT	Control	LDR	HDR	LDR plus EBRT	HDR plus EBRT
Any UAE										
Cumulative incidence, %	7.03	10.53	11.6	15.36	15.39	13.76	15.67	17.37	22.16	26.61
95% CI, %	6.83-7.23	9.94-11.15	8.7-15.37	14.46-16.31	13.68-17.29	13.36-14.16	14.77-16.63	13.12-22.82	20.87-23.51	23.76-29.73
Absolute excess risk over control, %	-	3.5	4.57	8.33	8.36	-	1.91	3.61	8.4	12.85
Number needed to harm	-	29	22	12	12	-	52	28	12	8
Bladder outlet obstruction										
Cumulative incidence, %	5.99	8.48	9.34	12.44	13.11	11.81	12.33	14.08	17.75	21.19
95% CI, %	5.81-6.18	7.95-9.05	6.79-12.78	11.62-13.31	11.54-14.88	11.44-12.19	11.53-13.18	10.21-19.25	16.59-18.98	18.68-23.98
Absolute excess risk over control, %	-	2.49	3.35	6.45	7.12	-	0.52	2.27	5.94	9.38
Number needed to harm	-	40	30	16	14	-	192	44	17	11

Abbreviations: CI = confidence interval; EBRT = external beam radiation therapy; HDR = high dose rate; LDR = low dose rate; UAE = urinary adverse event.



	Number at Risk Years After Therapy										
	0	1	2	3	4	5	6	7	8	9	10
Control	93748	66008	48863	36338	26615	19075	13121	8662	5695	3275	1522
HDR	493	381	298	235	193	164	132	84	51	24	13
HDRBEAM	1842	1434	1091	829	645	477	339	240	162	93	46
LDR	11765	9239	7123	5576	4263	3211	2303	1597	1017	574	273
LDRBEAM	6971	5413	4275	3378	2644	2040	1456	991	628	363	173

Fig. 1. Weighted cumulative incidence of grade 3 urinary adverse events by treatment. *Abbreviations:* HDR = high-dose-rate brachytherapy; HDRBEAM = high-dose-rate brachytherapy with external beam radiation therapy; LDR = low-dose-rate brachytherapy; LDRBEAM = low-dose-rate brachytherapy with external beam radiation therapy.

relevant if missing covariates would bias the results. We attempted to minimize bias by adjusting for known prognostic features that include age, grade, race, T category, socioeconomic status, education level, income, year of treatment, comorbidities, and geographic location within the United States.

Although the number needed to harm was calculated to be fewer for HDR monotherapy versus LDR monotherapy, we cannot conclude that HDR is more toxic than LDR because the 95% CIs of the hazard ratios for LDR monotherapy and HDR monotherapy overlapped before and after every cutpoint in time tested. It may be possible that HDR

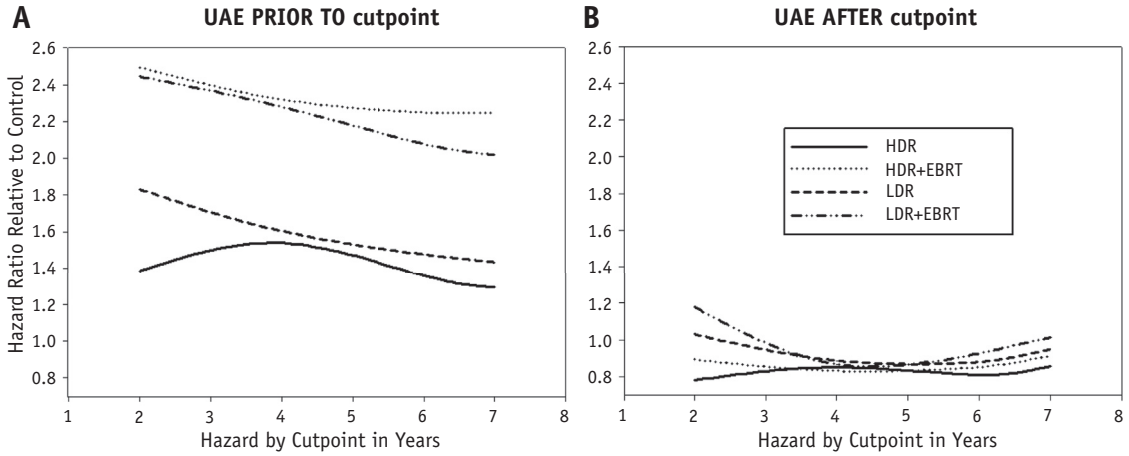


Fig. 2. The relative risk of development of any grade 3 urinary adverse event (UAE), according to the Common Terminology Criteria for Adverse Events, compared with the control population is nonproportional and varies over time. The Cox regression–derived hazard ratio for an adverse event changes depending on the time reference used in the model. The hazard ratio of a UAE before the time reference (left) and the hazard ratio of a UAE after the time reference (right), by treatment received, are shown. *Abbreviations:* HDR = high-dose-rate brachytherapy; HDR + ERBT = high-dose-rate brachytherapy with external beam radiation therapy; LDR = low-dose-rate brachytherapy; LDR + ERBT = low-dose-rate brachytherapy with external beam radiation therapy.

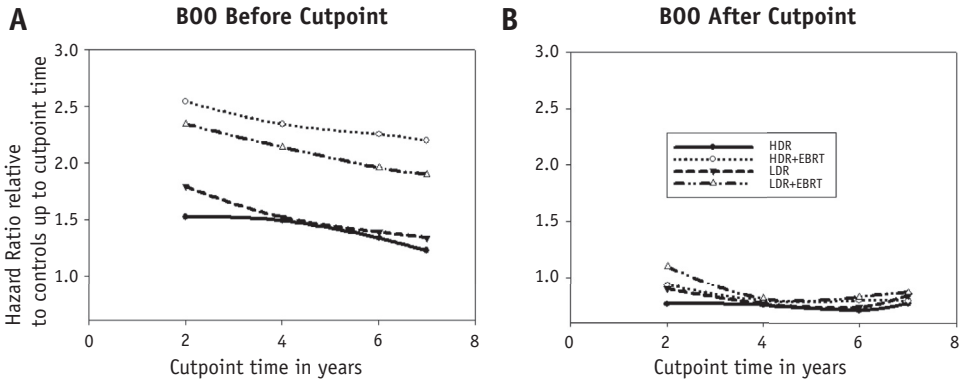


Fig. 3. The relative risk of development of any grade 3 bladder outlet obstruction (BOO) event, according to the Common Terminology Criteria for Adverse Events, compared with the control population is nonproportional and varies over time. The Cox regression–derived hazard ratio for an adverse event changes depending on the time reference used in the model. The hazard ratio of a BOO event before the time reference (left) and the hazard ratio of a BOO event after the time reference (right), by treatment received, are shown. *Abbreviations:* HDR = high-dose-rate brachytherapy; HDR + ERBT = high-dose-rate brachytherapy with external beam radiation therapy; LDR = low-dose-rate brachytherapy; LDR + ERBT = low-dose-rate brachytherapy with external beam radiation therapy.

monotherapy is more toxic than LDR; however, HDR monotherapy was infrequently practiced during the years 1998 to 2007, and as such, the HDR monotherapy cohort is significantly smaller than the LDR monotherapy cohort, which may lead to a power issue to resolve a statistical difference. What we can conclude is that the differences in toxicity observed between the HDR and LDR cohorts do not meet the statistical requirement of being due to chance <5% of the time. In addition, the CIs of the hazard ratios for LDR plus EBRT overlapped with those for HDR plus EBRT, and similar conclusions can be drawn. In our analyses, we were not able to adjust for prostate size and baseline bladder function. It is possible that these parameters were worse in patients receiving HDR over LDR (both as monotherapy or in combination with EBRT), which may lead to an apparent increase in toxicity of HDR over LDR. The combination therapies, however, clearly had an increased risk of treatment for genitourinary toxicities over the monotherapies.

It is often taught in both urology and radiation oncology training programs that radiation therapy–induced side effects are "the gift that keeps on giving." This study demonstrates that the cumulative incidence of genitourinary toxicity increases over time but that the risk is highest immediately after treatment, decreases over time, and drops to a rate as low as that in controls in just a few years. When one looks at the hazard ratio plots before the time cutpoints, one can see that in general, the highest risk of increased toxicity comes relatively early (first 2 years), with a diminishing toxicity risk that seems to be abrogated over that of controls by the 4-year time point. As an example, we can look at the risk of a UAE for LDR monotherapy at a 2-year versus 4-year cutpoint. Before the 2-year cutpoint, the hazard ratio is 1.8, and after, it is 1.0; before the 4-year cutpoint, the hazard ratio is 1.6, and after, it is 0.9. The best way to interpret these data is that the increased risk is decelerating over time and that the highest increase in risk occurs within the first 2 years, with some residual risk occurring up to year 4, in this example. HDR monotherapy was the only treatment in this analysis whose risk of UAEs accelerated up until year 4 and then decelerated afterward. When one looks exclusively at the plots after the time cutpoints, it appears that the hazard ratios may be trending upward again after 6 years but do not approach the risk within the first 4 years. Our study, which observed a population in which diagnoses were made between 1998 and 2007, does not have further follow-up that would allow us to discern if this "later" upward trend is due to actual increasing very-late-effect risk versus statistical noise. In a small institutional case series of severe CTCAE grade 3 urologic toxicity performed at the University of Utah, the average latency period to the first grade 3 event was 77 months (14). Like the findings of this study, combination therapies appeared to put persons at higher risk of toxicity, but HDR also appeared to be a risk factor versus LDR (14).

For the clinician in practice, we recommend the following: men should undergo closer monitoring for UAEs within the first few years after brachytherapy, and this is especially true for men undergoing brachytherapy and EBRT. Afterward, because their risk of a UAE is the same as that in a control population, no special interventions to evaluate for urinary morbidity specifically are needed if a UAE has not already developed in these patients (although men should still be evaluated for biochemical failure).

In general, most comparative-effectiveness studies of LDR- and HDR-based techniques, when matched stage for stage, showed equivalent efficacy for biochemical failure–free survival (15-17). In our literature search, there were very few articles specifically performing comparative-effectiveness studies of HDR versus LDR therapies for toxicity using the same diagnostic criterion of each population. The Technology Assessment Program at the Agency

Table 3 Other studies using CTCAE or ICD criteria that quantify grade 3 GU toxicity risks

Author, year of publication	Treatment	Scoring system	Median follow-up	Toxicities	No. of patients
Barkati (20), 2012	HDR BT	CTCAE, RTOG, EPIC	39.5 mo	Late GU grade 3: dysuria, 8%; gross hematuria, 1%; urinary retention, 7%; urinary incontinence, 0% EPIC (baseline and 48 mo, respectively): urinary, 93.1 and 84.1; bowel, 96.4 and 94.6; sexual, 70.2 and 35.9; hormonal, 93.2 and 95.5	79
Buckstein (21), 2013	BT or BT + EBRT	CTCAE, RTOG, IPSS	11.5 y	GU grade 3: 3%	131
Crook (22), 2008	BT	CTCAE	41 mo (range, 12-93 mo)	Urinary retention requiring catheterization or surgery: 3.4%; severe urinary urgency: 6.4%	484
Elliott (23), 2007	RP, EBRT, BT, cryotherapy, androgen-deprivation therapy, RP + EBRT, BT + EBRT, or watchful waiting	CPT, ICD-9	2.7 y	Urethral stricture: 5.2% (range by prostate cancer treatment type, 1.1%-8.4%)	6597
Ghadjar (24), 2009	HDR BT + IMRT	CTCAE	3.1 y	Late GU grade 3: 10.9%; grade 4: 1.6%	64
Gomez-Iturriaga Pina (25), 2009	LDR BT	CTCAE	63 mo (range, 30-108 mo)	Acute GU grade 3: 0%; late GU grade 3: 3.2%	96
Jarosek (2), 2015	EBRT, BT, EBRT + BT, RP, RP + EBRT, or cryotherapy	CTCAE	4.14 y (with 10-y cumulative)	10-y propensity-weighted cumulative incidence of grade 3 or 4 events Incontinence: EBRT, 0.28%; BT, 0.61%; BT + EBRT, 0.95%; RP, 6.24%; RP + EBRT, 7.11%; cryotherapy, 2.44% Ureteral stricture: EBRT, 2.22%; BT, 1.78%; BT + EBRT, 1.86%; RP, 1.72%; RP + EBRT, 2.7%; cryotherapy, 1.05% Fistula: EBRT, 0.06%; BT, 0.11%; BT + EBRT, 0.28%; RP, 0.33%; RP + EBRT, 0%; cryotherapy, NA Bladder outlet obstruction: EBRT, 13.29%; BT, 15.68%; BT + EBRT, 23.26%; RP, 20.35%; RP + EBRT, 27.03%; cryotherapy, 15.03%	100,970
Kim (26), 2013	EBRT, BT, EBRT + BT, or surveillance	CPT, ICD-9	94 mo	GU grade 2-4 toxicity rate/1000: EBRT, 35; BT, 43; EBRT + BT, 60; surveillance, 32	86,038

(*continued on next page*)

Table 3 (*continued*)

Author, year of publication	Treatment	Scoring system	Median follow-up	Toxicities	No. of patients
Matzinger (27), 2009	3D-CRT or IMRT	CTCAE	- (1 mo after RT)	Grade 3: 1.8%	791
Mohammed (28), 2012	BT, LDR, EBRT-IGRT, or HDR + EBRT	CTCAE	4.8 y	Acute GU grade 2+: BT, 35%; EB-IGRT, 43%; HDR + EBRT, 50% Acute GU grade 3+: BT, 8%; EB-IGRT, 4%; HDR + EBRT, 7% Late GU grade 2+: BT, 22%; EB-IGRT, 21%; HDR + EBRT, 28% Late GU grade 3+: BT, 5%; EB-IGRT, 4%; HDR + EBRT, 12%	1903
Sathya (29), 2005	BT + EBRT or EBRT	NCIC-CTG Expanded Common Toxicity Criteria	8.2 y	Acute GU grade 3 or 4: BT + EBRT, 2%; EBRT, 3.8% Late GU grade 3 or 4: BT + EBRT, 13.7%; EBRT, 3.8%	104
Whalley (30), 2012	HDR BT + EBRT	CTCAE	56 mo	Late GU toxicity grade 3 at 4 y: 1%	101
Wilcox (31), 2015	EBRT	CTCAE	59 mo	GU grade 3 at 5 y: 0.3%	675
Zelefsky (32), 2006	IMRT	CTCAE	7 y (range, 5-9 y)	8-y actuarial GU grade 3: 3%	561
Zelefsky (33), 2007	BT	CTCAE	63 mo	Late GU grade 3: 4%	367
Zelefsky (34), 2008	3D-CRT or IMRT	CTCAE	10 y (range, 5-18 y)	Late GU grade 3: 3%	1571
Current study	LDR, HDR, LDR + EBRT, or HDR + EBRT	CTCAE	4.3 y (range, 0-12 y)	8-y late GU grade 3: control, 13.8%; LDR, 15.7%; HDR, 17.4%; LDR + EBRT, 22.2%; HDR + EBRT, 26.6%	

Abbreviations: BT = brachytherapy; CPT = Current Procedural Terminology; CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; EPIC = Extended Prostate Index Composite; GU = genitourinary; HDR = high dose rate; ICD = *International Classification of Diseases*; ICD-9 = *International Classification of Diseases, Ninth Revision*; IGRT = image guided radiation therapy; IMRT = intensity modulated radiation therapy; IPSS = International Prostate Symptom Score; LDR = low dose rate; NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group; RP = radical prostatectomy; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; 3D-CRT = 3-dimensional conformal radiation therapy.

for Healthcare Research and Quality was tasked by the Centers for Medicare & Medicaid Services to perform a comparative-effectiveness study of various treatment techniques for prostate cancer for both efficacy and toxicity (18). The report showed that there was "insufficient" evidence to compare HDR and LDR brachytherapy for toxicity and that the data were inconsistent across studies. In the only study referenced in the Agency for Healthcare Research and Quality report, Martinez et al (19) showed that for Radiation Therapy Oncology Group−scored late grade 3 urologic toxicity, HDR and LDR were statistically indistinguishable. In our study, we are scoring toxicity that, by definition, would have resulted in CTCAE grade 3 to 4 toxicity, as opposed to the more limited Radiation Therapy Oncology Group scoring system used by Martinez et al. Our literature review of radiation therapy studies specifically evaluating toxicity by CTCAE criteria, or by *International Classification of Diseases* and Current Procedural Terminology coding as can be applied to CTCAE, is summarized in Table 3. This study's grade 3 toxicity report falls within the range of the studies reported in Table 3. Unlike the other studies, our study is unique in having a comparator to a baseline population of men who had not been treated for prostate cancer, which allowed us to quantify the number needed to harm, as reported in the Results section.

From a radiobiological point of view, HDR brachytherapy and LDR brachytherapy are substantively different (35). Classical radiobiological studies and teaching have shown that multiple, low-dose fractions of radiation therapy have a therapeutic ratio advantage over fewer, higher-dose fractions and should therefore create less long-term toxicity

with similar efficacy. As applied to brachytherapy, HDR can be considered extremely hypofractionated radiation therapy (delivering all of its dose over a few hours of total treatment time and calendar days), whereas LDR can be considered extremely hyperfractionated (delivering very low doses continually over many months). Risk estimates of toxicity for any given tissue, however, are based on the intrinsic radiosensitivity of that specific tissue and can be modeled by the linear-quadratic equation based on experimental data derived from cell-survival curves for treatment with increasing doses of radiation therapy (36). This results in an α/β ratio that characterizes the radiosensitivity of tissues. In general, radiosensitive tissues, such as fast-growing tumors, have a high α/β ratio, whereas "normal" tissues have a low α/β ratio. In these scenarios, multiple, low-dose fractions would be predicted to result in lower toxicity than fewer, higher-dose fractions, and LDR exposures would be predicted to have lower toxicity. In the case of tissues abutting the prostate gland, however, the α/β ratio for the cancer may be similar to or lower than that of the rectum and bladder, which would imply that there is no therapeutic advantage to using multiple, low-dose treatments, and HDR-like fractions may be superior for late toxicity (37, 38). In a sense, this debate is an academic one, based on predictions from equations modeling toxicity. Therefore, real-world toxicity data, such as those based on our study, as well as others, ultimately inform the provider and the patient more than radiobiological modeling.

How can both LDR and HDR therapies produce such similar urologic toxicity profiles despite such extreme differences in radiobiological dose delivery over the time frame studied? One explanation may be that both HDR and LDR treatments have such extreme conformality. Unlike external beam therapies, including x-ray—based therapies (eg, intensity modulated radiation therapy, volumetric modulated arc therapy, and 3-dimensional conformal radiation therapy with or without image guidance) and proton therapy, brachytherapy achieves very high doses to the target volume (prostate) with extremely rapid falloff of dose gradients away from the target. Therefore, doses to large volumes of critical neighboring structures (organs at risk [OARs]), like the bladder and rectum, are minimized. It is possible that with such little exposure of OARs to wide-field, low-dose exposures or with lower absolute volumes of OAR structures to the highest-dose regions, we cannot discern significant differences between the LDR and HDR techniques.

A limitation of this comparative toxicity study is that we are only evaluating the time to a first event. As such, the study may be underestimating the actual severity of toxicities by ignoring additional events in the same patient or the duration of the toxicity. For example, if a person who underwent HDR and a person who underwent LDR both received a suprapubic catheter by 2 years, they look equivalent in this study, even if one person had the catheter for 1 week and the other had it for a lifetime. In addition, if the person who underwent HDR then went on to receive additional interventions whereas the person who underwent LDR did not, it would imply HDR could be more toxic. We are currently designing additional studies to capture this "persistence-of-toxicity" data, which will lead to a better understanding of severity and quality-of-life implications. Additional limitations include the fact that we have restricted our analysis to UAEs and have not yet quantified toxicity to the bowel or sexual dysfunction. These additional studies are also planned.

In conclusion, this study is the most highly powered urologic toxicity comparative-effectiveness study of brachytherapy performed to date, showing that HDR brachytherapy and LDR brachytherapy have a similar incidence of clinically significant grade 3 toxicity. The excess risk of toxicity occurs primarily in the first 2 to 4 years after therapy and then falls to a rate similar to the baseline hazard of untreated men over the next decade. Because we used CTCAE criteria as applied to wide swaths of the US population, as opposed to single-institutional reports from centers of excellence, persons designing multi-institutional National Cancer Institute—funded prospective studies could use these toxicity results to guide their power calculations on toxicity endpoints and as a historic comparator group. Finally, as payers and legislators struggle with alternative payment models for competing oncologic treatments, studies such as this are valuable in providing real-world data on competing toxicities that, when integrated with competing survival data, will prove useful in formulating policy and payment models.

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