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Cancer-specific survival after radical prostatectomy versus external beam radiotherapy in high-risk and very high-risk African American prostate cancer patients

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Abstract

Background: To test for differences in cancer-specific mortality (CSM) rates between radical prostatectomy (RP) vs external beam radiotherapy (EBRT) in National Comprehensive Cancer Network (NCCN) high-risk African American patients, as well as Johns Hopkins University (JHU) high-risk and very high-risk patients.

Materials and methods: Within the Surveillance, Epidemiology, and End Results database (2010–2016), we identified 4165 NCCN high-risk patients, of whom 1944 (46.7%) and 2221 (53.3%) patients qualified for JHU high-risk or very high-risk definitions. Of all 4165 patients, 1390 (33.5%) were treated with RP versus 2775 (66.6%) with EBRT. Cumulative incidence plots and competing risks regression

models addressed CSM before and after 1:1 propensity score matching between RP and EBRT NCCN high-risk patients. Subsequently, analyses were repeated separately in JHU high-risk and very high-risk subgroups. Finally, all analyses were repeated after landmark analyses were applied.

Results: In the NCCN high-risk cohort, 5-year CSM rates for RP versus EBRT were 2.4 versus 5.2%, yielding a multivariable hazard ratio of 0.50 (95% confidence interval [CI] 0.30–0.84, $p = 0.009$) favoring RP. In JHU very high-risk patients 5-year CSM rates for RP versus EBRT were 3.7 versus 8.4%, respectively, yielding a multivariable hazard ratio of 0.51 (95% CI: 0.28–0.95, $p = 0.03$) favoring RP. Conversely, in JHU high-risk patients, no significant CSM difference was recorded between RP vs EBRT (5-year CSM rates: 1.3 vs 1.3%; multivariable hazard ratio: 0.55, 95% CI: 0.16–1.90, $p = 0.3$). Observations were confirmed in propensity score-matched and landmark analyses adjusted cohorts.

Conclusions: In JHU very high-risk African American patients, RP may hold a CSM advantage over EBRT, but not in JHU high-risk African American patients.

KEYWORDS

external beam radiotherapy, high-risk, prostate cancer, radical prostatectomy, very high-risk

1 | INTRODUCTION

African Americans with prostate cancer have been studied in relatively great detail with respect to local treatment.[1–5] However, data is scarce, whether cancer-specific mortality (CSM) differences distinguish between African American radical prostatectomy (RP) versus external beam radiotherapy (EBRT) patients in the specific context of high-risk prostate cancer according to the National Comprehensive Cancer Network (NCCN) criteria and subsequently, in the specific groups of Johns Hopkins University (JHU) high-risk and very high-risk prostate cancer. The JHU risk classification can be seen as a more precise stratification approach of the overall cohort of the NCCN high-risk prostate cancer patients.[6,7] To the best of our knowledge, no large scale, population-based analyses tested for treatment modalities which may hold an advantage in regard to CSM, especially in the JHU high-risk and very high-risk African American patients. We addressed this knowledge gap and tested for CSM differences according to RP versus EBRT in high-risk African American PCa patients. Our analyses addressed the overall NCCN high-risk cohort and subsequently, selectively focused on JHU high-risk and very high-risk African American patients. Propensity score matching (PSM) addressed baseline differences between RP versus EBRT treated patients. We hypothesized that no CSM differences would distinguish between RP versus EBRT in (a) the overall NCCN high-risk and in (b) both JHU high-risk and JHU very high-risk African Americans. We addressed this knowledge gap within the Surveillance, Epidemiology, and End Results (SEER) database (2010–2016) (Figures 1–3).

2 | MATERIAL AND METHODS

2.1 | Study population

The current SEER database samples 34.6% of the US population and approximates it in demographic composition and cancer incidence.[8] Within SEER database 2010–2016, we identified and included all patients more than or equal to 18 years old with histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9) that fulfilled high-risk National Comprehensive Cancer Network (NCCN) prostate cancer criteria (defined as Gleason sum 8–10, or PSA > 20 ng/ml, or clinical stage ≥T3).[9] Patients with missing vital status, unknown prostate-specific antigen (PSA), unknown clinical T-stage/M-stage, and unknown biopsy Gleason score were excluded. Moreover, we excluded autopsy or death certificate only cases and all patients with treatment other than RP or EBRT. Subsequently, we applied the JHU criteria to stratify NCCN high-risk patients between (a) JHU high-risk (presence of at least one of the following criteria: cT3a or GGG IV/V or PSA > 20 ng/ml) and (b) JHU very high-risk (presence of at least one of the following criteria: cT3b–cT4 and/or primary Gleason pattern 5 and/or 2–3 high-risk features, and/or ≥5 positive biopsy cores and biopsy pathology of

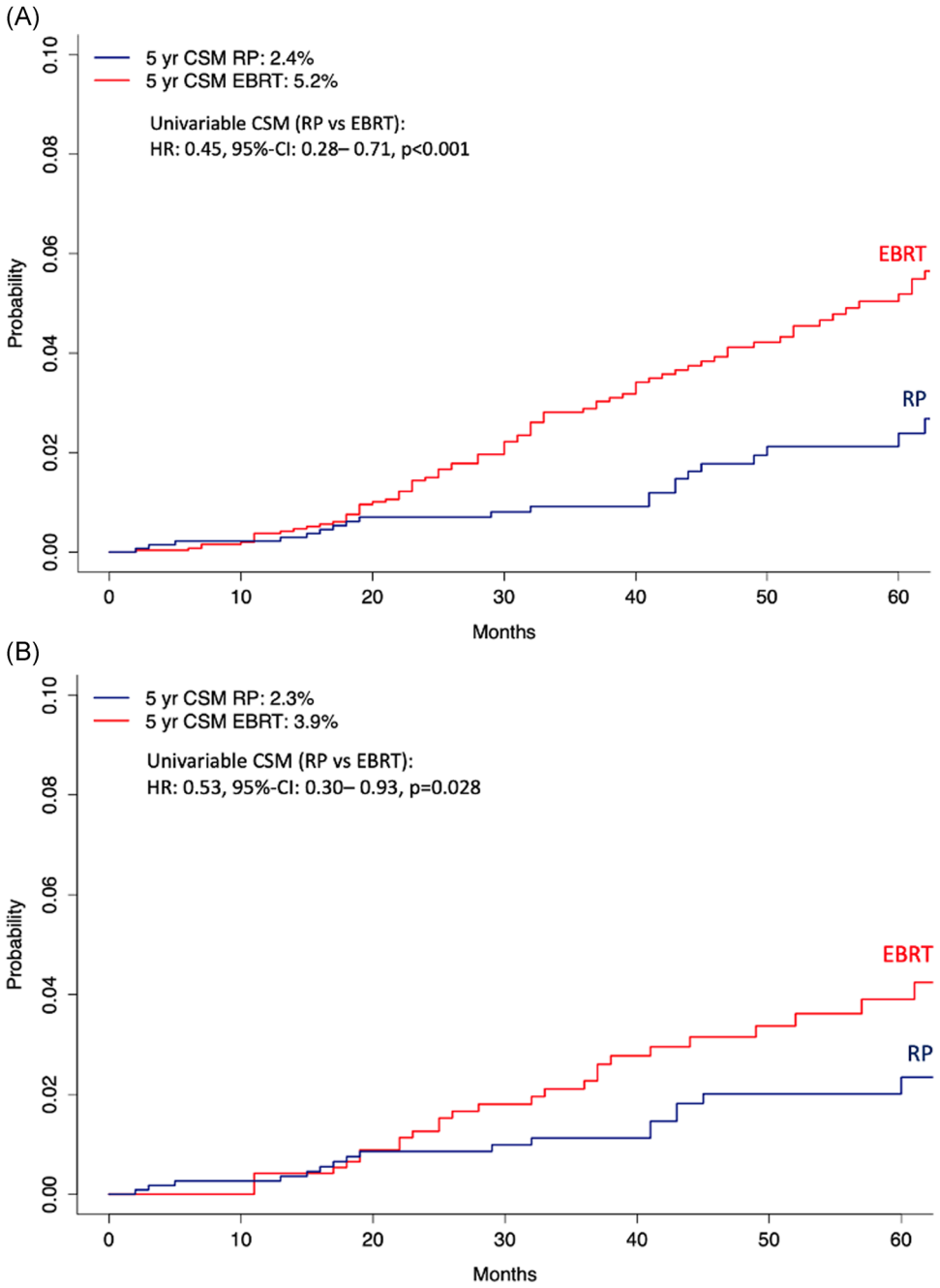

FIGURE 1 Cumulative incidence plots (A) before and (B) after 1:1 propensity score matching depicting cancer-specific mortality (CSM) after adjusting for other cause mortality (OCM) in radical prostatectomy versus external beam radiotherapy in NCCN high-risk African American prostate cancer patients. CI, confidence interval; EBRT, external beam radiotherapy; RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

GGG IV/V).[9,10] Since biopsy GGG characteristics are unavailable for each separate biopsy core in the SEER database, we relied on more than or equal to five positive biopsy cores and biopsy pathology of GGG IV or V as proxy, according to previously defined methodology.[11] CSM was defined as deaths attributable to prostate cancer. Conversely, other cause mortality (OCM) was defined as deaths attributable to other causes than prostate cancer. Follow-up was defined as the time from diagnosis to the end of the study period, loss to follow-up, CSM, or OCM.

2.2 | Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. The χ^2 tested the statistical significance in proportions' differences. The *t*-test and Kruskal–Wallis test examined the statistical significance of means' and distributions' differences. The first part of the analysis was to test for differences in CSM between RP and EBRT in the entire cohort of

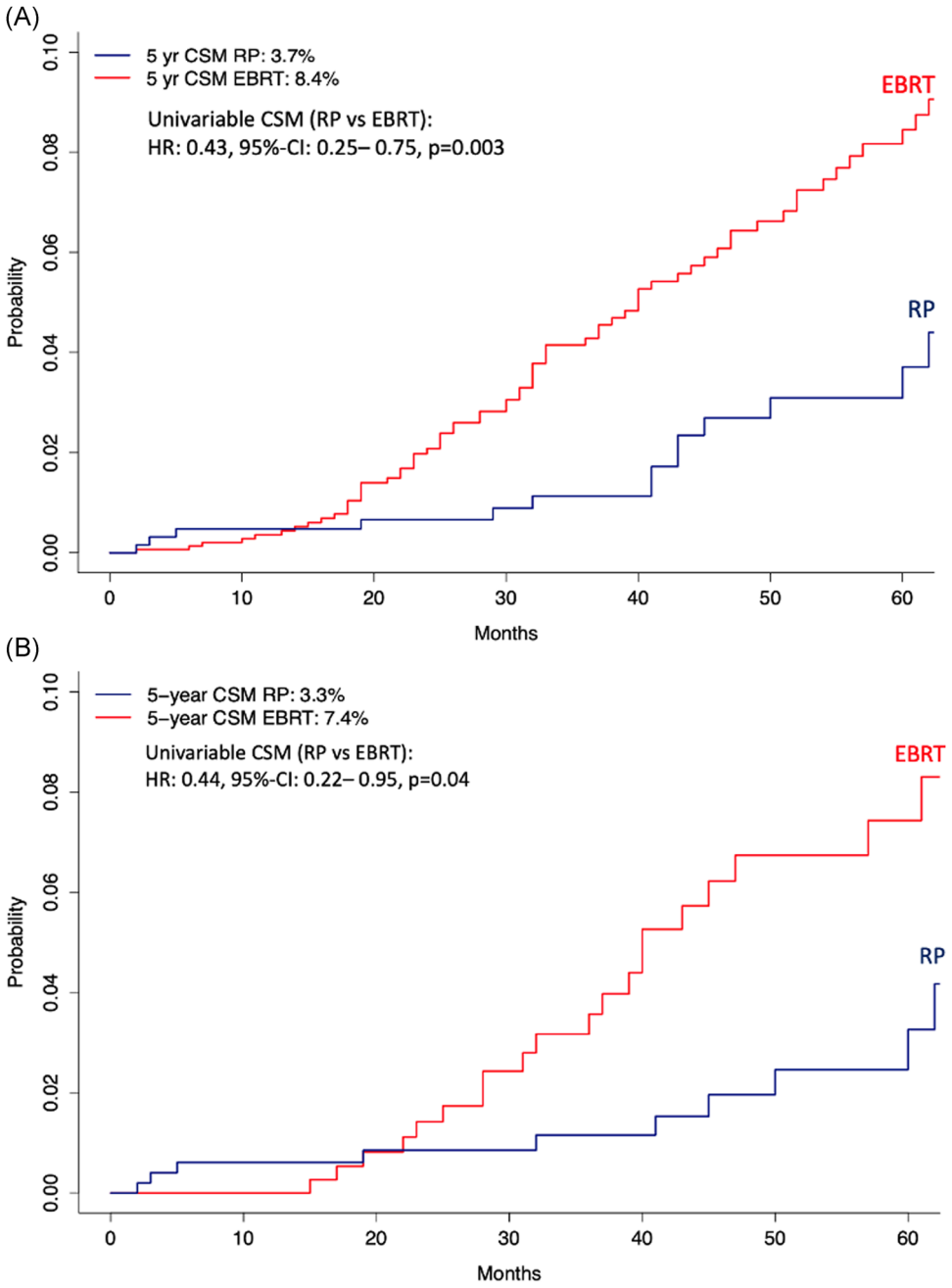

FIGURE 2 Cumulative incidence plots (A) before and (B) after 1:1 propensity score matching depicting cancer-specific mortality (CSM) after adjusting for other cause mortality (OCM) in radical prostatectomy versus external beam radiotherapy in JHU very high-risk African American prostate cancer patients. CI, confidence interval; EBRT, external beam radiotherapy; RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

NCCN high-risk patients. The second part of the analysis was to repeat survival analyses within the JHU high-risk and very high-risk subgroups. Formal interaction testing was performed to statistically validate the subgroup approach that differentiates between JHU high-risk and very high-risk patients.

Statistical analyses were based on four steps for NCCN high-risk patients. First, we separately addressed CSM before PSM in the overall cohort of NCCN high-risk prostate cancer patients. We relied on cumulative incidence plots to illustrate CSM and competing risks regression models to test for CSM differences, after adjustment for OCM between RP and EBRT prostate cancer patients. Adjustment covariates consisted of age (year intervals), PSA (in 1 ng/ml intervals), cT-stage (cT1/cT2, cT3a/cT3b/cT4), and cN-stage (cN0, cN1, and cNx). Second, we relied on PSM and matched all RP with EBRT NCCN high-risk patients in 1:1 fashion using 'nearest neighbor' method and caliper of 0.01. Matching

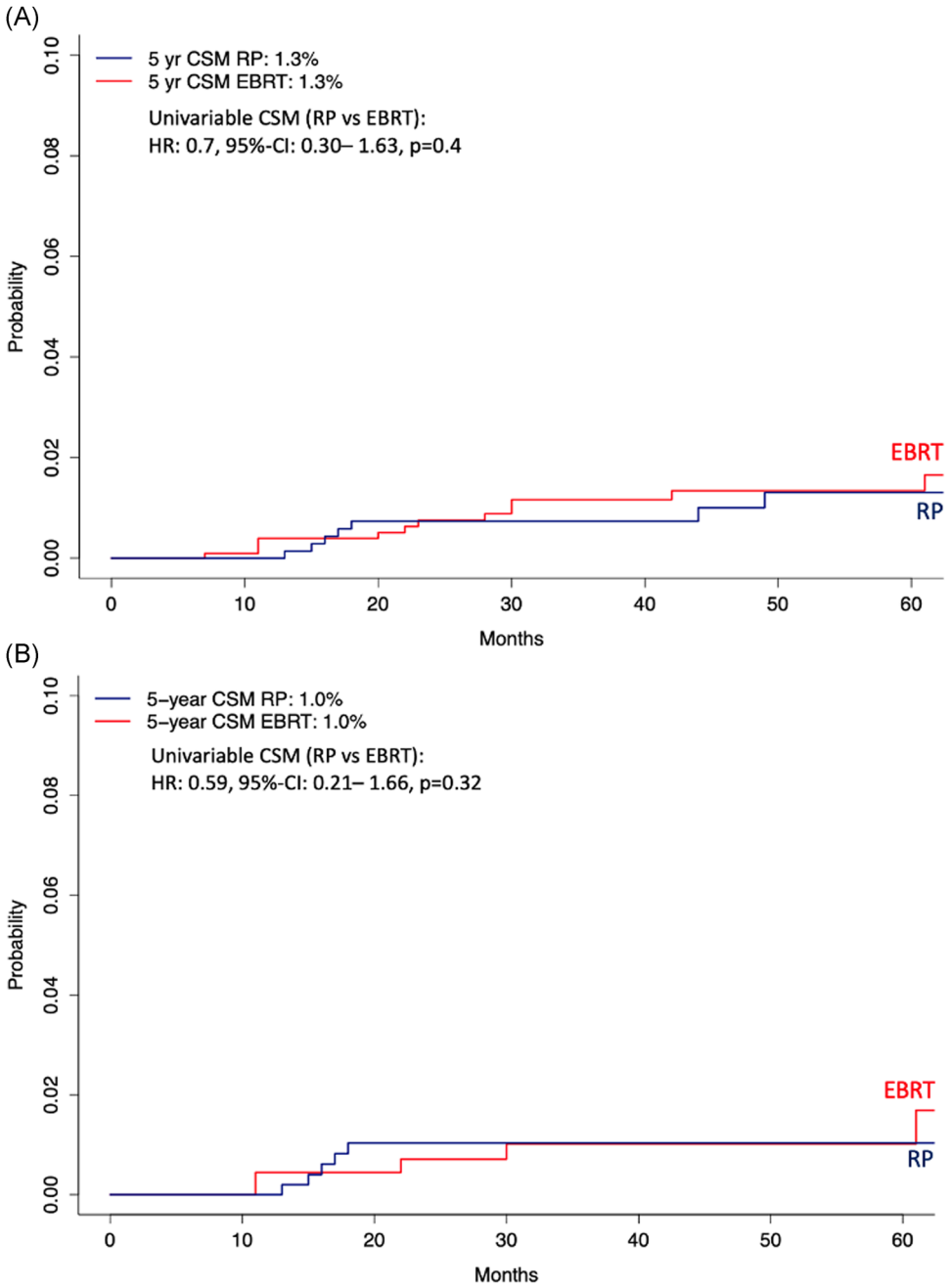

FIGURE 3 Cumulative incidence plots (A) before and (B) after 1:1 propensity score matching depicting cancer-specific mortality (CSM) after adjusting for other cause mortality (OCM) in radical prostatectomy versus external beam radiotherapy in JHU high-risk African American prostate cancer patients. CI, confidence interval; EBRT, external beam radiotherapy; HR, hazard ratio; RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

variables consisted of age (year intervals), PSA (in 1 ng/mL intervals), biopsy Gleason score (3 + 3, 3 + 4, 3 + 5, 4 + 3, 4 + 4, 4 + 5, 5 + 3, 5 + 4, 5 + 5), cT-stage (cT1, cT2, cT3a, cT3b, cT4) and cN-stage (cN0, cN1, cNx). Furthermore, we added into the competing risks regression model the JHU risk category, as well as the interaction term defined by JHU risk category (high-risk vs. very high-risk) and treatments (RP vs EBRT). Third, we repeated cumulative incidence and competing risks regression models in the overall NCCN high-risk cohort after PSM. The same covariates were used as above. Fourth, all analyses were repeated after landmark analyses at 6 months were applied to account for potential immortal biases. Finally, all analyses were separately and specifically repeated for JHU high-risk and very high-risk PCa patients as the second part of the statistical analyses.

For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used.[12] All tests were two-sided with a level of significance set at $p < 0.05$.

3 | RESULTS

3.1 | Descriptive characteristics of the study population

We identified 4165 JHU high-risk and very high-risk African American prostate cancer patients. Of those, 1390 (33.4%) underwent RP versus 2775 (66.6%) underwent EBRT. Applying JHU criteria resulted in 1944 (46.7%) high-risk and 2221 (53.3%) very high-risk patients. Of JHU high-risk patients, 750 (39%) underwent RP versus 1194 (61%) underwent EBRT. Of JHU very high-risk patients, 640 (29%) underwent RP versus 1581 (71%) underwent EBRT (Table 1).

In general, RP patients were younger, harbored lower PSA values, and less aggressive tumor characteristics in both JHU high-risk and very high-risk patients (all $p < 0.001$, Table 2 and Table 3).

3.2 | Competing risk regression models prior and after PSM (1:1) in the overall NCCN high-risk cohort

In cumulative incidence plots depicting CSM at 5 years of follow-up before PSM, rates were 2.4 versus 5.2% ($p = 0.003$) for RP versus EBRT patients. This translated into (Table 4) a multivariable competing-risks hazard ratio (HR) of 0.50 (95% confidence interval [CI]: 0.30–0.84, $p = 0.009$). Relying on the entire NCCN high-risk cohort ($n = 4165$), 1:1 PSM resulted in two equally sized groups of 1141 RP versus 1141 EBRT patients, with no residual statistically significant differences in patient or tumor characteristics (all $p \geq 0.1$, Table 1). In cumulative incidence plots depicting CSM at 5 years of follow-up after to PSM, rates were 2.3 versus 3.9% ($p = 0.003$) for RP versus EBRT patients, respectively. This translated into (Table 4) a multivariable competing-risks HR of 0.52 (95% CI: 0.29–0.92, $p = 0.02$). No statistically significant interaction was identified between JHU risk groups and treatment type for CSM (HR: 0.7; 95% CI: 0.25–1.94; $p = 0.5$). Results remained unchanged after landmark analyses at 6 months were applied before analyses.

3.3 | Competing risk regression models prior and after PSM (1:1) in the JHU very high-risk cohort

In cumulative incidence plots depicting CSM at 5 years of follow-up before PSM, rates were 3.7 versus 8.4% ($p = 0.003$) for RP versus EBRT patients'. This translated into (Table 4) a multivariable competing-risks HR of 0.51 (95% CI: 0.28–0.95, $p = 0.03$). Relying on the entire JHU very high-risk cohort ($n = 2221$), 1:1 PSM resulted in two equally sized groups of 501 RP versus 501 EBRT patients, with no residual statistically significant differences in patient or tumor characteristics (all $p \geq 0.4$, Table 2). In cumulative incidence plots depicting CSM at 5 years of follow-up after to PSM, rates were 3.3 versus 7.4% ($p = 0.04$) for RP versus EBRT patients, respectively. This translated into (Table 4) a multivariable competing-risks HR of 0.42 (95% CI: 0.25–0.89, $p = 0.02$). Results remained unchanged after landmark analyses of 6 months were applied before analyses.

3.4 | Competing risk regression models prior and after PSM (1:1) in the JHU high-risk cohort

In cumulative incidence plots depicting CSM at 5 years of follow-up before PSM, rates were 1.3 versus 1.3% ($p = 0.4$) for RP versus EBRT patients, respectively. This translated into (Table 4) a multivariable competing-risks HR of 0.55 (95% CI: 0.16–1.90, $p = 0.3$). Relying on the entire JHU high-risk cohort ($n = 1944$), 1:1 PSM resulted in two equally sized groups of 532 RP versus 532 EBRT patients, with no residual statistically significant differences in patient or tumor characteristics (all $p \geq 0.3$, Table 3). In cumulative incidence plots depicting CSM at 5 years of follow-up after to PSM, rates were 1.0 versus 1.0% ($p = 0.3$) for RP versus EBRT patients, respectively. This translated into (Table 4) a multivariable competing-risks HR of 0.53 (95% CI: 0.18–1.56, $p = 0.3$).

4 | DISCUSSION

No previous investigators tested for CSM differences between RP versus EBRT patients in NCCN high-risk, as well as JHU high-risk and very high-risk African American PCa patients. We hypothesized that no difference exists in CSM rates of NCCN high-risk patients treated with RP versus EBRT. Moreover, we hypothesized that no difference exists in CSM rates between RP versus EBRT African American patients, after further stratification into JHU high-risk and very high-risk risk categories. We addressed this knowledge gap and tested this hypothesis within a large, population-based sample. Our study resulted in several noteworthy observations.

First, we recorded very important differences in age, PSA, clinical stage, and biopsy Gleason score characteristics in the entire cohort of African American NCCN high-risk RP patients, relative to their EBRT counterparts (Table 1). Moreover, in both JHU very high-risk and high-risk groups, RP patients were younger and presented with less aggressive disease. Based on these very important differences, meaningful comparisons without strict statistical adjustment may result in severely biased results. In consequence, we applied PSM and additional multivariable adjustments to control for such differences. A similar methodology was previously applied in comparisons between RP versus EBRT.[13,14] However, these comparisons did not address specific race/ethnicity groups, including African American JHU high-risk versus very high-risk prostate cancer patients.

Second, within African American patients, JHU very high-risk patients (53%) account for a marginally larger proportion than high-risk patients (47%). This distribution, where the majority of NCCN high-risk patients represent very high-risk individuals according to the JHU definition, is different than previously reported. Specifically, in previous reports, that predominantly relied on Caucasian patients, JHU very high-risk patients accounted for a minority relative to JHU high-risk patients (15%–30%).[7,10,15] However, the current proportion is highly comparable with Wenzel et al.[11] that addressed JHU high-risk and very high-risk (60%) prostate cancer patients across all race/ethnicity groups in a population-based analysis.

TABLE 1 Descriptive characteristics of 4165 African American nonmetastatic NCCN high-risk prostate cancer patients within the Surveillance, Epidemiology and End Results (2010–2016) database, stratified by treatment type (radical prostatectomy vs. external beam radiotherapy before and after propensity score matching (according to age, PSA, Biopsy Gleason score, cT-stage, and cN-stage)

	Unmatched data					Propensity score-matched data				
	Overall *n* = 4165	Radical prostatectomy *n* = 1390	External beam radiotherapy *n* = 2775	*p* value	Absolute standardized mean difference	Overall *n* = 2282	Radical prostatectomy *n* = 1141	External beam radiotherapy *n* = 1141	*p* value	Absolute standardized mean difference
Age in years, median (IQR)	64 (59–70)	61 (56–66)	66 (61–72)	<0.001	0.8190	62 (57–67)	62 (58–66)	62 (57–67)	0.6	0.0009
PSA in ng/ml, median (IQR)	16 (7–31)	10 (6–24)	20 (8–36)	<0.001	0.0481	12 (7–26)	11 (6–26)	13 (7–26)	0.1	0.0024
Biopsy Gleason Score, *n* (%)				<0.001					>0.9	
3 + 3	268 (6.4%)	113 (8.1%)	155 (5.6%)		0.0931	174 (7.6%)	87 (7.6%)	87 (7.6%)		0.0000
3 + 4	557 (13%)	193 (14%)	364 (13%)		0.0222	303 (13%)	159 (14%)	144 (13%)		0.0380
3 + 5	210 (5.0%)	80 (5.8%)	130 (4.7%)		0.0460	126 (5.5%)	63 (5.5%)	63 (5.5%)		0.0000
4 + 3	423 (10%)	125 (9.0%)	298 (11%)		0.0610	213 (9.3%)	111 (9.7%)	102 (8.9%)		0.0276
4 + 4	1,644 (39%)	603 (43%)	1,041 (38%)		0.1184	978 (43%)	480 (42%)	498 (44%)		0.0318
4 + 5	815 (20%)	229 (16%)	586 (21%)		0.1251	394 (17%)	194 (17%)	200 (18%)		0.0142
5 + 3	31 (0.7%)	9 (0.6%)	22 (0.8%)		0.0181	18 (0.8%)	9 (0.8%)	9 (0.8%)		0.0000
5 + 4	159 (3.8%)	32 (2.3%)	127 (4.6%)		0.1517	63 (2.8%)	32 (2.8%)	31 (2.7%)		0.0058
5 + 5	58 (1.4%)	6 (0.4%)	52 (1.9%)		0.2200	13 (0.6%)	6 (0.5%)	7 (0.6%)		0.0134
cT-stage, *n* (%)				<0.001					0.6	
cT1	2606 (63%)	848 (61%)	1758 (63%)		0.0481	1429 (63%)	701 (61%)	728 (64%)		0.0485
cT2	1154 (28%)	407 (29%)	747 (27%)		0.0519	648 (28%)	328 (29%)	320 (28%)		0.0154
cT3a	222 (5.3%)	86 (6.2%)	136 (4.9%)		0.0534	125 (5.5%)	69 (6.0%)	56 (4.9%)		0.0473
cT3b	141 (3.4%)	46 (3.3%)	95 (3.4%)		0.0064	75 (3.3%)	40 (3.5%)	35 (3.1%)		0.0245
cT4	42 (1.0%)	3 (0.2%)	39 (1.4%)		0.2563	5 (0.2%)	3 (0.3%)	2 (0.2%)		0.0189
cN-stage, *n* (%)				<0.001					>0.9	
cN0	3906 (94%)	1254 (90%)	2652 (96%)		0.1801	2140 (94%)	1069 (94%)	1071 (94%)		0.0059
cN1	232 (5.6%)	132 (9.5%)	100 (3.6%)		0.2010	135 (5.9%)	68 (6.0%)	67 (5.9%)		0.0030
cNx	27 (0.6%)	4 (0.3%)	23 (0.8%)		0.1010	7 (0.3%)	4 (0.4%)	3 (0.3%)		0.0164

Abbreviations: NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; IQR, interquartile range.

TABLE 2 Descriptive characteristics of 2221 African American nonmetastatic JHU very high-risk prostate cancer patients within the Surveillance, Epidemiology and End Results (2010–2016) database, stratified by treatment type (radical prostatectomy vs. external beam radiotherapy before and after propensity score matching (according to age, PSA, Biopsy Gleason score, cT-stage, and cN-stage)

	Unmatched data					Propensity score-matched data				
	Overall *n* = 2221	Radical prostatectomy *n* = 640	External beam radiotherapy *n* = 1581	*p* value	Absolute standardized mean difference	Overall *n* = 1002	Radical prostatectomy *n* = 501	External beam radiotherapy *n* = 501	*p* value	Absolute standardized mean difference
Age in years, median (IQR)	65 (60–70)	61 (56–65)	66 (61–72)	<0.001	0.8680	63 (58–67)	63 (58–66)	62 (57–67)	>0.9	0.0011
PSA in ng/ml, median (IQR)	13 (7–30)	9 (6–19)	16 (8–36)	<0.001	0.5446	10 (6–21)	10 (6–20)	10 (6–22)	0.5	0.0570
Biopsy Gleason Score, *n* (%)				<0.001					0.8	
3 + 3	19 (0.9%)	11 (1.7%)	8 (0.5%)		0.0933	10 (1.0%)	4 (0.8%)	6 (1.2%)		0.0307
3 + 4	48 (2.2%)	17 (2.7%)	31 (2.0%)		0.0433	24 (2.4%)	12 (2.4%)	12 (2.4%)		0.0000
3 + 5	164 (7.4%)	56 (8.8%)	108 (6.8%)		0.0679	84 (8.4%)	38 (7.6%)	46 (9.2%)		0.0565
4 + 3	43 (1.9%)	16 (2.5%)	27 (1.7%)		0.0507	20 (2.0%)	14 (2.8%)	6 (1.2%)		0.1023
4 + 4	1,038 (47%)	332 (52%)	706 (45%)		0.1445	501 (50%)	255 (51%)	246 (49%)		0.0360
4 + 5	661 (30%)	161 (25%)	500 (32%)		0.1491	277 (28%)	136 (27%)	141 (28%)		0.0230
5 + 3	31 (1.4%)	9 (1.4%)	22 (1.4%)		0.0013	16 (1.6%)	8 (1.6%)	8 (1.6%)		0.0000
5 + 4	159 (7.2%)	32 (5.0%)	127 (8.0%)		0.1392	58 (5.8%)	28 (5.6%)	30 (6.0%)		0.0183
5 + 5	58 (2.6%)	6 (0.9%)	52 (3.3%)		0.2440	12 (1.2%)	6 (1.2%)	6 (1.2%)		0.0000
cT-stage, *n* (%)				0.018					0.6	
cT1	1274 (57%)	368 (57%)	906 (57%)		0.0039	657 (60%)	317 (58%)	340 (62%)		0.0888
cT2	629 (28%)	189 (30%)	440 (28%)		0.0373	316 (29%)	165 (30%)	151 (27%)		0.0481
cT3a	135 (6.1%)	34 (5.3%)	101 (6.4%)		0.0480	57 (5.2%)	30 (5.4%)	27 (4.9%)		0.0356
cT3b	141 (6.3%)	46 (7.2%)	95 (6.0%)		0.0456	68 (6.2%)	36 (6.5%)	32 (5.8%)		0.0386
cT4	42 (1.9%)	3 (0.5%)	39 (2.5%)		0.2925	4 (0.4%)	3 (0.5%)	1 (0.2%)		0.0584
cN-stage, *n* (%)				<0.001					0.4	
cN0	2048 (92%)	568 (89%)	1480 (94%)		0.1539	936 (93%)	463 (92%)	473 (94%)		0.0632
cN1	153 (6.9%)	71 (11%)	82 (5.2%)		0.1881	65 (6.5%)	37 (7.4%)	28 (5.6%)		0.0572
cNx	20 (0.9%)	1 (0.2%)	19 (1.2%)		0.2647	1 (<0.1%)	1 (0.2%)	0 (0%)		0.0505

Abbreviations: JHU, Johns Hopkins University; IQR, interquartile range; PSA, prostate-specific antigen.

TABLE 3 Descriptive characteristics of 1944 African American nonmetastatic JHU high-risk prostate cancer patients within the Surveillance, Epidemiology and End Results (2010–2016) database, stratified by treatment type (radical prostatectomy vs. external beam radiotherapy before and after propensity score matching (according to age, PSA, Biopsy Gleason score, cT-stage, and cN-stage)

	Unmatched data					Propensity score-matched data				
	Overall *n* = 1944	Radical prostatectomy *n* = 750	External beam radiotherapy n = 1194	*p* value	Absolute standardized mean difference	Overall *n* = 1064	Radical prostatectomy *n* = 532	External beam radiotherapy *n* = 532	*p* value	Absolute standardized mean difference
Age in years, median (IQR)	64 (58–69)	61 (55–66)	66 (60–71)	<0.001	0.7562	63 (58–67)	63 (58–67)	62 (57–67)	0.5	0.0172
PSA in ng/ml, median (IQR)	21 (8–33)	14 (6–27)	23 (9–37)	<0.001	0.3702	18 (7–29)	17 (6–29)	19 (7–29)	0.5	
Biopsy Gleason Score, *n* (%)				<0.001					>0.9	
3 + 3	249 (13%)	102 (14%)	147 (12%)		0.1231	134 (13%)	64 (12%)	780 (13%)		0.0329
3 + 4	509 (26%)	176 (23%)	333 (28%)		0.1044	256 (24%)	129 (24%)	127 (24%)		0.0089
3 + 5	46 (2.4%)	24 (3.2%)	22 (1.8%)		0.0771	30 (2.8%)	17 (3.2%)	13 (2.4%)		0.0427
4 + 3	380 (20%)	109 (15%)	271 (23%)		0.2316	172 (16%)	87 (16%)	85 (16%)		0.0107
4 + 4	606 (31%)	271 (36%)	335 (28%)		0.1681	384 (36%)	188 (35%)	196 (36%)		0.0313
4 + 5	154 (7.9%)	68 (9.1%)	86 (7.2%)		0.0649	88 (8.3%)	47 (8.8%)	47 (7.7%)		0.0393
cT-stage, *n* (%)				<0.001					0.3	
cT1	1332 (69%)	480 (64%)	852 (71%)		0.1533	735 (69%)	357 (67%)	378 (71%)		0.0822
cT2	525 (27%)	218 (29%)	307 (26%)		0.0739	280 (26%)	147 (28%)	133 (25%)		0.0580
cT3a	87 (4.5%)	52 (6.9%)	35 (2.9%)		0.0293	49 (4.6%)	28 (5.3%)	21 (3.9%)		0.0518
cN-stage, *n* (%)				<0.001					0.8	
cN0	1858 (96%)	686 (91%)	1172 (98%)		0.2395	1031 (97%)	517 (97%)	514 (97%)		0.0202
cN1	79 (4.1%)	61 (8.1%)	18 (1.5%)		0.2424	28 (2.6%)	13 (2.4%)	15 (2.8%)		0.0138
cNx	7 (0.4%)	3 (0.4%)	4 (0.3%)		0.0103	5 (0.5%)	2 (0.4%)	3 (0.6%)		0.0298

Abbreviations: JHU, Johns Hopkins University; IQR, interquartile range; PSA, prostate-specific antigen.

TABLE 4 Uni- and multivariable competing risks regression models testing for differences in cancer-specific mortality between radical prostatectomy versus external beam radiotherapy before and after 1:1 propensity score matching (according to age, PSA, biopsy Gleason score, cT-stage, and cN-stage) within the Surveillance, Epidemiology and End Results (2010–2016) database in (a) 4165 National Comprehensive Cancer Network high-risk (NCCN) PCa patients, (b) 1944 Johns Hopkins University high-risk PCa patients, and (c) 2221 Johns Hopkins University very high-risk PCa patients

		Univariable competing risks regressions			Multivariable competing risks regressions		
		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
NCCN high-risk (*n* = 4165)	Unmatched data	0.45	0.28–0.71	<0.001	0.50	0.30–0.84	0.009
	PSM matched data	0.53	0.30–0.93	0.03	0.52	0.29–0.92	0.02
JHU high-risk (*n* = 1944)	Unmatched data	0.70	0.30–1.63	0.4	0.55	0.16–1.90	0.3
	PSM matched data	0.59	0.21–1.66	0.3	0.53	0.18–1.56	0.3
JHU very high-risk (*n* = 2212)	Unmatched data	0.43	0.25–0.75	0.003	0.51	0.28–0.95	0.03
	PSM matched data	0.44	0.25–0.95	0.04	0.42	0.20–0.89	0.02

Abbreviations: CI, confidence interval; JHU, Johns Hopkins University; NCCN, National Comprehensive Cancer Network high-risk; PSM, propensity score matching.

Third, we tested for CSM differences in the entire cohort of NCCN high-risk patients, which includes JHU very high-risk and high-risk. Here, we observed significant differences in CSM rates between RP versus EBRT treated African American patients, favoring RP treated patients. These observations remained virtually unchanged after PSM was used to maximally reduce patient and tumor characteristics' differences at baseline. In consequence, RP holds a CSM advantage over EBRT in NCCN high-risk African American patients.

Fourth, despite the lack of statistically significant interaction between the JHU risk category (high-risk vs. very high-risk) and treatments (RP vs. EBRT), based on clinical considerations, we also separately tested for CSM differences between RP versus EBRT patients in JHU high-risk and very high-risk African American patients. The comparison of treatments regarding their effect on CSM before adjustment for baseline patient and tumor characteristics revealed a CSM advantage for JHU very high-risk RP treated patients versus EBRT treated patients. Since such an advantage may have originated from an unbalanced baseline patient composition, we not only relied on multivariable adjustments but also used advanced statistical matching techniques, namely PSM. The aim was to maximally reduce patient and tumor characteristics' differences at baseline. After PSM, two homogenous groups of JHU very high-risk patients remained (RP vs EBRT). Their composition was homogenous as evidenced by the lack of residual statistically significant differences ($p \geq 0.4$). After additional multivariable adjustment and adjustment for OCM, RP patients still exhibited lower CSM relative to RP patients in JHU very high-risk patient group (HR: 0.42, 95% CI: 0.20–0.89, $p = 0.02$). Conversely, we did not record a CSM difference between RP versus EBRT in JHU high-risk patients, regardless of analytical methodology.

Our study is not devoid of limitations. Our findings originate from an observational cohort and are of retrospective nature. Lack of randomized design may contribute to uncontrollable biases. However, the limitations of a retrospective design, apply to other institutional and population-based studies, which previously addressed RP versus EBRT in NCCN high-risk patients of all race/ethnicity groups.[16,17] In consequence our observations should be validated using similarly large-scale databases. Unfortunately, the NCBD that relies on an even larger number of African American patients, cannot be used for purpose of CSM comparisons, since CSM is not recorded.[18] Instead, it may allow OM comparisons between the two treatment arms. However, such metric may not be sensitive enough in the context of (NCCN) high-risk prostate cancer, based on an elevated proportion of OCM.[1]

Alternatively, our observations could ideally be validated within a prospective design that compares RP versus EBRT in African American prostate cancer patients. However, it is highly unlikely that such a study will ever be designed or completed. For example, several prospective randomized trials investigating treatment modalities across disease stages did not record the composition of the study population regarding race/ethnicity. Alternatively, many trials only enrolled a very small proportion of African Americans.[19–22] Their numbers were far from sufficient for allowing pre-planned subgroup analyses, focusing on African Americans. In consequence, retrospective designs, such as ours, will need to suffice, for possibly many years to come.

The SEER database does not include information regarding comorbidities, which could affect treatment assignment. However, we relied on adjustment for OCM, which represents a well-established proxy of comorbidities, that may predispose to death.[13,23,24] Unfortunately, only the SEER-Medicare database allows the concomitant use of comorbidities and OCM. However, it only holds a fraction (approximately 30%) of the SEER database population. Consequently, SEER-Medicare derived observations may not allow a sufficient sample size for statistically valid comparisons.[25] Besides adjustment for OCM, we repeated analyses after landmark analyses at 6 months to account for a potential immortal time bias.[26] Since the results remained unchanged after landmark analyses were used, it is unlikely that the observations derive from an immortal time bias. Moreover, the absence of earlier cancer-control outcomes, such as

biochemical recurrence, progression-free survival, or metastatic progression may also be criticized. However, these endpoints are clearly not as definitive and not as established as the ultimate endpoint of CSM. Finally, the absence of a central pathology review and the lack of information on the type and duration of androgen deprivation and type and dosage of radiation therapy may represent additional limitations.

5 | CONCLUSIONS

After adjustment for OCM and baseline PCa clinical characteristics among African American prostate cancer patients, the current study demonstrates that RP is associated with a CSM advantage in NCCN high-risk African American prostate cancer patients compared with their EBRT counterparts. Moreover, our data analyses provide evidence of a benefit for RP treatment in JHU very high-risk African American patients as well.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

DATA AVAILABILITY STATEMENT

All data generated for this analysis were from the SEER 2018 database. The code for the analyses will be made available upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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