Original Article

Oncologic Outcomes Among Black and White Men With Grade Group 4 or 5 (Gleason Score 8-10) Prostate Cancer Treated Primarily by Radical Prostatectomy

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BACKGROUND: The aim of this study was to describe pathologic and short-term oncologic outcomes among Black and White men with grade group 4 or 5 prostate cancer managed primarily by radical prostatectomy. **METHODS:** This was a multi-institutional, observational study (2005-2015) evaluating radical prostatectomy outcomes by self-identified race. Descriptive analysis was performed via nonparametric statistical testing to compare baseline clinicopathologic data. Univariable and multivariable time-to-event analyses were performed to assess biochemical recurrence (BCR), metastasis, cancer-specific mortality (CSM), and overall survival between Black and White men. **RESULTS:** In total, 1662 men were identified with grade group 4 or 5 prostate cancer initially managed by radical prostatectomy. Black men represented 11.3% of the cohort (n = 188). Black men were younger, demonstrated a longer time from diagnosis to surgery, and were at a lower clinical stage (all $P < .05$). Black men had lower rates of pT3/4 disease (49.5% vs 63.5%; $P < .05$) but higher rates of positive surgical margins (31.6% vs 26.5%; $P = .14$) on pathologic evaluation. There was no difference in BCR, CSM, or overall survival over a median follow-up of 40.7 months. Black men had a lower 5-year cumulative incidence of metastasis-free survival (93.6%; 95% confidence interval [CI], 86.5%-97.0%) in comparison with White men (85.8%; 95% CI, 83.1%-88.0%), which did not persist in an age-adjusted analysis. **CONCLUSIONS:** Black and White men with high-grade prostate cancer at diagnosis demonstrated similar oncologic outcomes when they were managed by primary radical prostatectomy. Our findings suggest that racial disparities in prostate cancer mortality are not related to differences in the efficacy of extirpative therapy. ***Cancer* 2021;127:1425-1431**. © *2021 American Cancer Society*.

KEYWORDS: African American, Black, high grade, high risk, prostate cancer, prostatectomy.

INTRODUCTION

Racial disparities in prostate cancer mortality have persisted between Black and White men in the United States over the last 3 decades despite a 50% reduction in prostate cancer mortality among all men since the introduction of prostate-specific antigen (PSA) screening in the mid-1980s.[1] Data from the Surveillance, Epidemiology, and End Results program demonstrate that Black men in the United States have a 2-fold increased risk of cancer-specific mortality (CSM) in comparison with men of other ethnicities.[2] It is unclear to what extent the difference in prostate cancer mortality is driven by biology, health factors, and/or social determinants of health. An argument in favor of potentially unique biological drivers of prostate cancer risk and aggressiveness among Black men is supported by a higher lifetime incidence, younger age, and a higher likelihood of metastatic disease at diagnosis.[2] Data from 3 natural history microsimulation models suggest that Black men have a 28% to 56% higher risk of preclinical disease and a 44% to 75% higher risk of developing metastases before diagnosis. However, the increased risk of metastatic disease at diagnosis may also reflect issues surrounding access to care and delays in diagnosis—both correlates of social factors such as socioeconomic[3] and insurance status.[4]

There have been mixed results in the findings of oncologic disparities between Black and White men with localized prostate cancer treated primarily by radical prostatectomy. Studies have suggested that Black men with low-risk prostate cancer may have higher rates of adverse oncologic outcomes after treatment.[5-7] Conversely, studies conducted

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in equal-access settings have demonstrated similar rates of survival and mortality between Black and White men receiving definitive therapy for localized prostate cancer, even among high-risk strata.[8,9] The question remains whether a contemporary cohort of Black men with high-grade/risk prostate cancer undergoing prostatectomy harbor any differences in their posttreatment oncologic outcomes in comparison with White men. This is especially important because radical prostatectomy continues to be increasingly used as a primary therapy for higher risk prostate cancer.[10,11]

The primary objective of this study is to describe oncologic outcomes among Black and White men with high-grade prostate cancer at diagnosis managed at 3 high-volume prostatectomy centers in the United States. Secondarily, we report pathologic findings at the time of prostatectomy by race. We hypothesize that clinical and pathologic outcomes in this cohort of men with high-grade prostate cancer will not vary by race because of the inherently aggressive nature of these cancers.

MATERIALS AND METHODS

This is an observational analysis of men with grade group 4 or 5 prostate cancer selected from a multi-institutional cohort of men with high-risk prostate cancer managed by radical prostatectomy at 3 large, urban academic medical centers in the United States (Cleveland Clinic, Johns Hopkins University, and MD Anderson Cancer Center). Consecutive surgical cases from 2005 to 2015 were identified from radical prostatectomy databases at each participating institution. The time period studied was chosen to reflect contemporary practices and techniques for prostatectomy in addition to contemporary changes in the pathologic definitions of prostate cancer grade.[12] A general summary of diagnostic evaluation and posttreatment follow-up has been provided in a previous publication.[13] Pathologic specimens were reviewed centrally by expert genitourinary pathologists at each participating institution. In total, 1981 men were identified from the 3 institutions (Fig. 1). Men were excluded from the final cohort if they were diagnosed with Gleason score 6 or 7 prostate cancer on initial biopsy (n = 319; Supporting Table 1). The cohort included men with National Comprehensive Cancer Network[14] (NCCN) high-risk (ie, grade group 4 or 5, cT3a, or PSA > 20 ng/mL) or very high-risk (primary Gleason pattern 5, cT3b-4, or >4 cores with grade group 4 or 5) prostate cancer at diagnosis. Data share agreements were reached with each institution. Institutional review board approval was obtained at each participating site.

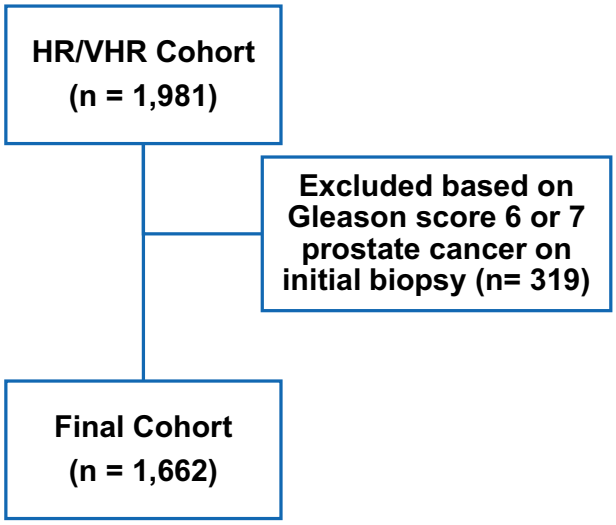

Figure 1. Consolidated Standards of Reporting Trials flow diagram. HR indicates high risk; VHR, very high risk.

Clinical and Pathologic Data

Age and self-reported race were extracted from institutional data. The only other demographic information extracted from the 3 institutions was age at diagnosis. Patient-level data included PSA at diagnosis, clinical stage at diagnosis, biopsy grade, pathologic TNM stage, pathologic grade, and margin status. Oncologic events, including biochemical recurrence (BCR), metastases, and prostate cancer–specific mortality (PCSM), were also obtained from each institutional database. BCR was defined as any postoperative PSA level above 0.2 ng/mL or detectable nadir PSA after surgery. Receipt of secondary therapy such as radiotherapy and/or androgen deprivation was also noted.

Statistical Analysis

Descriptive statistics were performed with the Wilcoxon rank-sum test for continuous variables and with the chi-square test for categorical variables. Data are generally presented as medians and interquartile ranges unless otherwise specified. The cumulative incidence of overall survival and survival free from BCR, metastasis, and CSM were calculated at 3 and 5 years. The Kaplan-Meier test was used to compare the same oncologic outcomes by race. Time zero was defined as the date of diagnosis for metastases and PCSM and as the date of surgery for BCR. All Kaplan-Meier analyses were censored at death of any cause or last known follow-up, and statistical significance was calculated with the log-rank test. A multivariable Cox regression analysis was used to assess outcomes that differed by race on univariable analysis. Age-adjusted multivariable models were constructed with an a priori

TABLE 1. Baseline Demographic and Clinical Characteristics of Black and White Men With Clinical Grade Group 4 or 5 Prostate Cancer Managed by Radical Prostatectomy (n = 1662)

Characteristic	Black (n = 188)	White (n = 1474)	*P*
Continuous, median (IQR)			
Age at diagnosis, y	60.0 (54.5-65.0)	63.3 (58.8-68.5)	<.001
PSA at diagnosis, ng/mL	6.9 (4.9-13.6)	6.6 (4.8-10.6)	.13
No. of biopsy cores with grade group 4 or 5	2 (1-3)	2 (1-4)	.89
Time from diagnosis to surgery, d	89 (60-126)	70 (51-103)	<.001
Year of diagnosis	2010 (2008-2013)	2011 (2008-2013)	.12
Follow-up, mo	45.8 (23.5-63.5)	39.9 (20.2-67.4)	.32
Categorical, No. (%)			
Gleason score at initial biopsy			
Grade group 4	120 (64.2)	875 (59.8)	.25
Grade group 5	67 (35.8)	588 (40.2)	
Clinical T stage			
cT1	115 (62.8)	671 (46.6)	<.001
cT2	56 (30.6)	645 (44.8)	
cT3	11 (6.0)	120 (8.3)	
cT4	1 (0.6)	3 (0.2)	
PSA category, ng/mL			
0.0-10.0	124 (66.0)	1078 (73.1)	.10
10.1-20.0	42 (22.3)	274 (18.6)	
>20	22 (11.7)	122 (8.3)	
NCCN risk strata			
High	123 (65.4)	958 (65.0)	.91
Very high	65 (34.6)	516 (35.0)	
Neoadjuvant ADT	22 (11.7)	258 (17.5)	.04

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

selection of clinically relevant pretreatment variables, which included PSA at diagnosis, clinical stage, grade group, number of cores with grade group 4 or 5, and race. All statistical tests were 2-sided, with significance defined as $P < .05$. Statistical analyses were performed with Stata 14.1 (StataCorp, College Station, Texas). The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used to ensure the reporting of this observational study.[15]

RESULTS

Baseline clinical data for the cohort are presented in Table 1. The median follow-up in the cohort was 40.7 months (interquartile range, 20.5-67.0 months). In total, 188 Black men (11.3%) were identified from the 3 institutions. The Black men in the cohort were younger than the White men but otherwise demonstrated no differences in PSA at diagnosis, the length of follow-up, or the number of cores with grade group 4 or 5 disease at diagnosis. Black men had a longer median time from diagnosis to surgery of 19 days ($P < .001$). Although Black men had lower stage disease in this cohort, there was no difference in the rate of NCCN high-risk disease by race. Black men had 50% lower use of neoadjuvant androgen deprivation therapy in comparison with White men.

Black men had a lower proportion of aggressive pathologic features (ie, grade group 5, extraprostatic disease, seminal vesicle invasion, and lymph node involvement) at radical prostatectomy in comparison with White men (Table 2). Positive surgical margins were more common among Black men. Black men were less likely to receive androgen deprivation therapy and had lower utilization of secondary treatment with radiotherapy (ie, adjuvant or salvage) in comparison with White men. Among men receiving radiotherapy after treatment, 22 Black men (51.2%) and 232 non-Black men (60.1%) received concurrent androgen deprivation.

The median follow-up was similar between Black men (45.8 months; interquartile range, 23.5-63.5 months) and White men (39.9 months; interquartile range, 20.2-67.4 months). In total, 937 men (56.4%) and 506 men (30.4%) had a minimum of 3 and 5 years of total follow-up, respectively. In all, there were 709, 185, and 32 BCRs, metastases, and cancer-related deaths in the cohort, respectively. There were no differences in the cumulative incidence of overall survival between Black and White men at 3 and 5 years (Table 3). There were also no differences in the cumulative incidence of BCR and CSM at 3 and 5 years (Fig. 2). Black men demonstrated a lower rate of metastatic disease in our cohort than White men (Fig. 2). In a multivariable analysis, Black race was not associated with metastasis (hazard ratio, 0.58; 95% confidence interval, 0.31-1.07; $P = .08$) in a model adjusted for

TABLE 2. Pathologic Findings at Radical Prostatectomy and Postoperative Clinical Data for Black and White Men With Clinical Grade Group 4 or 5 Prostate Cancer Managed by Radical Prostatectomy (n = 1662)

Characteristic	Black (n = 188)	White (n = 1474)	*P*
Gleason score at prostatectomy, No. (%)			
Unable to assess/ ADT changes	27 (14.4)	254 (17.3)	.052
Grade group 1	1 (0.5)	9 (0.6)	
Grade group 2	37 (19.8)	200 (13.6)	
Grade group 3	30 (16.0)	201 (13.7)	
Grade group 4	40 (21.4)	263 (17.9)	
Grade group 5	52 (27.8)	545 (37.0)	
Pathologic T stage, No. (%)			
pT0	3 (1.6)	3 (0.2)	<.001
pT2	92 (48.9)	535 (36.3)	
pT3a	61 (32.5)	555 (37.7)	
pT3b	32 (17.0)	376 (25.5)	
pT4	0 (0.0)	5 (0.3)	
Pathologic lymph node metastasis, No. (%)	32 (17.0)	333 (22.6)	.08
Positive surgical margin, No. (%)	59 (31.6)	390 (26.5)	.14
Adjuvant ADT, No. (%)	36 (19.2)	382 (25.9)	.04
Adjuvant RT, No. (%)	43 (22.9)	386 (26.2)	.33

Abbreviations: ADT, androgen deprivation therapy; RT, radiotherapy.

TABLE 3. Oncologic Events and Overall Survival Among Black and White Men With Grade Group 4 or 5 Prostate Cancer Managed by Radical Prostatectomy

	Rate, % (95% CI)		
Event	Overall	Black	White
Freedom from biochemical recurrence			
3 y	57.3 (54.6-60.0)	58.9 (50.8-59.9)	57.1 (54.2-59.9)
5 y	47.1 (44.0-50.1)	55.3 (46.7-63.2)	46.1 (42.8-49.3)
Freedom from metastasis			
3 y	91.9 (90.2-93.3)	96.2 (90.9-98.4)	91.3 (89.3-92.9)
5 y	86.7 (84.3-88.8)	93.6 (86.5-97.0)	85.8 (83.1-88.0)
Cancer-specific survival			
3 y	99.1 (98.4-99.5)	100 (—)	99.0 (98.2-99.5)
5 y	97.2 (95.7-98.2)	98.3 (88.4-99.8)	97.0 (95.4-98.1)
Overall survival			
3 y	98.6 (97.7-99.1)	100 (—)	98.4 (97.4-99.0)
5 y	94.2 (92.4-95.7)	95.8 (87.4-98.7)	94.0 (92.0-95.5)

Abbreviation: CI, confidence interval.

age, PSA, clinical stage, grade group at diagnosis, and number of total cores with grade group 4 or 5 disease (Supporting Table 2).

DISCUSSION

To our knowledge, this is the first comparative analysis of race and oncologic outcomes in men with grade group 4 or 5 prostate cancer at diagnosis. On pathologic assessment, Black men had higher rates of organ-confined disease and lower rates of positive lymph nodes in comparison with White men. Black men also demonstrated a higher rate of positive surgical margins at prostatectomy in comparison with White men. Black men in our multi-institutional cohort did not demonstrate any significant difference in BCR or CSM. Lower rates of metastases were observed among Black men in our cohort on univariable analysis; however, this difference did not remain in the adjusted analysis. We conclude that radical prostatectomy is an effective primary treatment choice in high-risk Black men that provides outcomes similar to those for White men.

Numerous studies have demonstrated that Black and White men harbor some biological differences in their prostate tumors.[16-20] Powell et al[17] found low androgen-dependent and high immune-mediated molecular markers and pathways in tumors from a large cohort of men of African ancestry. However, none of these biological differences have demonstrated any robust associations with clinical outcomes in Black men. Previous studies evaluating oncologic outcomes between Black and White men have demonstrated mixed results.[21-26] Moses et al[21] showed that young Black men (<50 years old) demonstrated similar rates of BCR in comparison with White men despite more aggressive disease at prostatectomy. Similar results were demonstrated by Cross et al,[27] who showed that the rates of BCR at 5 years were 28% and 32% among Black and White men, respectively. In contrast, Schreiber et al[22] demonstrated 2.5-fold higher rates of BCR among Black men managed by prostatectomy in the Veterans Affairs–derived Shared Equal Access Regional Cancer Hospital (SEARCH) database. Subsequent studies using the SEARCH database—and with longer follow-up—have demonstrated that these differences in outcomes are greatly attenuated when adjustments are made for socioeconomic status.[28] In our analysis, Black men demonstrated similar rates of BCR and PCSM. Univariable differences in metastasis between Black and White men dissipated in the adjusted analysis, and this likely reflected lower rates of pT3 and node-positive disease among Black men in this cohort.

Various studies have demonstrated more aggressive disease at final pathology among Black men with predominantly lower risk prostate cancer at diagnosis.[5,6,29,30] A 1998 study by Pettaway et al[31] of 40 Black men with localized disease matched to 148 White men demonstrated higher rates of seminal vesicle invasion and high Gleason sum (8-9) cancers. In addition, Black men had a higher rate of high-grade disease at diagnosis even after matching.

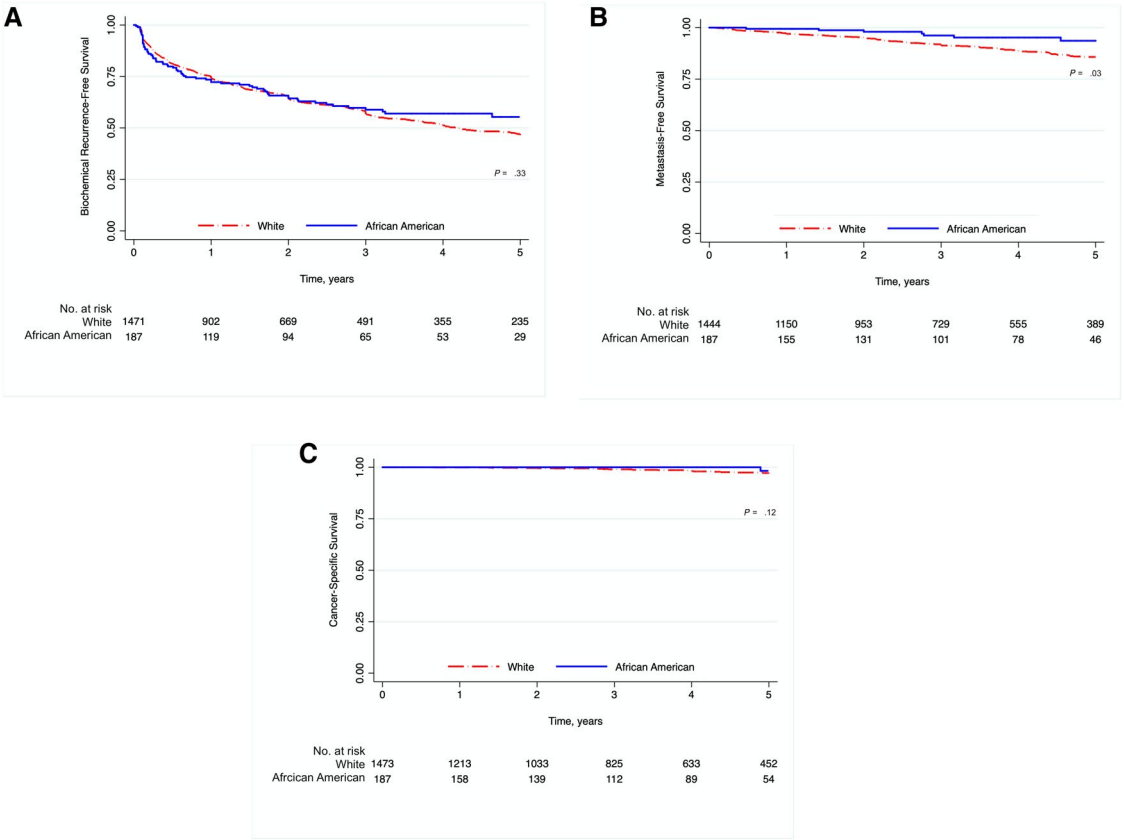

Figure 2. Comparison of (A) biochemical recurrence, (B) metastases, and (B) cancer mortality between Black and White men with high-grade prostate cancer primarily managed by radical prostatectomy.

Yamoah et al[30] demonstrated higher rates of seminal vesicle invasion among Black men in a cohort of 1104 men with localized disease; however, it is worth noting that Black men in this cohort had more aggressive baseline disease. A larger study by Nielsen et al,[25] evaluating 326 Black men and 4926 White men from 1988 to 2004 at a single institution, found no statistically significant differences in the rates of adverse pathologic features despite Black men having higher grade disease in the cohort. We focused our analysis specifically on high-grade disease and found that Black men had higher rates of organ-confined disease (50.5% vs 36.5%; $P < .001$) and lower rates of node-positive disease (17.0% vs 22.6%; $P = .08$). Black men also demonstrated a higher rate of positive surgical margins (31.6% vs 26.5%; $P = .14$). Despite epidemiologic data demonstrating a 2-fold risk of mortality, Black men with high-grade/risk disease at prostatectomy demonstrated no major differences in adverse pathologic findings—especially seminal vesicle invasion or lymph node–positive disease—in comparison with White men.

The underutilization of radical prostatectomy among Black men, especially those with higher risk disease, has been well documented over the past 2 decades.[32] Black men represented only 11.3% of our multi-institutional cohort, which spanned a 10-year study period at 3 high-volume prostatectomy centers. In a recent analysis of data from the National Cancer Database, Weiner et al[33] showed that Black ethnicity was associated with a 31% lower rate of radical prostatectomy use for high-risk, localized disease. Gray et al[10] showed that Black ethnicity was associated with a lower rate of prostatectomy utilization in men with localized prostate cancer in both unadjusted and adjusted analyses using National Cancer Database data from 2004 to 2012. This is concerning because various studies in equal-access settings have shown that Black and White men have similar prostate cancer outcomes after definitive therapy when they are matched by stage and grade,[8,9] and this is similar to the findings in our analysis. Disparities in the utilization of secondary

treatments are an additional potential source of disparities in care. To date, there are no studies on this topic. Zeliadt et al,[34] however, demonstrated that Black men are more likely to undergo less frequent PSA surveillance after primary treatment. This suggests that there is potential for disparities in the utilization of secondary therapies as well.

The determinants of treatment choice among Black men are complex and are driven by health care, social, and patient factors. It is important to understand what drives differences in treatment choice because it likely affects the disparities in outcomes observed. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor database have demonstrated that Black men are less likely to receive definitive therapy for localized prostate cancer in comparison with White men.[35,36] Mahal et al[37] demonstrated that Black men with intermediate- and high-risk disease have significantly lower rates of definitive therapy utilization. Registry-based studies have demonstrated that income and insurance status likely modify the low utilization of definitive therapies in Black men with localized high-risk prostate cancer.[38-40] Findings from our analysis suggest that strategies that aim to increase equitable use of definitive therapies such as radical prostatectomy for Black men with unfavorable-risk prostate cancer could have a significant impact in reducing racial/ethnic mortality disparities.

It is important to note that Black men accessing care at the 3 institutions in this cohort are very likely to be insured and of a higher social standing in comparison with Black men who do not have access to medical care. This likely results in differences in access to and utilization of health care, in medical knowledge, in access to medical information, in social support, in economic and financial standing, and in other social factors that influence timely and appropriate use of definitive therapy for localized prostate cancer. It is possible that some of these social factors also contribute to parity in prostate cancer outcomes by influencing screening and posttreatment behaviors among Black men. Unfortunately, the design of this cohort does not allow for a granular analysis of social variables that may shed light on these social and health-related factors for prostate cancer treatment and outcomes. It is important to acknowledge this context as we aim to identify strategies that can deliver equity in prostate cancer outcomes for Black men in the United States.

This study is also limited by selection biases inherent to the institutions that were studied and their patient populations. Black men are underrepresented in this cohort, and the smaller number of Black men in comparison with White men decreases the power of our comparative analyses. The median follow-up in this cohort was 40.7 months, which did not allow for a more robust analysis of outcomes such as CSM that require longer follow-up for events to occur. However, we presume that the rate and time to adverse oncologic events are somewhat accelerated in this group of men with more aggressive disease at diagnosis. There are multiple strengths of this analysis, including the multi-institutional nature of the cohort, the contemporary nature of the cohort, and the reported outcomes of 3 institutions with robust pathologic and prostatectomy experiences.

In conclusion, among men with grade group 4 or 5 prostate cancer at diagnosis managed at 3 high-volume prostatectomy centers, we found no difference in the rate of adverse oncologic outcomes when they were stratified by race/ethnicity. These findings suggest that definitive therapy with prostatectomy with appropriate adjuvant therapy could be an important mediator of racial disparities seen in prostate cancer. More efforts are needed to understand the impact of treatment choices among Black men and their ultimate impact on mortality disparities in prostate cancer.

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CONFLICT OF INTEREST DISCLOSURES

Jeffrey J. Tosoian reports personal fees and other from LynxDx outside the submitted work. John W. Davis reports research support from Janssen and GenomeDx and consulting/speaking for Intuitive Surgical. Brian F. Chapin reports other from Janssen Pharmaceutical and Blue Earth Diagnostic outside the submitted work. The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Lamont J. Wilkins: Data curation, analysis and interpretation of data, drafting of manuscript, and writing–review and editing. **Jeffrey J. Tosoian:** Conceptualization, data curation, investigation, methodology, and writing–review and editing. **Chad A. Reichard:** Data curation and writing–review and editing. **Debasish Sundi:** Data curation and writing–review and editing. **Weranja Ranasinghe:** Data curation and writing–review and editing. **Ridwan Alam:** Data curation and writing–review and editing. **Zeyad Schwen:** Data curation and resources. **Chandana Reddy:** Data analysis. **Mohamad Allaf:** Data curation and writing–review and editing. **John W. Davis:** Data curation and writing–review and editing. **Brian F. Chapin:** Writing–review and editing. **Ashley E. Ross:** Writing–review and editing and resources. **Eric A. Klein:** Writing–review and editing and resources. **Yaw A. Nyame:** Responsibility for overall content, conceptualization, data curation, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for intellectual content, and overall project supervision.

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