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

Running Title: RP Outcomes of Black men with GG ≥4 PCa

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Condensed Abstract: Black and white men with high-grade prostate cancer at diagnosis demonstrated similar oncologic outcomes when 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.

ABSTRACT

Objective: The aim of this study is to describe pathologic and short-term oncologic outcomes among Black and white men with grade group 4-5 prostate cancer managed primarily by radical prostatectomy.

Methods: This is a multi-institutional observational study (2005-2015) evaluating radical prostatectomy outcomes by self-identified race. Descriptive analysis was performed using non-parametric 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 (OS) between Black and white men.

Results: In total, 1,662 men were identified with grade group 4-5 prostate cancer initially managed by radical prostatectomy. Black men represented 11.3% (188) of the cohort. Black men were younger, demonstrated longer time from diagnosis to surgery, and lower clinical stage (all $p < 0.05$). Black men had lower rates of pT3 disease (49.5% vs. 63.5%, $p < 0.05$), but higher rates of positive surgical margins (31.6% vs. 26.5%, $p = 0.14$) on pathologic evaluation. There was no difference in BCR, CSM, and OS 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% CI 86.5, 97.0] vs. 85.8% [95% CI 83.1, 88.0] for white men), which did not persist on age-adjusted analysis.

Conclusion: Black and white men with high-grade prostate cancer at diagnosis demonstrated similar oncologic outcomes when 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.

Key words: Black, African American, high-risk, high-grade, prostatectomy, prostate cancer

INTRODUCTION

Racial disparities in prostate cancer mortality have persisted between Black and white men in the United States (US) over the last three decades, despite a 50% reduction in prostate cancer mortality among all men following the introduction of PSA screening in the mid 1980s.[1] Data from the Surveillance, Epidemiology and End Results (SEER) program demonstrates that Black men in the US have a two-fold increased risk of cancer specific mortality when compared to men of other ethnicities.[2] It is unclear to what extent difference in prostate cancer mortality is driven by biology, health factors, and/or social determinants of health. An argument in favor of potentially unique biologic drivers of prostate cancer risk and aggressiveness among Black men is supported by higher lifetime incidence, younger age, and higher likelihood of metastatic disease at diagnosis.[2] Data from three natural history microsimulations models suggest that Black men have a 28-56% higher risk of preclinical disease and 44-75% higher risk of developing metastases prior to diagnosis. However, 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 following treatment.[5–7] Conversely, studies conducted 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 a high-risk strata.[8,9] Questions remain whether a contemporary cohort of Black men with high-grade/risk prostate cancer undergoing prostatectomy harbor any differences in their post-treatment oncologic outcomes when compared to white men. This is especially important as radical prostatectomy continues to be increasingly utilized 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 three high-volume prostatectomy centers in the US. 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, given the inherently aggressive nature of these cancers.

MATERIAL AND METHODS

This is an observational analysis of men with grade group 4-5 prostate cancer selected from a multi-institutional cohort of men with high-risk prostate cancer managed by radical prostatectomy at three large, urban academic medical centers in the US (CCF, JHU, MDA). Consecutive surgical cases from 2005-2015 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 post-treatment follow-up has been summarized in a previous publication.[13] Pathologic specimens were reviewed centrally by expert genitourinary pathologists at each participating institution. In total, 1,981 men were identified from the three institutions (Figure 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, Supplemental Table 1). The cohort includes men with National Comprehensive Cancer Network[14] (NCCN) high-risk—i.e., grade group 4/5, cT3a, or PSA > 20 ng/mL—and very high-risk—primary Gleason pattern 5, cT3b-4, or >4 cores with grade group 4/5—prostate cancer at diagnosis. Data share agreements were reached between each institution. Institutional review board approval was obtained at each participating site.

Clinical and Pathologic Data

Age and self-reported race were extracted from institutional data. The only other demographic data extracted from the three 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 post-operative PSA above 0.2 ng/mL or detectable nadir PSA following surgery. Receipt of secondary therapy such as radiotherapy and/or androgen deprivation were also noted.

Statistical Analysis

Descriptive statistics were performed using Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Data is generally presented as median (IQR), unless otherwise specified. The cumulative incidence of overall survival and survival free from BCR, metastasis, and cancer-specific mortality (CSM) were calculated at 3- and 5-years. Kaplan Meier test was used to compare the same oncologic outcomes by race. Time zero was defined as date of diagnosis for metastases and PCSM, and 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 using 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 selection of clinically relevant pre-treatment variables, which included PSA at diagnosis, clinical stage, grade group, number of cores with grade group 4/5, and race. All statistical tests were two-sided with significance defined as $p < 0.05$. Statistical analyses were performed using Stata 14.1 (StataCorp, College Station, TX). The STROBE (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. Median follow-up in the cohort was 40.7 (20.5, 67.0) months. In total, 188 (11.3%) Black men were identified from the three institutions. Black men in the cohort were younger than white men, but otherwise demonstrated no differences in PSA at diagnosis, length of follow-up, or the number of cores with grade group 4-5 disease at diagnosis. Black men had a longer median time from diagnosis to surgery of 19-days ($p < 0.001$). 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% relatively lower use of neoadjuvant androgen deprivation therapy compared to white men.

Black men had a lower proportion of aggressive pathologic features (i.e., grade group 5, extraprostatic disease, seminal vesicle invasion, and lymph node involvement) at radical prostatectomy compared to 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 (i.e., adjuvant or salvage) when

compared to white men. Among men receiving radiotherapy after treatment, 22 (51.2%) Black men and 232 (60.1%) non-Black men received concurrent androgen deprivation.

Median follow-up was similar between Black (45.8 [23.5, 63.5] months) and white (39.9 [20.2, 67.4] months) men. In total, 937 (56.4%) and 506 (30.4%) men had a minimum of 3- and 5-years of total follow-up, respectively. There was a total of 709, 185, and 32 BCR, 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 (Figure 2). Black men demonstrated a lower rate of metastatic disease in our cohort compared to white men (Figure 2). On multivariable analysis, Black race was not associated with metastasis (hazard ratio 0.58, 95% CI 0.31, 1.07, p = 0.08), in a model adjusted for age, PSA, clinical stage, Grade group at diagnosis, and number of cores total cores with grade group 4-5 disease (Supplemental Table 2).

DISCUSSION

To our knowledge, this is the first comparative analysis of race and oncologic outcomes in men with Grade group 4-5 prostate cancer at diagnosis. On pathologic assessment, Black men had higher rates of organ-confined disease and lower rates of positive lymph nodes compared to white men. Black men also demonstrated a higher rate of positive surgical margin at prostatectomy compared to 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 on adjusted analysis. We conclude that radical prostatectomy is an effective primary treatment choice in high-risk Black men that provides similar outcomes to white men.

Numerous studies have demonstrated that Black and white men harbor some biologic differences in their prostate tumors.[16–20] Powell and colleagues found low androgen-dependent and high immune-mediated molecular markers and pathways in tumors from a large cohort of men of African ancestry.[17] However, none of these biologic 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 and

colleagues showed that young Black men (< 50 years-old) demonstrated similar rates of BCR compared to white men, despite more aggressive disease at prostatectomy.[21] Similar results were demonstrated by Cross et al[27], who showed that the rates of BCR at 5-years was 28% and 32% among Black and white men, respectively. In contrast, Schreiber et al[22] demonstrated 2.5-fold higher rates of biochemical recurrence among Black men managed by prostatectomy in the Veterans Affairs derived SEARCH database. Subsequent studies using the SEARCH database—and with longer follow-up—have demonstrated these differences in outcomes are greatly attenuated when adjusted 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 on adjusted analysis, likely reflecting 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] with 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. Yamoah and colleagues[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, evaluating 326 Black and 4926 white men from 1988 to 2004 at a single institution, found no statistically significant differences in the rate of adverse pathologic features despite Black men having higher grade disease in the cohort.[25] 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%, $p < 0.001$) and lower rates of node positive disease (17.0% vs. 22.6%, $p = 0.08$). Black men also demonstrated a higher rate of positive surgical margins (31.6% vs. 26.5%, $p = 0.14$). Despite epidemiologic data demonstrating a two-fold risk of mortality, Black men with high-grade/risk disease at prostatectomy demonstrated no major differences in adverse pathologic findings—especially seminal vesicle or lymph node positive disease—when compared to white men.

The underutilization of radical prostatectomy among Black men, especially those with higher risk disease, has been well documented over the past two decades. Black men only represented 11.3% of our multi-institutional cohort, spanning a 10-year study period at three high-volume prostatectomy centers. In a recent analysis of data from the National Cancer Database (NCDB), Weiner et al showed that Black ethnicity was associated with a 31% lower rate of radical prostatectomy use for high-risk, localized disease.[33] Gray and colleagues 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 NCDB data from 2004-2012.[10] This is concerning given that various studies in equal-access settings have shown that Black and white men have similar prostate cancer outcomes following definitive therapy when matched by stage and grade,[8,9] which is similar to the findings in our analysis. Disparities in the utilization of secondary treatments is an additional potential source of disparities in care. To date, there are no studies on this topic. Zeliadt et al however demonstrated that Black men are more likely to undergo less frequent PSA surveillance following primary treatment.[34] 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 both healthcare, social, and patient factors. It is important to understand what drives differences in treatment choice, as it likely impacts the disparities in outcomes observed. Data from the CaPSURE database has demonstrated that Black men are less likely to receive definitive therapy for localized prostate cancer compared to white men.[35,36] Mahal et al demonstrated that Black men with intermediate- and high- risk disease have significantly lower rates of definitive therapy utilization.[37] 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 suggests 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 three institutions in this cohort are very likely to be insured and of a higher social standing compared to Black men who do not have access to medical care. This likely results in differences in access to and utilization of

healthcare, medical knowledge, access to medical information, social support, economic and financial standing, and 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 post-treatment 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 on 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 US.

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 compared to the white men decreases the power of our comparative analyses. Median follow-up in this cohort is 40.7 months, which does not allow for more robust analysis of outcomes such as CSM which require longer follow-up for events to occur. However, we presume the rate and time to adverse oncologic events is 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 three institutions with robust pathologic and prostatectomy experiences.

CONCLUSIONS

Among men with grade group 4-5 prostate cancer at diagnosis managed at three high-volume prostatectomy centers, we found no difference in the rate of adverse oncologic outcomes when 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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Figure Legends:

Figure 1 – CONSORT Flow Diagram

Figure 2 – Comparison of (a) biochemical recurrence, (b) metastases, and (c) cancer mortality between Black and white men with high-grade prostate cancer primarily managed by radical prostatectomy

Table 1: Baseline demographic and clinical characteristics of Black and white men with clinical grade group 4-5 prostate cancer managed by radical prostatectomy (n = 1,662)

Characteristic	Black (n = 188)	White (n = 1474)	p-value
Continuous, median (IQR)			
Age at diagnosis, years	60.0 (54.5, 65.0)	63.3 (58.8, 68.5)	< 0.001
PSA at diagnosis, ng/ml	6.9 (4.9, 13.6)	6.6 (4.8, 10.6)	0.13
No. of biopsy cores with grade group 4-5	2 (1, 3)	2 (1, 4)	0.89
Time from diagnosis to surgery, days	89 (60, 126)	70 (51, 103)	< 0.001
Year of diagnosis	2010 (2008, 2013)	2011 (2008, 2013)	0.12
Follow-up, months	45.8 (23.5, 63.5)	39.9 (20.2, 67.4)	0.32
Categorical, No. (%)			
Gleason score at initial biopsy			
Grade group 4	120 (64.2)	875 (59.8)	0.25
Grade group 5	67 (35.8)	588 (40.2)	
Clinical T stage			
cT1	115 (62.8)	671 (46.6)	< 0.001
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)	0.10
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)	0.91
Very high	65 (34.6)	516 (35.0)	
Neoadjuvant ADT, yes	22 (11.7)	258 (17.5)	0.04

Abbreviations: ADT, Androgen deprivation therapy; GS, Gleason score; IQR, Interquartile range; NCCN, National Comprehensive Cancer Network; PSA, Prostate specific antigen.

Table 2: Pathologic findings at radical prostatectomy and post-operative clinical data among Black and white men with clinical Grade group 4-5 prostate cancer managed by radical prostatectomy (n = 1,662)

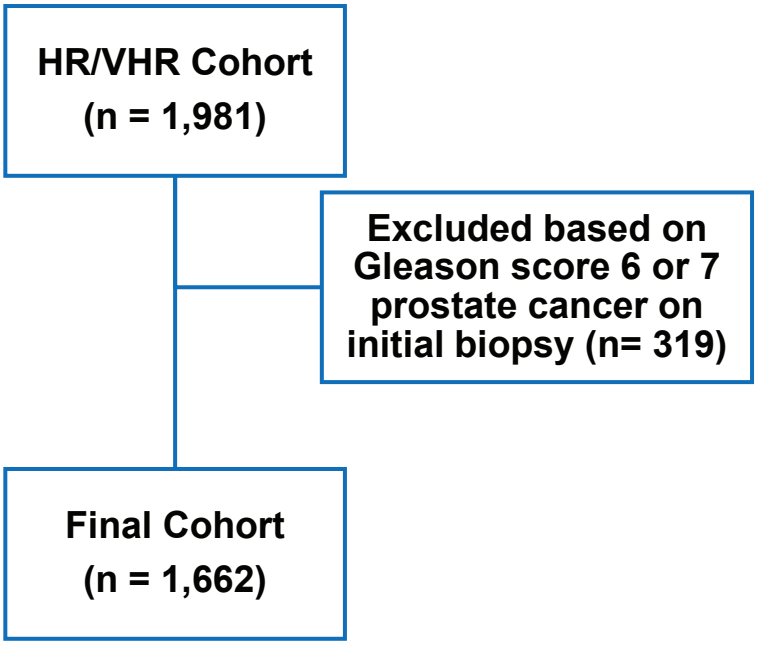
Characteristic, No. (%)	Black (n = 188)	White (n = 1474)	p-value
Gleason score at prostatectomy			
Unable to assess / ADT changes	27 (14.4)	254 (17.3)	0.052
Grade group 1	1 (0.5)	9 (0.6)	
Grade group 2	37 (19.8)	200 (13.6)	
Grade group 3	30 (16.0)	201 (13.7)	
Grade group 4	40 (21.4)	263 (17.9)	
Grade group 5	52 (27.8)	545 (37.0)	
Pathologic T stage			
pT0	3 (1.6)	3 (0.2)	< 0.001
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	32 (17.0)	333 (22.6)	0.08
Positive surgical margin	59 (31.6)	390 (26.5)	0.14
Adjuvant ADT	36 (19.2)	382 (25.9)	0.04
Adjuvant RT	43 (22.9)	386 (26.2)	0.33

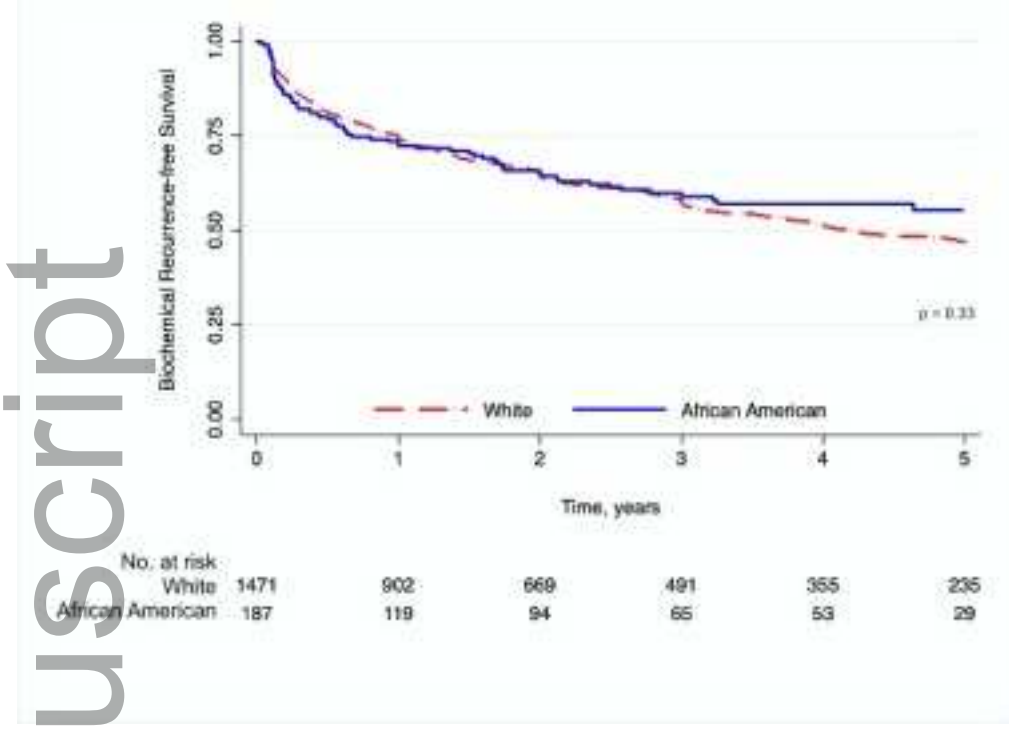
Abbreviations: ADT, Androgen deprivation therapy; RT, Radiotherapy

Table 3: Oncologic events and overall survival among Black and white men with grade group 4-5 prostate cancer managed by radical prostatectomy

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

Abbreviations: CI, Confidence Interval.





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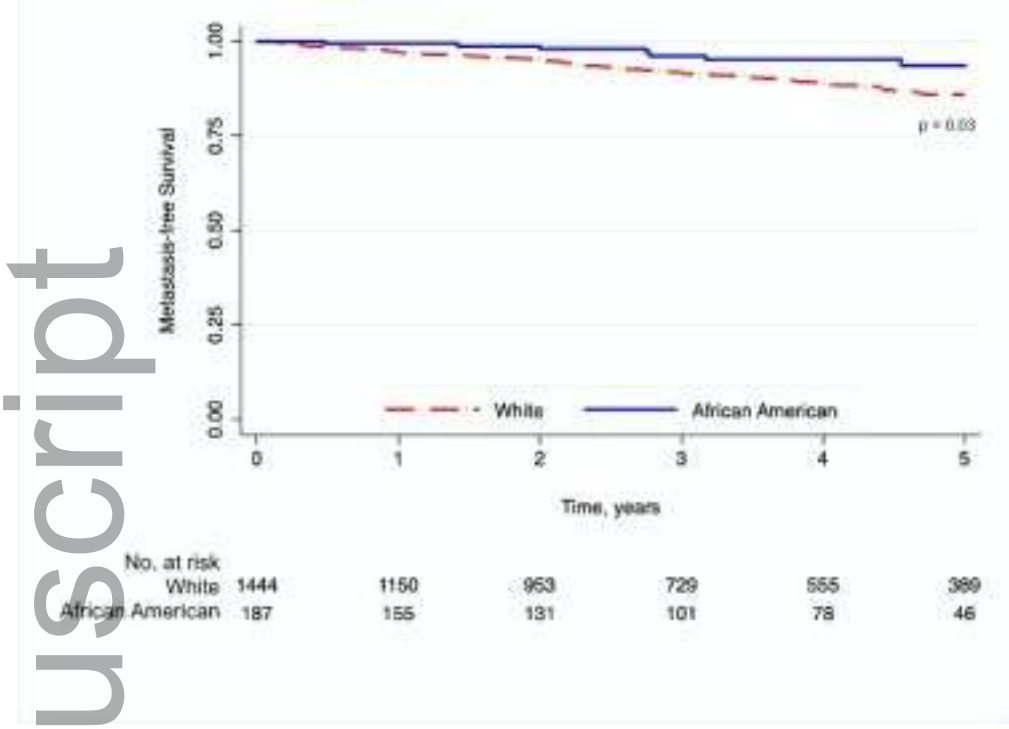

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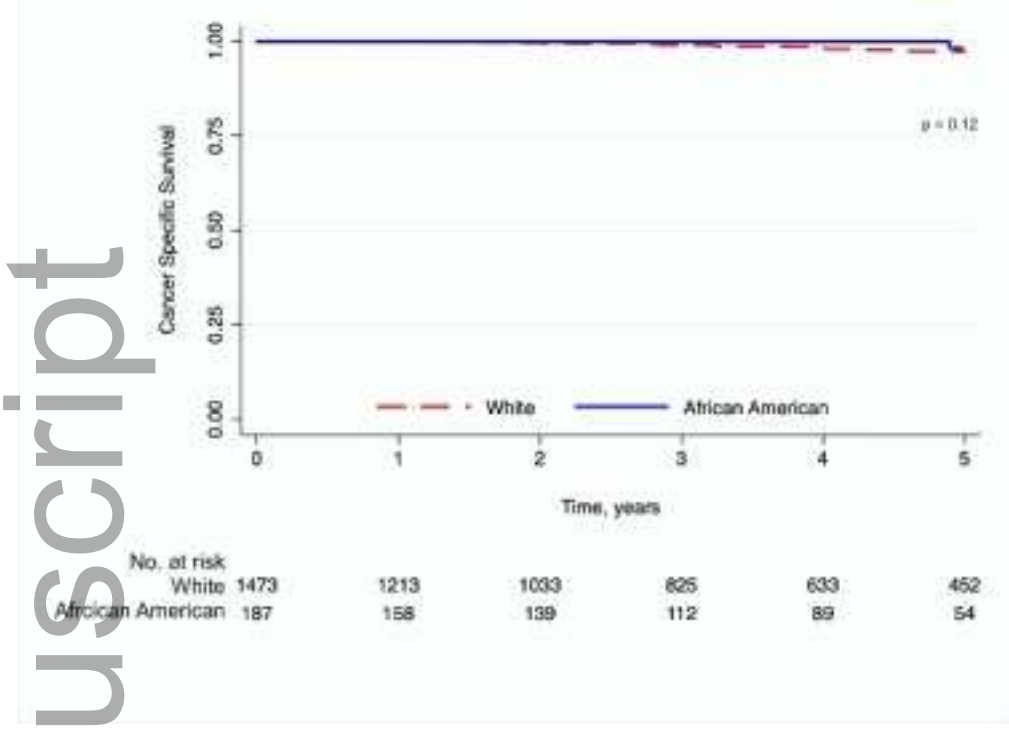

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