Title

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Does race predict development of metastases in men on ADT after biochemical recurrence following radical prostatectomy?

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Abstract

BACKGROUND: In a study among men undergoing radical prostatectomy (RP), we found African American men (AAM) were 28% more likely to recur. However, in men with non-metastatic castration-resistant PC (CRPC), we found race did not predict metastases or overall

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AUTHOR CONTRIBUTIONS STATEMENT:

SJF, WJA, MKT, CLA, CJK, MRC, SL, SCF, ACV contributed to the formulation of overarching research goals and aims, writing, reviewing and editing of the manuscript; SJF, WJA, MKT, CLA, CJK, MRC provided the resources (patients and data); ADH helped in the coordination of the study and data collection; LEH, SJF, ACV conducted the study and performed the analysis; SJF, WJA, MKT secured funding for this study.

CONFLICTS OF INTEREST STATEMENT:

Dr. Lechpammer is an employee of Pfizer Inc. Dr. Flanders is an employee of Astellas Pharma, Inc.

survival. Whether race predicts metastases among men receiving androgen deprivation therapy (ADT) after biochemical recurrence (BCR) (i.e. earlier than CRPC but after BCR) is untested.

METHODS: We identified 595 AAM and Caucasian men (CM) who received ADT after BCR following RP between 1988–2015 in the SEARCH database. Cox models, uni- and multivariable, were used to test the association between race and time from ADT to metastases. Secondary outcomes included time to CRPC, all-cause mortality, and PC specific mortality.

RESULTS: During a 65-month median follow-up after ADT, 62/354 CM (18%) and 38/241 AAM (16%) developed metastases. AAM were younger at ADT (63 vs. 67, p<0.001), had more recent year of ADT (2008 vs. 2006, p<0.001), higher PSA at RP (11.1 vs. 9.2, p<0.001), lower pathological Gleason (p=0.004), and less extracapsular extension (38% vs. 48%, p=0.022). On multivariable analysis, there was no association between race and metastases (HR=1.20, p=0.45), or any of the other secondary outcomes (all p>0.5).

CONCLUSIONS: Among veterans treated with ADT following BCR after RP, race was not a predictor of metastases or other adverse outcomes. This suggests research efforts to understand racial differences in PC biology should focus on early stages of the disease (i.e. closer to the time of diagnosis).

PRECIS:

In an equal-access setting of men treated with ADT following BCR after RP, race was not a predictor of metastases or any other longer-term outcome. PSADT was a stronger predictor of metastases in CM vs. AAM, however, it was predictive of metastases in both races.

Keywords

race; prostate cancer; metastasis; ADT; outcomes

INTRODUCTION

African American men (AAM) have a higher risk of prostate cancer (PC) and PC-specific mortality (PCSM) than Caucasian men (CM).[1–4] The exact steps in PC biology that result in PC death (i.e. initiation, progression to clinically detectable disease, failure after initial treatment, failure after subsequent therapy, metastases, etc.) that are influenced by race are unclear. For example, we previously showed that at the time of biopsy, AAM have higher risk of PC and particularly aggressive PC.[5] In contrast, for men undergoing radical prostatectomy (RP), we recently showed that AAM have a higher risk of recurrence, but similar risks of progression to metastases and PC death.[6] As androgen deprivation therapy (ADT) is routinely used for advanced and especially metastatic PC, it is rare that a patient dies of PC without first receiving ADT. As such, disease progression (rising PSA) despite treating with ADT to castrate levels, results in advance disease known as castration-resistant PC (CRPC) – with or without metastasis. Despite many studies examining outcomes after primary therapy (i.e. surgery or radiation), it is notable that no prior study to date has examined whether AAM are at higher risk of CRPC after the initiation of ADT.

To address this gap in the literature and using an equal access setting of care, i.e. multiple VA centers, we tested whether race is associated with distant metastasis in men receiving ADT after biochemical recurrence (BCR) following radical prostatectomy. Secondly, we tested whether variables associated with distant metastases differ between AAM and CM. We hypothesized race is associated with distant metastases or other adverse outcomes, and certain variables associated with distant metastases differ between AAM and CM.

MATERIALS AND METHODS

Patient population

After receiving Institutional Review Board approval (Durham VAMC), data from patients undergoing RP from 1988 to 2015 were combined in the Shared Equal Access Regional Cancer Hospital (SEARCH) database. SEARCH is composed of six surgical sites (San Diego, West Los Angeles, and Palo Alto, CA; Augusta, GA; Durham and Asheville, NC) and includes information on demographic, clinicopathological, secondary treatments, and survival data.

Of 5515 patients in the SEARCH database, 1984 (36%) had a BCR during follow-up, defined as two PSA levels of 0.2 ng/mL or one PSA level >0.2 ng/mL after RP, or secondary treatment for a rising PSA. Of patients who had a BCR, 856 (43%) went on to receive ADT after BCR. We excluded patients who developed metastases before receiving ADT (n=105), and patients of other or missing race (n=24). That is, after excluding men who did not recur or receive ADT, those with metastases at the time of ADT, or those of other races, there were 727 men eligible. Among these, n=132 were missing at least one of the covariates listed below, resulting in a study cohort of 595 men (Figure 1). Of note, AAM were less likely to be missing covariates compared to CM (10% vs. 23%, respectively, $p<0.001$).

Study outcomes

CRPC was defined as a PSA rise of ≥2 ng/ml and ≥25% from the post-ADT nadir while being castrate. Castration was defined as testosterone <50ng/dL, bilateral orchiectomy, or continuous receipt of luteinizing hormone releasing hormone agonist or antagonist. All imaging was done at the discretion of the treating physician. Imaging reports (bone scan, MRI, CT, X-ray) after surgery were assessed by trained personnel to determine development of metastases. PCSM was defined as progressive metastatic disease after hormonal therapy with no other obvious cause of death. Mortality was determined from the electronic medical records.

Statistical Analysis

Variables were compared between AAM and CM using rank sum tests for continuous variables and chi-squared tests or Fisher's exact test (for any variable with expected cell count <5) for categorical variables.

Kaplan-Meier estimates stratified by race were graphed for each of the outcomes as the time from ADT to metastasis, CRPC, all-cause mortality (ACM), and PCSM. The difference in survival between AAM and CM for each outcome was tested using the log-rank test. Cox

proportional hazards models were used to test the association between race (African American vs. Caucasian) and time from ADT to each outcome. Multivariable models were adjusted for age at ADT initiation (continuous), year of ADT initiation (continuous), surgical center, BMI at ADT initiation (<25 kg/m^2, 25–29.9, ≥30, unknown), pre-ADT PSA (continuous, log-transformed), PSA doubling time (PSADT) leading up to ADT (≥9 months, 3–8.9, <3, not calculable), pathological grade group (1, 2–3, 4–5), positive surgical margins (no, yes), extracapsular extension (no, yes), seminal vesicle invasion (no, yes), positive lymph nodes (no, yes, not done), early BCR (BCR within 2 years of RP) (no, yes), salvage radiation therapy (no, yes; time-dependent), months from BCR to ADT (continuous), and months from surgery to BCR (continuous). Interactions between each predictor and race were tested for each outcome by including the cross product and main effects in a model with metastases as the primary outcome and the other outcomes as exploratory. The Wald test was used to test the interaction term. As fifteen separate predictors were tested, a Bonferroni correction of 0.05/15=0.0033 was made to the threshold for significance for interaction testing.

Results were performed using Stata 14.2 (Stata Corp., College Station, TX). P<0.05 was used as the threshold for statistical significance for testing the primary effect of race.

RESULTS

Patient characteristics

Our cohort consisted of 354 CM (59%) and 241 AAM (41%) (Table 1). Compared to CM, AAM were younger at ADT (median age 63 vs. 67, p<0.001), had more recent year of ADT (median year 2008 vs. 2006, p=0.003), fewer had pathological grade group 5 (12% vs. 20%, p=0.015), and fewer had extracapsular extension (38% vs. 48%, p=0.025). However, there were no statistically significant differences between any other characteristics, including PSA and PSADT at ADT.

Survival outcomes

During a median follow-up of 66 months after ADT, there were 39, 40, 76, and 25 AAM who developed metastasis, CRPC, died from any cause, and died from PC, respectively. Whereas, there were 63, 68, 146, and 44 CM who developed metastasis, CRPC, died from any cause, and died from PC, respectively. Follow-up was similar in AAM and CM (p=0.77). The Kaplan Meier graphs (Figures 2–5) showed similar time to metastasis (log-rank, p=0.70), CRPC (p=0.50), ACM (p=0.14), and PCSM (p=0.54) between AAM and CM. On both univariable and multivariable analysis, there was no association between race and any of the outcomes (Table 2, all p≥0.14). Though we adjusted for grade group, we noted a higher rate of pathological grade group 4–5 in CM. Given the strong link between grade group and poor outcome, we performed a post-hoc stratification by grade group – 1–3 vs. 4–5. Within both strata, there remained no associations between race and CRPC, overall survival and PCSM (all p>0.05). Moreover, there was no interaction between race and pathological grade group to predict CRPC, overall survival and PCSM (all p-interaction>0.05). Race was borderline associated, although not statistically significant, with higher risk of metastasis with grade group 1–3 (HR 1.86, 95%CI 0.99–3.51, p=0.054) but

there was no association in grade group 4–5 (HR 0.48, 95%CI 0.19–1.21, p=0.12; p-interaction=0.03). However, these models only had 54 and 48 events, respectively, and were overfit. Therefore, race was not associated with any outcomes independent of any racial differences in pathological grade group.

Interactions with race

Using a p-value threshold of 0.0033, the only statistically significant interaction with race was with PSADT in predicting metastases (p=0.002) in that PSADT was a stronger predictor of metastases in white men (p<0.001) than AAM (p=0.016). No other interactions were statistically significant (Table 3).

DISCUSSION

Although it is known that AAM have higher PC incidence and mortality rates compared to CM,[1–4] the exact steps in the clinical setting of PC (diagnosis, progression after primary treatment, progression after secondary treatment, etc.) that drive these health disparities is not clear. In the present study, we evaluated VA patients who were initiating ADT for BCR after RP. Importantly, and contrary to our hypothesis, we found race was not associated with metastases or any long-term outcome. Though we found PSADT was a stronger predictor of metastases in CM vs. AAM, it was associated with metastases in both races. As such, the clinical relevance of this observation is not clear. Our results, coupled with other studies from our group showing no differences in long-term outcomes either at the time of RP[6] or at the time of non-metastatic CRPC,[7] suggest that in order to understand PC health disparities, research should focus on why AAM present with a greater risk of more aggressive cancers at the time of diagnosis.[5]

While our study is the first to examine the impact of race on outcomes after ADT, our null results are in agreement with our previous results among 837 CRPC patients (306 AAM and 531 CM) with no known metastases (M0/Mx), where AAM were equally likely to be diagnosed with any metastases and had similar overall survival rates as CM.[7] Similarly, these results are also in agreement with another prior study from the SEARCH database, in which we found AAM undergoing RP were not at increased risk of aggressive recurrence or the longer-term outcomes of metastasis, PCSM, or ACM compared to CM.[6] Importantly, our studies were all from the VA Health System, an equal access healthcare system. As such, it is noteworthy that our null results of race and outcomes among men already diagnosed with PC are consistent with other studies of men receiving standardized care within a clinical trial setting whether it be men undergoing radiation[8] or receiving therapy for CRPC.[9, 10] As such, these results suggest that when care is provided equally, whether at an equal access center of within a clinical trial, race is not associated with outcomes among men diagnosed with PC.

Despite the fact that race does not independently influence outcomes among men diagnosed with PC, AAM continue to present with aggressive PC at younger ages, leading to an overall increased risk of PC death at the population level.[4] Moreover, a recent study used data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) to identify 25,445 men aged ≥45 years diagnosed with clinically metastatic PC, and found that as of year 2013, the incidence of metastatic PC among AAM is almost twice as high

compared to CM.[11] Given the accumulating research suggesting that race is not a prognostic factor in men diagnosed with PC, research efforts to understand differences by race in PC biology should focus on understanding why AAM present at higher rates than CM with more aggressive disease at diagnosis.[5, 12] Potential causes for more aggressive PC at diagnosis in AAM may include genetics and lifestyle factors. For example, a combination of differences in androgen levels and androgen receptor biology, with dietary factors and lifestyle factors affecting PC carcinogenesis pathways, such as smoking,[13] may lead to increased risk of aggressive PC in AAM. At the molecular level, a study suggested aggressive PC in AAM may be related to the presence of the Broad11934905 risk allele, which is unique to AAM and is present on chromosome 8q24 (a known PC risk loci).[14] We also found several aggressive PC markers including Ki67, androgen receptor, and alpha-methyl-acyl-racemase (AMACR) were more highly expressed in AAM.[12] Moreover, there are genetic differences in inflammatory-related genes by race. A study showed AAM have lower expression of DARC, a Duffy antigen/receptor for chemokines such as CXCL1 and CXCL8, on endothelial cells and erythrocytes.[15] DARC acts as a sink for cytokines and thus loss of DARC leads to higher systemic cytokines,[16] leading to higher inflammation which is linked to higher PC risk.[17] Finally, others have shown that AAM PCs express higher levels of inflammatory-related genes.[18, 19] All this evidence supports the hypothesis that PC maybe biologically different in AAM and CM.

Given differences in disease biology, we tested whether variables associated with distant metastases differed between AAM and CM on secondary analyses. In general, the same factors were associated with progression in CM and AAM with one exception: PSADT. PSADT was a stronger predictor of metastases in CM vs. AAM, though PSADT was associated with metastases in both races. Moreover, there was no significant interaction between race and PSADT for predicting other outcomes such as CRPC, ACM, or PCSM. Though this interaction was significant after Bonferroni correction, the lack of consistency for the interaction across other measures of disease progression, this raises questions of type I error. As such, further research is needed to test whether PSADT is indeed more predictive of metastases in CM vs. AAM.

Although this study has several strengths, there are also some limitations, including the retrospective design of the study. This resulted in some men being excluded for missing data. As mentioned in the methods section, AAM were less likely to be missing covariates compared to CM. Part of this is explained by some VA centers having all available data while others have not. How this may have affected our results is unknown, however all analyses were adjusted for surgical (VA) center, which is linked to race. The number of events at metastases, ACM, and PCSM, was modest. Thus, we were relatively underpowered and we cannot exclude a modest association between race and long-term outcomes. Furthermore, given the long natural history of PC and our modest ~5.5 year mean follow-up, it is possible results could be different with longer follow-up and larger sample sizes. The study occurred over a long time. Thus, changes in tumor grading and imaging may have affected our results. However, as these changes would apply equally to AAM and CM and we adjusted for year of ADT, it is not clear how these changes would influence the conclusion that there were no differences in long-term outcomes between races. Although we had data on when patients started ADT, we did not have good information on stopping

times for ADT, thus we assumed that once patients started ADT treatment, they stayed on it. Furthermore, differences in physician practice could have influenced outcomes. However, most men were managed in an era prior to modern treatment, including ADT drugs and these agents were unlikely to have largely influenced our results. Our study only evaluated men undergoing RP and thus represents a selection bias of men who are healthy enough to undergo surgery and excludes men who present with metastatic disease who are not typically offered surgery. Future studies should address progression endpoints in AAM undergoing other treatments such as radiotherapy. Nonetheless, our approach to analyze only surgical patients creates a more homogenous cohort wherein we can better ask do equal men (i.e. other factors adjusted for such as PSA, grade, etc.), when treated equally, have equal outcomes. Moreover, our study still represents the largest to date evaluating metastasis and death in AAM undergoing RP with equal access to care.

In summary, in an equal-access setting of men treated with ADT following BCR after RP, race was not a predictor of metastases or any other longer-term outcome. PSADT was a stronger predictor of metastases in CM vs. AAM, however, it was predictive of metastases in both races. Thus, future research efforts to understand racial differences in PC biology should focus on understanding why AAM present at higher rates than CM with more aggressive disease at diagnosis.

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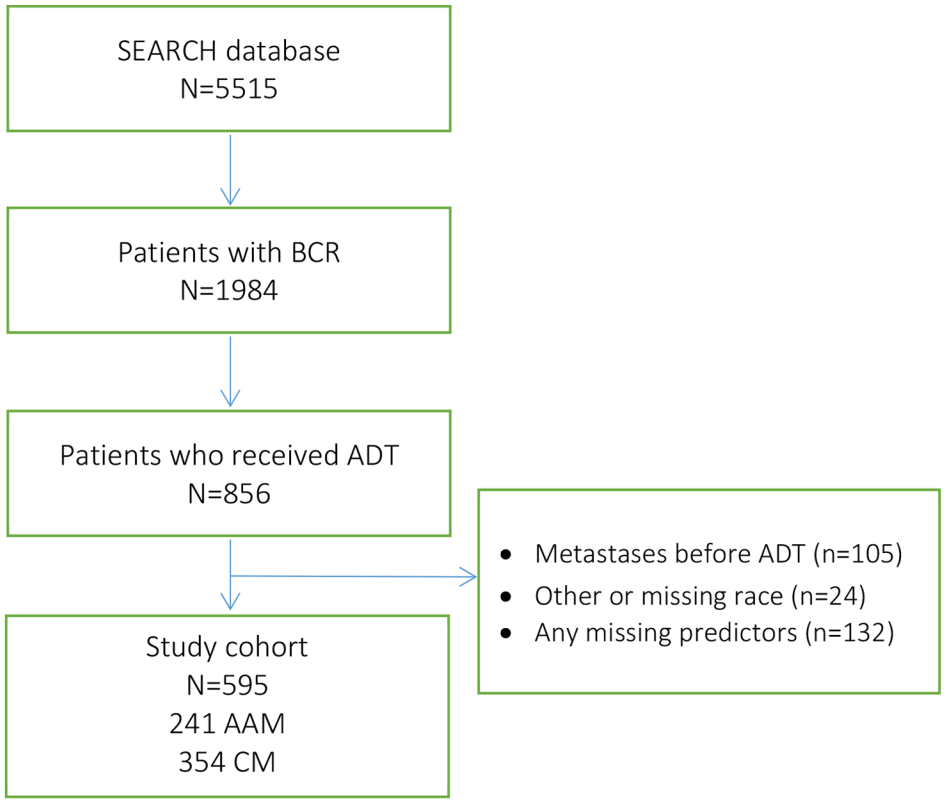
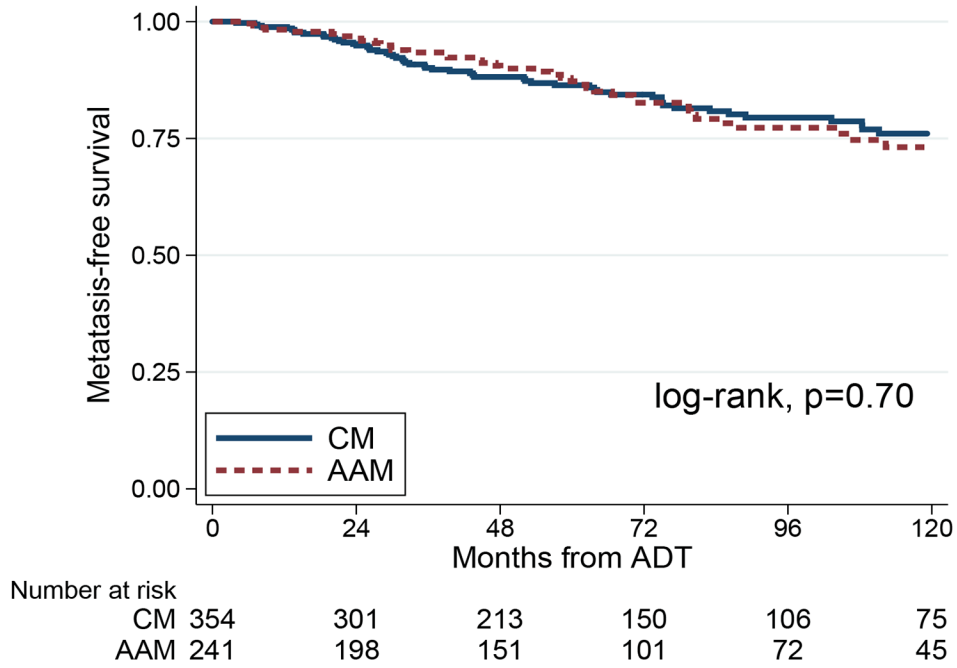


SEARCH=Shared Equal Access Regional Cancer Hospital
BCR=Biochemical recurrence
ADT=Androgen deprivation therapy
AAM=African American men
CM=Caucasian men

Figure 1:
Consort diagram of analysis cohort



Number at risk

CM	354	301	213	150	106	75
AAM	241	198	151	101	72	45

Figure 2.
Kaplan-Meier estimates of Metastasis-free survival stratified by race at surgery.

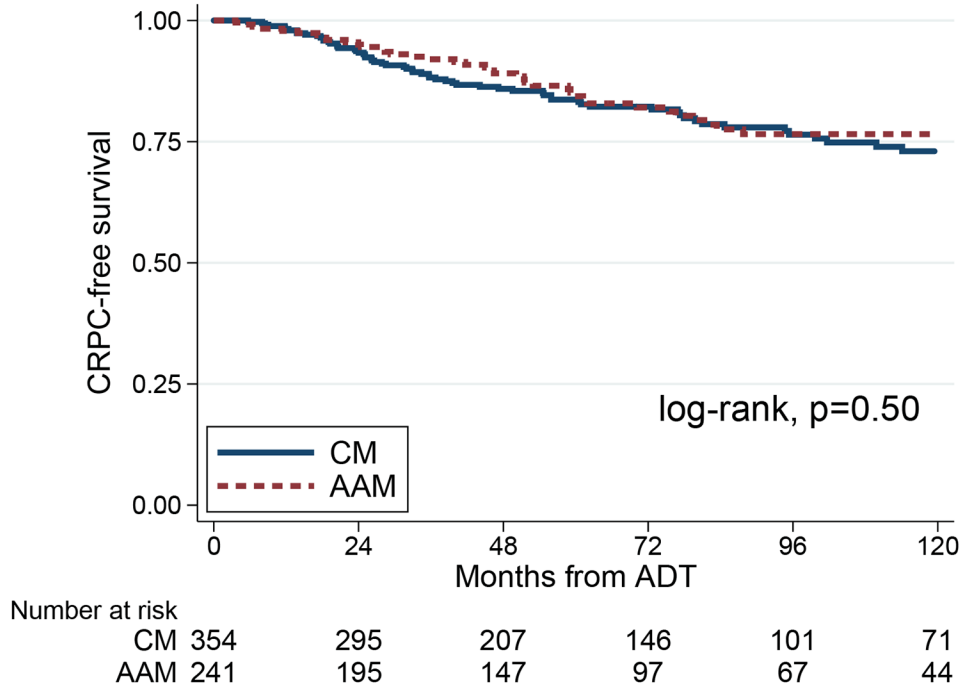


Figure 3.
Kaplan-Meier estimates of time CRPC-free survival stratified by race at surgery.

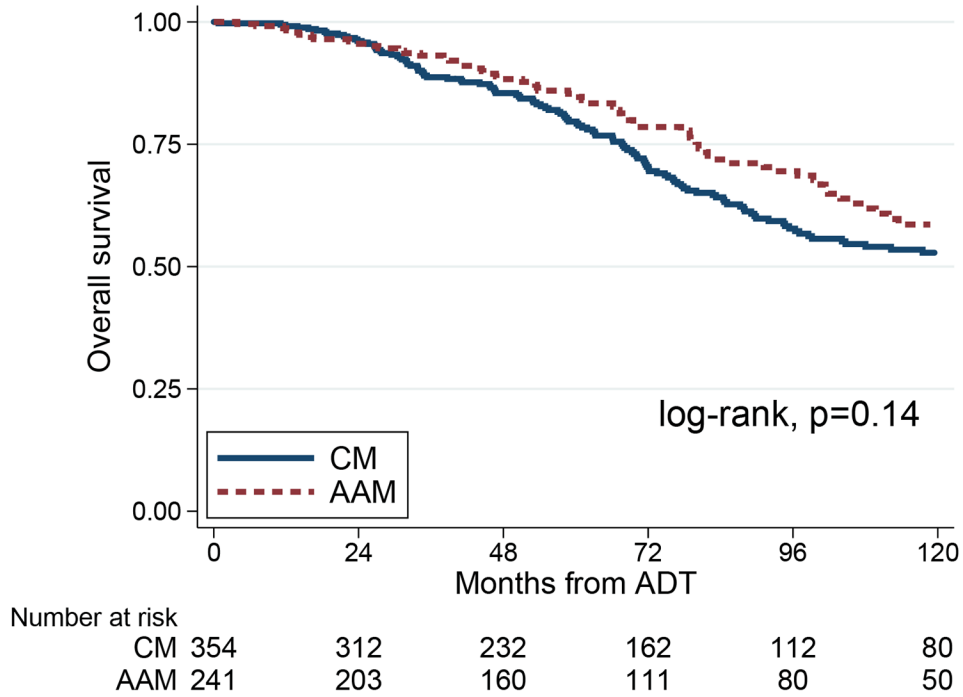


Figure 4.
Kaplan-Meier estimates of time to Overall survival stratified by race at surgery.

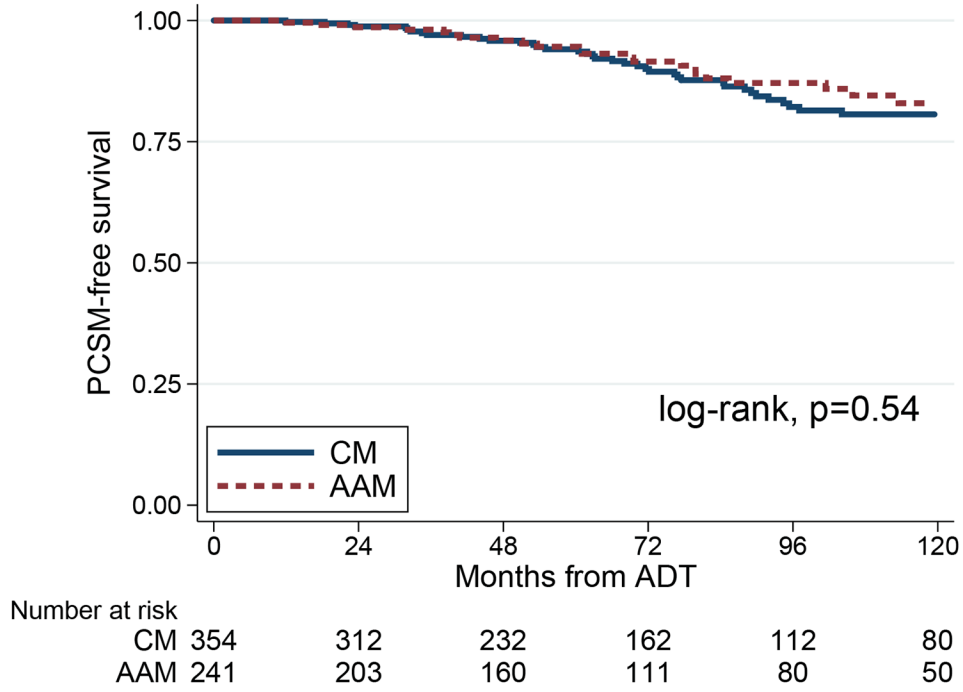


Figure 5.
Kaplan-Meier estimates of time to PCSM-free survival stratified by race at surgery.

Table 1:

Patient characteristics

Variable	Caucasian	African American	P-value*
No. Patients	354 (59)	241 (41)	
Age at ADT	67 (62–71)	63 (58–69)	<0.001
Year of ADT initiation	2006 (2001–2012)	2008 (2003–2012)	0.003
BMI (kg/m^2)			0.31
<25	55 (16)	33 (14)	
25–29.9	99 (28)	63 (26)	
≥30	78 (22)	44 (18)	
Unknown	122 (34)	101 (42)	
Pre-ADT PSA (ng/mL)	1.5 (0.3–5.4)	1.2 (0.3–4.7)	0.45
Pre-ADT PSADT (months)			0.42
≥9	115 (32)	78 (32)	
3–8.9	119 (34)	68 (28)	
<3	29 (8)	20 (8)	
Not calculable	91 (26)	75 (31)	
Pathological Gleason grade group			0.015
1	51 (14)	35 (15)	
2	114 (32)	87 (36)	
3	65 (18)	64 (27)	
4	52 (15)	25 (10)	
5	72 (20)	30 (12)	
Positive surgical margins	201 (57)	148 (61)	0.26
Extracapsular extension	171 (48)	94 (39)	0.025
Seminal vesicle invasion	100 (28)	85 (35)	0.07
Positive lymph nodes			0.86
No	257 (73)	170 (70)	
Yes	32 (9)	24 (10)	
Not done	65 (18)	47 (20)	
Early BCR	207 (58)	137 (57)	0.69
Radiation therapy	222 (63)	153 (63)	0.85
Months from BCR to ADT	11 (1–36)	9 (1–37)	0.58
Months from surgery to BCR	9 (3–24)	9 (3–26)	0.71
Follow-up after ADT (months)	66 (34–117)	67 (37–112)	0.77

* P-value calculated using rank sum tests for continuous variables and chi-squared or Fisher's exact test for categorical variables

Cells show N (%) for categorical variables and median (Q1-Q3) for continuous variables

Table 2:

Race as a predictor of PC outcomes

	Univariable		Multivariable*	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Metastases				
Race (African American vs. Caucasian)	0.92 (0.62–1.38)	0.70	1.07 (0.68–1.70)	0.77
CRPC				
Race (African American vs. Caucasian)	0.87 (0.59–1.29)	0.50	1.05 (0.67–1.65)	0.82
ACM				
Race (African American vs. Caucasian)	0.81 (0.61–1.07)	0.14	0.94 (0.69–1.28)	0.69
PCSM				
Race (African American vs. Caucasian)	0.86 (0.52–1.40)	0.54	0.92 (0.51–1.65)	0.77

*Multivariable model adjusted for PSA at ADT, pathological Gleason score, pathological features (seminal vesicle invasion, extracapsular extension, positive surgical margins, lymph node invasion), age at ADT, year of ADT, surgical center, BMI at ADT, PSADT at ADT, radiation therapy, early BCR, time from surgery to ADT, time from surgery to recurrence

Table 3

: Interactions (p-values) between race and covariates in predicting outcomes

	Metastases	CRPC	ACM	PCSM
Age at ADT	0.18	0.44	0.50	0.21
Year of ADT initiation	0.43	0.40	0.98	0.41
BMI	0.12	0.36	0.93	0.34
Pre-ADT PSA	0.22	0.22	0.23	0.23
Pre-ADT PSADT	0.002	0.013	0.26	0.21
Pathological Gleason score	0.08	0.41	0.60	0.85
Positive surgical margins	0.10	0.10	0.55	0.26
Extracapsular extension	0.03	0.12	0.82	0.31
Seminal vesicle invasion	0.09	0.07	0.020	0.30
Positive lymph nodes	0.71	0.67	0.38	0.99
Early BCR	0.16	0.042	0.97	0.26
Radiation therapy	0.08	0.23	0.65	DNC
Months from BCR to ADT	0.45	0.61	0.76	0.79
Months from surgery to BCR	0.18	0.11	0.78	0.32

DNC=model did not converge