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TITLE: Novel Nomogram That Predicts Aggressive Disease and Treatment Failure Among African-American Men with Prostate Cancer

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14. ABSTRACT: Prostate cancer (PCa) has greatest incidence and mortality among African American (AA) as compared to their European American (EA) counterparts in the US. This disparity has been attributed to a number of factors including access to care, screening patterns, and behavior. More recent data suggest that genetic/biologic factors may at least in part contribute to more aggressive disease in AA men. Using the SCORE database, we studied PCa outcomes in AA vs. EA men after radical prostatectomy. We showed that AA race was a predictor of worse biochemical failure in patients with pathologic Gleason score ≤ 6 or low-grade disease and favorable pathologic features (Yamoah et, al., 2014). Next, immunohistochemistry for 20 biomarkers was undertaken on the FFPE tumors of 45 EA and 55 AA men within the SCORE database. To date, 6 biomarkers have been analyzed including TMPRSS2-ERG, AMACR, PSMA, RB, c-Myc, and AR. We observed statistically significant differences in biomarker expression between EA vs AA for AMACR (p=0.004), c-myc (p=0.005), and AR (p=0.002). These data suggest that biomarkers that have been reported to be associated with tumor aggressiveness may in					
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Introduction:

Globally, men of African descent are known to experience greater incidence of and mortality from prostate cancer (PCa) than their Caucasian or Asian counterparts¹. This observation has been partly attributed to socio-economic factors and inadequate access to healthcare²⁻⁴. However, there is also recent evidence suggesting that genetic differences in susceptibility play a major role in this disparity⁵⁻⁸. Due to the relatively indolent nature of PCa, the decision-making process for determining whether to pursue active surveillance, or to offer different treatment options, is complicated by the balance between life expectancy, comorbidities, clinical benefits, as well as the side effects of treatment⁹. The prediction of clinical outcomes through the use of nomograms is critical in recommending appropriate treatment options for PCa patients. However, it is uncertain whether the current nomograms used to risk-stratify PCa patients for treatment recommendations truly apply to AAM. The reasons include the fact that majority of the clinically useful nomograms were derived using data extrapolated from PCa patients of European ancestry¹⁰. Furthermore, several studies have demonstrated that the current nomograms, which were derived based on limited clinical and pathologic information such as Prostate Specific Antigen (PSA), T-stage and Gleason score, have a predictive accuracy of only 65% to 79%, and thus may be suboptimal^{11, 12}. The inclusion of other potentially informative clinical and pathologic features such as age, AA race, surgical margins, seminal vesicle involvement, lymphovascular involvement or lymph node status have only slightly improved the predictive accuracy of nomograms^{13, 14}. Despite increased disease recurrence and mortality trends among AAM with PCa, these nomograms have been suboptimal in predicting the subset of AAM patients who harbor aggressive disease and are at higher risk for disease recurrence. The genetic contribution to PCa disparity has been well established with the identification of significant racial differences in frequency and expression of various genes and biomarkers. Recently, several biomarkers (Table 1) have been shown to correlate with aggressive phenotypes in prostate cancer¹⁵⁻²². The most notable examples include the TMPRSS2:ERG gene fusion²³, Ki-67 expression¹⁷, and biomarkers involved in androgen metabolism^{8, 18}. The relevance of these biomarkers to the observed increased aggressiveness and disease recurrence among AAM is not known. We hypothesize that addition of these potentially informative biomarkers may significantly improve the predictive capacity of nomograms in predicting aggressive disease measured as the time to PSA failure after treatment among AAM. We propose to evaluate this hypothesis using the following Specific Aims 1) To develop a nomogram that significantly improves the accuracy of distinguishing aggressive from non-aggressive PCa in AAM. 2) To evaluate the incorporation of this novel nomogram into clinical practice.

Keywords: Prostate Cancer, racial disparity, African American Men, Predictive Biomarkers, Nomogram Development

Overall Project Summary:

Prostate cancer (PCa) is the most commonly occurring non-cutaneous malignant cancer in the U.S. African American men (AAM) are known to have the highest rates of PCa. They typically present with advanced disease, and have greater mortality rates than their Caucasian counterparts. Despite the importance of PCa in AAM, we are still unable to make optimal PCa treatment decisions in this group of men. As a result, many clinicians are uncertain about the value of the currently available tools that guide treatment decisions for AAM with PCa. The purpose of this project is to provide insights into the underlying causes of racial disparities in PCa outcomes and ultimately improve the current treatment recommendations in AAM with PCa. This project directly addresses the need to effectively identify aggressive disease in specific individuals or groups based on their unique characteristics. The research portion of this project

will have two basic goals. The first goal will be to develop a new predictive tool, also known as a nomogram, which will improve the ability to predict aggressive disease and make improved treatment decisions among AAM. This nomogram will include biomarkers predictive of aggressive PCa in addition to the predictors currently used in existing nomograms. The new nomogram's predictive accuracy will be evaluated using a large PCa database. The second goal will be to take steps towards the implementation of this new nomogram into decision-making among physicians in the clinical setting. We propose that the use of a novel nomogram that accurately identifies aggressive disease will help reduce prostate cancer health disparity among AAM and will directly impact treatment recommendations among physicians in the clinic setting.

Key Research Accomplishments:

I am particularly fortunate to be a recipient of the CDMRP- DOD Health Disparity Award since September 2013. During the first year of this award I have obtained superb clinical and research mentoring from my mentors; Drs Adam Dicker, Timothy R. Rebbeck and Michael Kattan. My educational experience has been enriched by obtaining two competitive grants: one from the Prostate Cancer Foundation-Young Investigator Award, and another from the NIH LRP program to carry out work on prostate cancer disparity in men of African descent. In my first year working in Dr. Timothy Rebbeck's laboratory, we performed an analysis of outcomes among African-American men with truly low-grade PCa. We showed that African-American race was a predictor of worse biochemical failure in patients with pathologic Gleason score ≤ 6 or low-grade disease and favorable pathologic features. This finding, recently published in *Urologic Oncology* (Yamoah, et, al., 2014), highlights the need for clinically useful biomarkers that will enable us to identify African-American men appropriate for active surveillance vs. those harboring aggressive disease. To this end, I am continuing work on prostate cancer related biomarker information to develop a novel biomarker signature that more accurately predicts aggressive disease in men of African descent with prostate cancer.

This work set the platform to begin to address the objective outline in Specific Aim 1 of the proposal. I have made major strides towards the completion the Specific Aim 1, as well as fulfilling the required training component outlined in the SOW.

AIM 1: To develop a nomogram that significantly improves the accuracy of distinguishing aggressive from non-aggressive PCa in AAM. We hypothesized that genetic differences between AAM and men of other racial groups significantly contributes to the aggressiveness of the PCa in AAM. To test this hypothesis:

A) We first performed a comprehensive literature search for biomarkers linked to PCa pathogenesis and disease aggressiveness.

B) Upon selection of a validated list of biomarkers we evaluated for any differences in expression in a matched cohort of AA and EA men.

A) Selection of Biomarkers

A comprehensive literature search was carried out for biomarkers associated with PCa pathogenesis and disease aggressiveness. Only biomarkers that have been reported at least twice in the current literature to be associated with aggressive PCa were selected for this study. Exploratory PCa biomarkers derived from GWAS studies alone were excluded from this study. The list consisting of 20 biomarkers associated with PCa pathogenesis and disease aggressiveness are shown in Table 1. These include PCa-associated factors, PCa-specific proteins, Androgen pathway factors, tumor suppressor genes and PCa-associated metabolic genes.

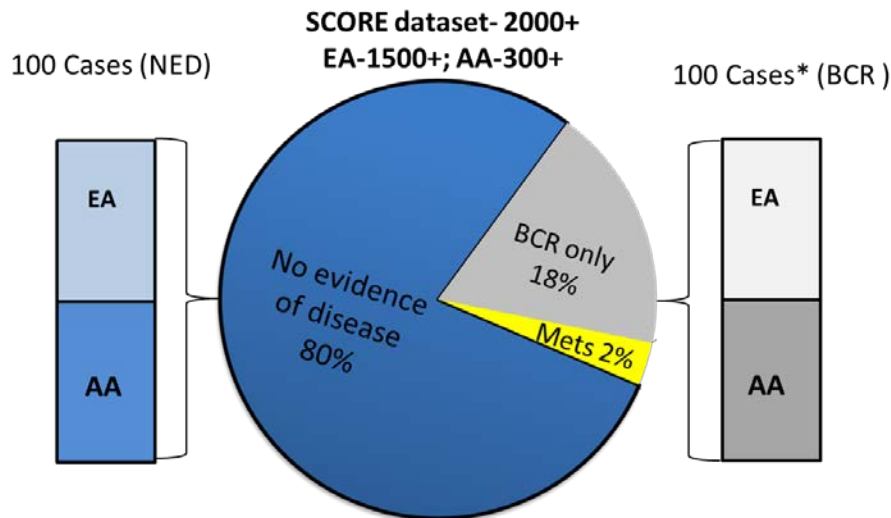
Biomarkers	Description	Function
<i>Pca-associated factors</i>		
TMPRSS2-ERG	Transmembrane protease S2 -(ETS-Related Gene) TF fusion product	Found in 36-78% samples; associated with aggressive Pca
MKI 67	Tumor proliferation rate protein	Correlates with cancer-specific and overall survival
GSTP1	glutathione S-transferase P1 gene	Hypermethylated in 60-80% Pca; in serum, urine, biopsy tissue
SPINK1/TAT1	Serine protease inhibitor Kazaltype/Tumor-associated trypsin inhibitor	Overexpressed in high-grade Pca
MYCBP	c-myc binding protein	Transcription factor repressor downregulated in Pca
EZH2	PcG histone H3 methyltransferase- transcription repressor	Implicated in the pathogenesis of metastatic Pca
<i>Prostate Specific proteins</i>		
MSMB	Prostate specific protein (10q11.2)	Independent predictor of recurrence
FOLH1/PSMA	Cell surface membrane protein	Associated with PSA recurrence in high risk cohort
NKX3-1	Prostate-specific androgen-regulated TF (Chr 8p21)	NKX3.1 loss associated with advanced stage and CRPC
<i>Androgen Pathway</i>		
AR	Intracellular receptor protein	Predictor of decreased biochemical recurrence-free survival
CYP3A4	CY3A4*1B/ CY3A43*3 enzymes (7q21)	Associated with Pca occurrence and severity
SRD5A2	5-alpha reductase II	A49T, V89L variant correlates with extracapsular disease
FOXP1	Novel androgen-responsive forkhead TF	Negatively regulates AR signalling in Pca
SPOP	E3 ubiquitin ligase (Cullin 3) adaptor- Tumor suppressor of AR activity	Mutations promotes AR activity and Pca metastatic potential
<i>Tumor suppressor genes</i>		
TP53	Tumor suppressor gene- TF often mutated in cancer	Exon 6 & 7 mutations correlate with Pca tumor progression
TP63	p53 homologue- Basal cell marker for normal prostate development	Downregulated in advanced or malignant Pca
PTEN	Tumor suppressor lipid phosphatase in the PI3K/AKT/mTOR pathway	Most commonly deleted/mutated tumor suppressor in Pca
RB1	Tumor suppressor gene- inhibits class of E2F TFs	Rb-1 loss coincides with emergence of metastatic CRPC
<i>Pca-Metabolism</i>		
AMACR (Racemase)	Mitochondrial enzyme in bile acid biosynthesis & β-oxidation of FA	Overexpressed in Pca relative to benign prostatic tissue
GOLM1	Gene coding the 73-kDa type II Golgi membrane antigen	Upregulated in >90% of Pca tissues (unknown function)

Abbreviations: TF- Transcription factors, Pca- Prostate cancer, AR- Androgen receptor, FA- Fatty acids, CRPC- Castrate-resistant prostate cancer, Chr- Chromosome

Table 1.

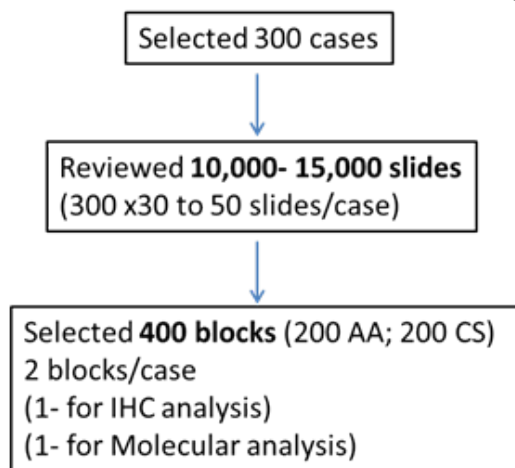
B) Compared biomarker expression between EA and AA men within SCORE database

Using the Study of Clinical Outcomes, Risk, and Ethnicity (SCORE) study, we identified prostate tumor tissues from men undergoing prostatectomy at the Hospital of the University of Pennsylvania between 1991-2008.



Pca- Prostate Cancer
 BCR- Biochemical Control Rate
 Mets- Metastasis
 EA- European-American men
 AA- African-American men

We targeted a matched cohort of 100 AA and 100 EA with a roughly equal number of BCR in each group. For this we selected 300 cases from the SCORE database and reviewed H&Es slides for each case and selected slides with dominant tumor lesion for IHC staining as shown below.



Immunohistochemistry staining for 12 biomarkers have been completed on the FFPE tumors of 45 EA and 55 AA men (mean age: 59.1 years, range: 41-71). Six biomarkers have been analyzed so far including TMPRSS2-ERG, AMACR, PSMA, RB, c-Myc, and AR. In this cohort we observed statistically significant differences in marker phenotype for AMACR (EA Mean: 188.1 vs. AA Mean: 144.7, $p=0.004$), c-myc (EA Mean: 54.7 vs. AA Mean: 21.6, $p=0.005$), and AR (EA Mean: 192.1 vs. AA Mean: 136.5, $p=0.002$).

Year 1 milestones Achieved:

Based on the SOW submitted, I am on track with the projected milestones set up for both research and training-specific tasks for this project. The research-specific task has been addressed above.

The Training-specific task was to develop an understanding of biomarker analysis and nomogram development. I have completed a course in Biostatistics at the University of Pennsylvania in 2013. I have also obtained mentorship from Dr. Kattan's group with the help of Changhong Yu, a biostatistician to work on nomogram development using the R-statistical platform. Through the mentorship of Dr. Rebbeck and Kattan's group, and relevant course work at UPENN I have achieved the milestone of developing an understanding of biomarker analysis and nomogram development.

Next Steps:

Next, we hope to finish analysis of all 20 biomarkers and incorporate the significant biomarkers into existing into existing nomograms. We will then test the novel nomogram to see if it improves the accuracy of predicting aggressive disease, as measured by the time to PSA failure after treatment. We will validate our nomogram using a database consisting of a cohort of patients, ~30% of whom are AAM treated for PCa at the University of Pennsylvania Hospitals (UPHS) in the SCORE program. We will then compare the relative predictive performance of our novel nomogram against the currently existing nomograms in predicting aggressiveness and disease recurrence among AAM in the SCORE consortium treated with radical prostatectomy.

AIM 2: To evaluate the incorporation of this novel nomogram into clinical practice.

Not yet addressed

Conclusion:

Of the 20 biomarkers selected, six have been interrogated by IHC including TMPRSS2-ERG, AMACR, PSMA, RB, c-Myc, and AR. Three showed statistically significant differential expression in AA men compared with EA men in one or more statistical models. These biomarkers include AMACR, c-Myc and AR.

Publications, Abstracts, and Presentations:

1. **Yamoah, K.**, Deville, C., Vapiwala, N., Malkowicz, B., Spangler, E., Kattan, M., Dicker, A.P., Rebbeck, T. African American men with low-grade prostate cancer exhibit worse outcomes after prostatectomy compared with Caucasian men. *Urologic Oncology*- (DOI: <http://dx.doi.org/10.1016/j.urolonc.2014.07.005>)
2. **Yamoah, K.**, Whittemore, A., Malkowicz, B., Spangler, E., Dicker, A.P., Kattan, M., Rebbeck, T. The impact of body mass index on treatment recommendations for patients with low-intermediate risk prostate cancer. (Manuscript submitted)
3. **Yamoah, K.**, Walker, A., Whittemore, A., Malkowicz, B., Spangler, E., Dicker, A.P., Kattan, M., Rebbeck, T., Lal, P. African American race is a predictor of seminal vesicle invasion following radical prostatectomy. *Clinical Genitourinary Cancer*- (Accepted)

Abstracts:

Lal, P., **Yamoah, K.**, Ziober, A., Walker, A.H., Zhou, W., Spangler, E., Zeigler-Johnson, C., Feldman, M., Rebbeck, T.R., Racial Differences in the Distribution of Prostate Tumor Biomarkers: The SCORE Study, USCAP

Poster Presentation:

2014 AACR-PCF meeting

Advancements in prostate cancer, San Diego, CA

Title: The impact of body mass index on treatment recommendations for patients with low-intermediate risk prostate cancer.

**Oral Presentation:*

2014 ACRO Annual Meeting, Oral presentation, Orlando, FL

Title: African American men with low-grade prostate cancer exhibit worse outcomes after prostatectomy compared with Caucasian men

Lay Press:

<http://www.sciencedaily.com/releases/2014/09/140908162119.htm>

<http://www.webmd.com/prostate-cancer/news/20140908/watchful-waiting-may-not-be-best-for-black-men-with-prostate-cancer>

Inventions, Patents and Licenses: None

Reportable Outcomes:

In this initial report, we have identified a set of biomarkers that demonstrate differences in expression pattern by race. These data suggest that there are differences in the biology and pathogenesis of PCa in AA as compared with EA tumor samples, and may in part explain the difference in clinical outcomes between EA and AA men.

Other Achievements:

I was among the few to be selected to participate in the AACR/ASCO methods in clinical trials workshop in 2014. The training and mentoring I received at this specialized workshop constitutes an important mechanism toward my goal of becoming an independent investigator.

I plan to submit the results of my work for presentation at meetings of the American Society of Clinical Oncology (ASCO) and the American Society of Therapeutic Radiation Oncology

Kosj Yamoah MD, PhD (W81XWH-13-1-0474-PC121189) (ASTRO), and the Prostate Cancer Foundation retreat, to get feedback from experts in the PCa field and to develop and maintain collaborations. The findings and ideas emerging from work supported by the CDMRP- DOD HDR program, along with the continued mentoring, should put me in a strong position towards the path to becoming an independent investigator.

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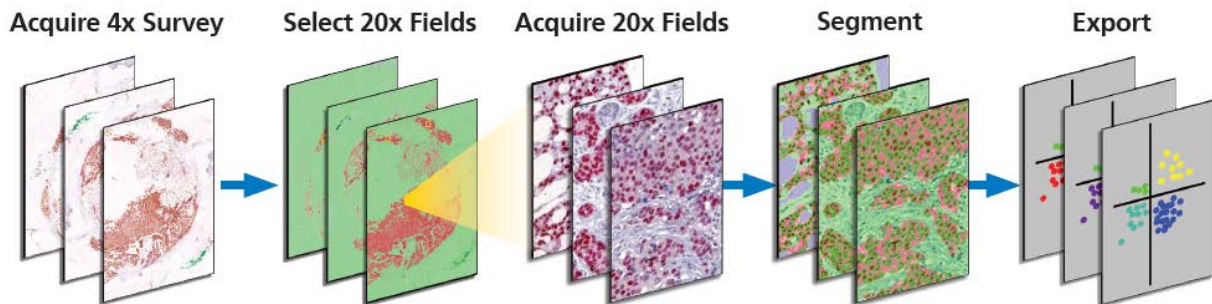
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Appendices:



Only useful for standardized markers or markers that give relative intensity

- **p53, p63, Ki67, PSMA, AR**
- Other 12 markers will be read as present/absent/indeterminate etc.
- **2000+** blocks stained so far
- Results coming in.....



Original article

African American men with low-grade prostate cancer have increased disease recurrence after prostatectomy compared with Caucasian men¹

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Abstract

Purpose: To explore whether disparities in outcomes exist between African American (AA) and Caucasian (CS) men with low-grade prostate cancer and similar cancer of the prostate risk assessment—postsurgery (CAPRA-S) features following prostatectomy (RP).

Methods: The overall cohort consisted of 1,265 men (234 AA and 1,031 CS) who met the National comprehensive cancer network criteria for low- to intermediate-risk prostate cancer and underwent RP between 1990 and 2012. We first evaluated whether clinical factors were associated with adverse pathologic outcomes and freedom from biochemical failure (FFbF) using the entire cohort. Next, we studied a subset of 705 men (112 AA and 593 CS) who had pathologic Gleason score ≤ 6 (low-grade disease). Using this cohort, we determined whether race affected FFbF in men with RP-proven low-grade disease and similar CAPRA-S scores.

Results: With a median follow-up time of 27 months, the overall 7-year FFbF rate was 86% vs. 79% in CS and AA men, respectively ($P = 0.035$). There was no significant difference in one or more adverse pathologic features between CS vs. AA men (27% vs. 31%; $P = 0.35$) or CAPRA-S score ($P = 0.28$). In the subset analysis of patients with low-grade disease, AA race was associated with worse FFbF outcomes ($P = 0.002$). Furthermore, AA race was a significant predictor of FFbF in men with low-grade disease (hazard ratio = 2.01, 95% CI: 1.08–3.72; $P = 0.029$).

Conclusions: AA race is a predictor of worse FFbF outcomes in men with low-grade disease after RP. These results suggest that a subset of AA men with low-grade disease may benefit from more aggressive treatment. © 2014 Elsevier Inc. All rights reserved.

Keywords: African American race; Disparities; Biochemical failure; Adverse pathologic features

1. Introduction

Men of African descent are known to experience greater incidence of and mortality due to prostate cancer (PCa) than men of other races [1]. African American (AA) men have

been shown to experience PCa at an earlier age than Caucasian (CS) men. Furthermore, AA men often present with higher grade and stage of disease at the time of diagnosis [2]. This observation has been partly attributed to socioeconomic factors and inadequate access to health care [3]. However, there is recent evidence suggesting that differences in genetic susceptibility play a major role in this disparity [4,5].

Owing to the relatively indolent nature of most PCAs diagnosed in the United States, the decision-making process for determining whether to pursue active surveillance (AS) or alternative management options is complicated by the

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balance between the life expectancy, comorbidities, clinical benefits and side effects of treatment [6]. The ability to predict clinical outcomes is critical in recommending appropriate treatment options for patients with PCa. Current National Comprehensive Cancer Network (NCCN) guidelines recommend AS as the preferred option for very low-risk PCa in men, defined as prostate-specific antigen (PSA) < 10 ng/ml, clinical stage \leq T1c, Gleason score (GS) \leq 6, positive cores \leq 2, and cancer involvement of \leq 50% per core. The goal of these recommendations is to prevent overtreatment of indolent cancers while identifying patients who develop disease progression and offering treatment with curative intent. However, most predictive tools currently used to risk stratify patients with PCa for treatment recommendations have not been developed or validated in AA men [7]. Furthermore, randomized clinical trials reporting on low-risk PCa treatment outcomes have been unable to effectively address whether interventions depend on race because of the inadequate numbers of AA participants [8].

Whether AA race acts as a prognostic factor for freedom from biochemical failure (FFbF) in patients with pathologic GS \leq 6 disease (referred to here as low-grade disease) and minimal adverse pathologic features after prostatectomy (RP) is poorly understood. The goal of this study is to determine whether disparities in adverse pathologic features and FFbF outcomes exist among an identical cohort of AA and CS men using a prospective cohort of patients with PCa treated with RP.

2. Patients and methods

2.1. Patient selection

The present study is a retrospective analysis of a prospective cohort of 2,012 men (298 AA, 1,673 CS, and 41 other race) with PCa treated with RP at the University of Pennsylvania Health System (UPHS; Philadelphia, PA) recruited to the Study of Clinical Outcomes, Risk and Ethnicity between 1990 and 2012 [9]. Patients without adequate preclinical data including initial PSA or biopsy GS at diagnosis were excluded from the analysis ($n = 457$). Patients of non-CS and non-AA ethnicity were excluded ($n = 41$). Patients with the following criteria were excluded from the study ($n = 249$): tumors > T3 category, GS between 7 (4 + 3) and 10, PSA level \geq 20 ng/ml, or regional lymph node metastasis on imaging or following bilateral pelvic lymph node dissection. We selected the remaining 1,265 patients for this study, which comprised the overall cohort who met the following NCCN criteria for low- to intermediate-risk PCa: biopsy GS \leq 7 (3 + 4), T-stage \leq T2c, PSA \leq 20 ng/ml, and undergoing a RP [10]. Of the 1,265 patients, a subset of 705 men (112 AA and 593 CS) with pathologic GS \leq 6 (low-grade disease determined post-RP) was further analyzed

in this study. We selected low- to intermediate-risk patients in the overall cohort to include patients with biopsy GS 7 (3 + 4) who were downgraded to pathologic GS 6 (3 + 3) following RP.

2.2. Preoperative staging

The patients were evaluated at the time of diagnosis by a thorough history and physical examination (including digital rectal examination) followed by routine laboratory studies, including serum PSA levels and GS determined by needle biopsy, and were reviewed at the UPHS. All the patients were staged according to the 1992 American Joint Committee on Cancer staging system [11].

2.3. Treatment

Surgical treatment consisted of a radical retropubic RP or robotic-assisted radical RP and bilateral pelvic lymph node sampling. All pathology slides were prepared as per standard institutional protocol. The RP specimen was initially coated with india ink and fixed in formalin. The whole gland was step-sectioned at 3-mm intervals and the resulting sections were fixed into tissue cassettes. Tissue sections were embedded in paraffin blocks, from which sections were prepared and stained with hematoxylin and eosin for routine histologic analysis by a dedicated genitourinary pathologist. Adverse pathologic features consisting of extraprostatic extension (EPE), seminal vesicle invasion (SVI), and surgical margin status (SM) were noted and recorded. At the discretion of the treating physician, patients with adverse pathologic features including EPE, SVI, or positive surgical margins were treated with adjuvant radiation therapy (RT) or androgen deprivation therapy (ADT) or a combination of both. ADT consisted of a gonadotropin-releasing hormone agonist (leuprolide acetate or goserelin acetate) with or without an antiandrogen (e.g., flutamide and bicalutamide).

2.4. Follow-up and treatment end points

Patient information at each follow-up visit including digital rectal examination and serial PSA values were noted and recorded. PSA failure was defined as a single PSA \geq 0.2 ng/ml along with documentation of failure by a physician or when 2 consecutive PSA values of 0.2 ng/ml were obtained after an undetectable value. Start of the prospective follow-up (i.e., time zero) was defined at the date of surgery for all patients. If PSA was never undetectable postoperatively, then PSA failure was assigned at time zero. Patients with no follow-up PSA measurements ($n = 190$, 14.5%) were included for the evaluation of differences in preoperative and pathologic characteristics but not for the analysis on FFbF outcomes.

2.5. Statistical analysis

Clinical and pathologic variables were compared across the race groups using an analysis of variance model for continuous variables or contingency table chi square test of homogeneity for categorical variables. Predictors of adverse pathologic features were examined using logistic regression models. Age, PSA, and year of surgery were examined as continuous variables. T category (T1a-c vs. T2), biopsy GS, and race were examined as categorical variables. Based on the pathologic findings following surgery, patients were further stratified using cancer of the prostate risk assessment—postsurgery (CAPRA-S), a validated postsurgical score that predicts the risk of cancer recurrence following RP [12]. Variables for determining CAPRA-S score included preoperative PSA, pathologic GS, SM, EPE, and SVI. Patients were categorized as having low (CAPRA-S < 3), intermediate (CAPRA-S: 3–5), and high (CAPRA-S > 5) risk of recurrence.

For survival analysis, the primary event of interest was PSA failure (biochemical disease recurrence). We excluded individuals who did not experience PSA failure at the time of last PSA measurement <0.2 ng/dl or were lost to follow-up. Time to PSA failure was used as a surrogate for FFbF. The FFbF rates were compared across the groups using the log-rank survivorship and the Kaplan-Meier analyses. For multivariate analysis, a forward-stepwise Cox proportional hazards model was used with $P < 0.2$ determining which variables were entered into the model at each step. The variable with the highest P value was successively deleted until only variables with $P < 0.2$ remained. The analyses were conducted using STATA statistical software version 13.0 (STATA Corporation). This study was approved by our Institutional Review Board.

3. Results

The baseline clinical and pathologic characteristics of overall cohort are listed in Table 1. Preoperative factors such as age at RP, PSA at diagnosis, and clinical T category were similar between groups. Compared with CS men, AA men had higher biopsy GS ($P < 0.001$). There was no difference in 1 or more adverse pathologic features among race groups (28% vs. 31%; $P = 0.41$). However, a greater number of AA men had pathologic GS ≥ 7 (52% vs. 43%; $P = 0.01$) and SVI (6% vs. 3%; $P = 0.02$). There was no difference in the use of radiotherapy or ADT between the groups.

Using the Kaplan-Meier survival analysis method, the effect of race on FFbF was evaluated in the overall cohort. The mean and median follow-up time from RP date until last follow-up PSA date was 45 months and 27 (range: 1–207) months, respectively. During this time period, 144 patients (11.5%) experienced biochemical failure. The 7-year FFbF rate between CS men and AA men was

Table 1

Pretreatment and posttreatment characteristics and pathologic outcomes of NCCN low- and intermediate-risk men undergoing radical prostatectomy at the University of Pennsylvania, 1990 to 2012 (overall cohort)

	Caucasian cohort (n = 1,031)	%	African American cohort (n = 234)	%	P value
Age, y					0.48 ^a
Median	60		58		
Mean	59.1		57.8		
IQR	54–64		52–62		
iPSA, ng/ml					0.89 ^a
0–4.0	271	26	59	25	
4.01–10	659	64	150	65	
10.01–20	101	10	25	11	
Median	5.1		5.6		
Mean	5.8		6.2		
IQR	4.1–6.7		4.1–7.8		
Biopsy Gleason score					<0.001 ^b
≤ 6	948	90	162	67	
7 (3 + 4)	103	10	54	23	
Clinical stage					0.63 ^b
T1A–C	583	81	149	85	
T2A	111	16	22	12	
T2B	8	1	4	2	
T2C	12	2	1	1	
Year of prostatectomy					0.006 ^a
Median	2003		2004		
Mean	2002.7		2003.7		
IQR	1999–2007		2000–2008		
Pathologic stage					0.07 ^b
pT2N0	802	77	175	74	
pT3aN0	202	20	44	19	
pT3bN0	23	2	13	6	
pT4aN0	4	1	2	1	
Pathologic Gleason score					<0.001 ^b
≤ 6	596	57	113	46	
7 (3 + 4)	229	22	81	36	
7 (4 + 3)	35	4	14	7	
7 (Unspecified)	145	14	22	9	
8–10	26	3	4	2	
Gleason score upgrading					0.25 ^b
6/7–7/ (8–10)	369	35	72	30	
Adverse pathologic features ^c					0.35 ^b
0	757	73	164	69	
1	147	15	33	15	
≥ 2	127	12	37	16	
Extraprostatic spread	223	22	58	25	0.32 ^b
Seminal vesicle invasion	27	3	13	6	0.02 ^b
Positive surgical margin	162	16	39	17	0.71 ^b
Radiotherapy	11	1	3	1	0.78 ^b
ADT	35	3	8	3	0.5 ^b

Note: Boldfaced values represent statistically significant differences between groups.

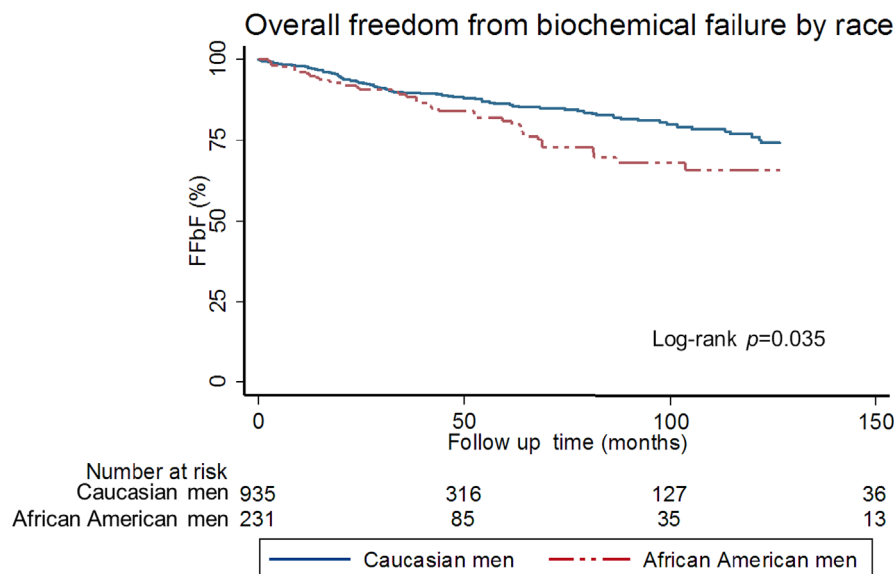
iPSA = initial Prostate-specific antigen, IQR = interquartile range.

^aP value derived from the analysis of variance model.

^bP value derived from Person's chi-square test.

^cAdverse pathologic features: extraprostatic extension, seminal vesicle invasion, and positive surgical margin.

86% vs. 79%, respectively (Fig. 1; $P = 0.035$). There was no difference in adverse pathologic features using the validated CAPRA-S score for risk of recurrence, (Fig. 2A; $P = 0.28$). However, the corresponding Kaplan-Meier estimates of FFbF showed worse outcomes among AA



Abbreviations: FFbF- Freedom From biochemical Failure, NCCN- National Comprehensive Cancer Network
P values derived from the Mantel-Cox log-rank test.

Fig. 1. The Kaplan-Meier curves for FFbF outcomes by race in NCCN low- and intermediate-risk men undergoing radical prostatectomy at the University of Pennsylvania, 1990 to 2012 (overall cohort). (Color version of figure is available online.)

men in the CAPRA-S < 3 group (Fig. 2B; $P = 0.01$). There was no statistically significant difference in the CAPRA-S 3 to 5 and >5 risk groups likely because of the small numbers in both groups (Fig. 2B; $P = 0.67$ and $P = 0.19$), respectively.

Using a Cox proportional hazard model, the predictors of FFbF following RP were determined (Table 2). In the multivariate model of the overall cohort, T category (hazard ratio [HR] = 2.92; 95% CI: 1.17–7.32; $P = 0.02$) serum PSA (HR = 1.14; 95% CI: 1.09–1.20; $P < 0.001$), clinical GS (HR = 1.51; 95% CI: 1.01–2.27; $P = 0.045$), pathologic GS (HR = 1.59; 95% CI: 1.18–2.15; $P = 0.002$), EPE (HR = 2.01; 95% CI: 1.33–3.04; $P = 0.001$), SVI (HR = 2.47, 95% CI: 1.48–4.12; $P = 0.001$), and SM (HR = 1.7; 95% CI: 1.13–2.56; $P = 0.01$) were predictors of FFbF.

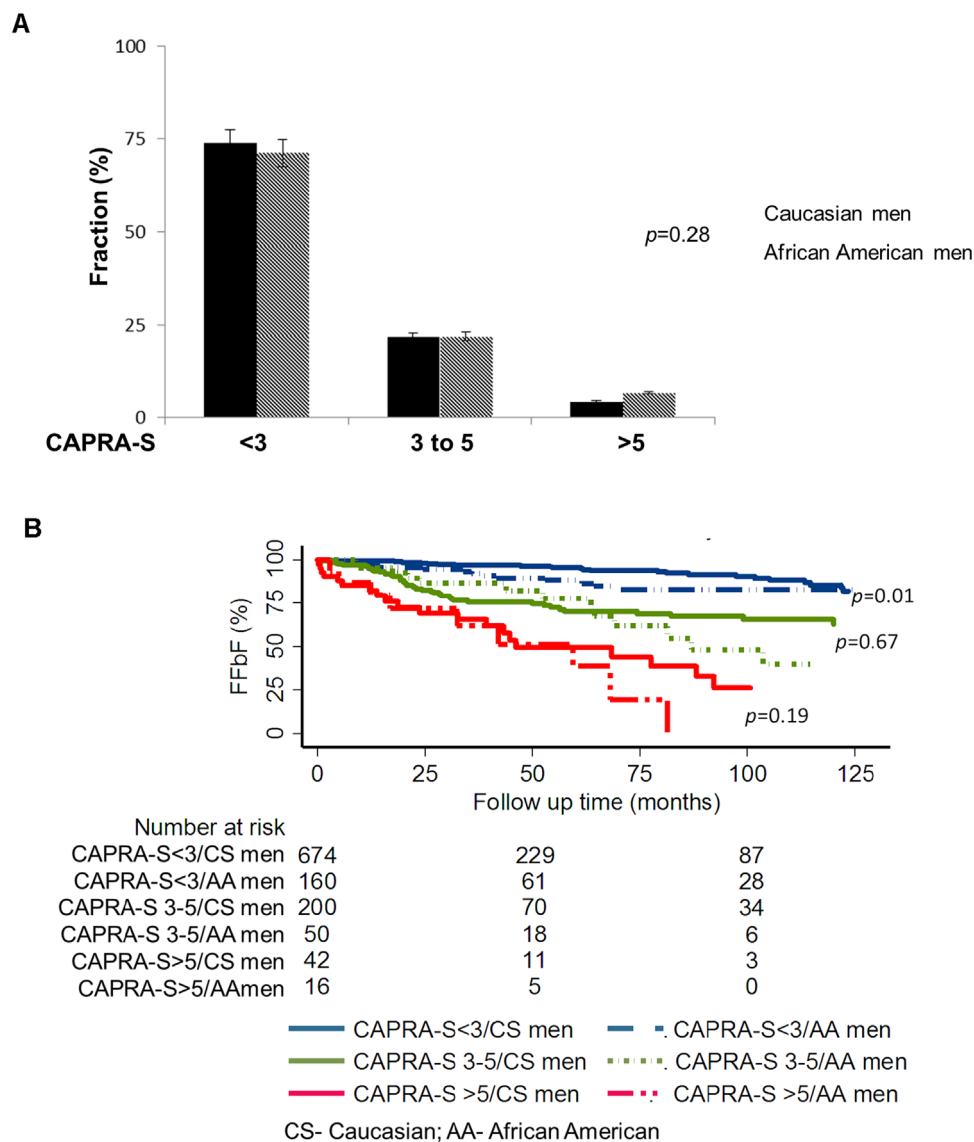
To study the outcomes in men with RP-proven low-grade PCa, we analyzed the characteristics of 705 men (112 AA and 593 CS) who had pathologic GS ≤ 6 (i.e., low-grade disease) following RP, using similar analytic methods employed in the overall cohort. For this analysis, patients who initially had biopsy GS < 7 and then on RP were upgraded to pathologic Gleason grade ≥ 7 were excluded. This represents a true cohort of patients with low-grade disease. In this cohort, there was no difference in any pretreatment and posttreatment characteristics between race groups among patients with low-grade disease (Table 3). To determine the effect of race on FFbF, we analyzed this cohort with low-grade disease with similar CAPRA-S score. This group underwent RP as monotherapy with <5% needing any additional therapy (Table 3). Among patients with low-grade

disease, AA men demonstrated worse 7-year FFbF (Fig. 3A; $P = 0.002$) despite similar CAPRA-S scores in comparison with CS men (Fig. 3B; $P = 0.90$).

Using a multivariate model, the significant predictors of risk for FFbF following RP were determined for patients with low-grade disease (Table 4). Serum PSA (HR = 1.24; 95% CI: 1.15–1.34; $P < 0.001$), EPE (HR = 3.77; 95% CI: 1.79–7.95; $P < 0.001$), and AA race (HR = 2.01, 95% CI: 1.08–3.72; $P = 0.029$) remained predictors of FFbF.

4. Discussion

In this report, we show that AA men with low-grade disease have worse FFbF in comparison with their CS counterparts (Fig. 3A). This observation is not likely because of treatment differences because patient groups had similar adverse pathologic features, as demonstrated by comparable CAPRA-S scores between AA and CS men (Fig. 3B), and there were no differences by race in the utilization of adjuvant radiotherapy or ADT. Additionally, there was no difference in the extent of positive margin status by race to suggest suboptimal surgical technique in AA patients (Table 3). Less than 5% of the entire cohort had documented treatment with additional RT or ADT. These data may reflect the low physician-referral patterns for adjuvant treatment for eligible patients [13,14]. However, these results should be interpreted with caution, as a number of patients may have undergone RP at UPHS and then received RT at another institution.



Abbreviations: FFbF- Freedom From biochemical Failure, NCCN- National Comprehensive Cancer Network, CAPRA-S- Cancer of the Prostate Risk Assessment Post-Surgical scoring system

Fig. 2. (A) Distribution of CAPRA-S score groups by race and (B) the Kaplan-Meier curves for FFbF outcomes by race stratified by CAPRA-S score groups in NCCN low- and intermediate-risk men undergoing radical prostatectomy at the University of Pennsylvania, 1990 to 2012 (overall cohort). (Color version of figure is available online.)

Overtreatment of $GS \leq 6$ PCa diagnosed on biopsies triggered by elevated PSA level remains an ongoing controversy [15]. In fact, a few recent studies have suggested that removing the label “cancer” from biopsy $GS \leq 6$ disease could potentially reduce overtreatment of low-grade disease [16,17]. However, our results suggest caution in applying this to some men and particularly AA men. Biopsy GS alone usually underestimates both grade and extent of disease, thus relabeling of biopsy $GS \leq 6$ disease as noncancer could result in a missed opportunity of curative treatment in some individuals. Consistent with our study (Table 1), the rate of upgrading from biopsy $GS \leq 6$ to pathologic $GS \geq 7$ at RP is estimated at 25% to 35% [18]. A number of studies have shown a suboptimal

correlation between biopsy Gleason scoring and radical RP, despite the migration from sextant biopsies to 12-core sampling. Cookson et al. [19] showed that evaluation of a biopsy GS was identical to that of a specimen core in 31% of cases, whereas it was discrepant by >2 GS in 26%. In more contemporary series using 12 or more biopsy cores, the upgrade rate is approximately 30% [20]. Furthermore, there is evidence to suggest that the zonal distribution of cancer foci within the prostate may differ between AA and CS men, thus influencing the result of evaluation of core biopsies [21]. Therefore, the current practice of recommending no active treatment for patients by relying heavily on parameters such as biopsy grade, number of positive cores on biopsy, and initial PSA may need to be validated in AA men.

Table 2

Univariate and multivariate regression models of factors predicting FFbF in NCCN low- and intermediate-risk men undergoing radical prostatectomy at the University of Pennsylvania, 1990 to 2012 (overall cohort)

	HR	95% CI	<i>P</i> value
Univariate analysis			
Age	0.99	0.96–1.01	0.48
Race	1.43	0.99–2.05	0.05
Serum PSA	1.16	1.11–1.21	<0.001
T-stage	3.79	1.55–9.26	0.003
Clinical Gleason score	2.63	1.80–3.83	<0.001
Year of prostatectomy	1.04	0.99–1.08	0.09
Extraprostatic spread	3.89	2.81–5.38	<0.001
Positive surgical margins	3.72	2.67–5.19	<0.001
Seminal vesicle invasion	5.9	3.71–9.38	<0.001
Pathologic Gleason score	2.63	2.01–3.44	<0.001
Multivariate analysis			
Age	0.99	0.96–1.02	0.50
Race	1.38	0.92–2.07	0.12
Serum PSA	1.13	1.08–1.19	<0.001
T category	2.92	1.17–7.32	0.02
Prostate-specific antigen	1.14	1.09–1.20	<0.001
Extraprostatic spread	2.01	1.33–3.04	0.001
Seminal vesicle invasion	2.47	1.48–4.12	0.001
Positive surgical margins	1.7	1.13–2.56	0.01
Clinical Gleason score	1.11	0.69–1.79	0.67
Pathologic Gleason score	1.59	1.18–2.15	0.009

Note: Boldfaced values represent statistically significant differences between groups.

P values derived from a Cox proportional hazards model.

As per the NCCN guidelines, AS is the preferred treatment option for men with very low-risk PCa and life expectancy ≤ 20 years or those with low-risk disease and life expectancy < 10 years [22]. The advantage of AS is to prevent overtreatment of indolent disease while actively monitoring the course of the disease and to intervene only when progression occurs in patients with more aggressive disease [23]. However, evidence for the benefit of AS was based on studies conducted in primarily CS cohorts [24,25]. In studies where race was reported, 5% to 10% of patients enrolled in AS program were AA men [20,26]. One retrospective study evaluated the effect of race on discontinuation of AS for patients with low-risk PCa. Their results showed that AA men had more aggressive disease and were more likely to progress on AS and proceed to treatment faster than CS men were [27]. A large study on pathologic and FFbF outcomes in very low-risk AA men who qualify for AS but underwent immediate RP showed that AA men had significantly higher rates of upgrading, positive surgical margins, and CAPRA-S score than CS men did [28]. However, data from our study showed worse FFbF even in AA patients despite similar CAPRA-S scores and low-grade disease when compared with their CS counterparts (Figs. 2 and 3). The discrepancies in pathologic outcomes between our low-grade study and the prior study are likely due to the fact that, unlike the prior study that evaluated low-risk patients as determined by biopsy Gleason grade, we analyzed a cohort of patients with truly low-grade (pathologic Gleason

Table 3

Pretreatment and posttreatment characteristics and pathologic outcomes of men with pathologic Gleason score ≤ 6 (low-grade disease) following radical prostatectomy at the University of Pennsylvania, 1990 to 2012

	Caucasian cohort (<i>n</i> = 593)	%	African American cohort (<i>n</i> = 112)	%	<i>P</i> value
Age, y					
Median	59		58		0.39 ^a
Mean	58.4		57.8		
IQR	54–63		52–62		
iPSA, ng/ml					
0–4.0	179	30	29	26	0.05 ^a
4.1–10	357	60	79	70	
10.1–20	57	10	4	4	
Median	5		5.4		
Mean	5.6		5.6		
IQR	3.7–6.5		4.1–7.0		
Clinical stage					
T1A–C	357	86	73	91	0.17 ^b
T2A	61	14	7	9	
Pathologic stage					
pT2N0	515	87	96	86	0.45 ^b
pT3aN0	72	12	13	12	
pT3bN0	4	1	2	2	
pT4aN0	2	0	0	0	
Adverse pathologic features ^c					
0	497	84	92	82	0.85 ^b
1	56	9	11	10	
≥ 2	40	7	9	8	
Extraprostatic spread	76	13	16	14	0.64 ^b
Seminal vesicle invasion	6	1	2	2	0.47 ^b
Positive surgical margin	54	9	11	10	0.81 ^b
Radiotherapy	3	0.5	1	1	0.62 ^b
ADT	28	5	5	5	0.94 ^b

iPSA = initial prostate-specific antigen; IQR = interquartile range.

^a*P* value derived from the analysis of variance model.

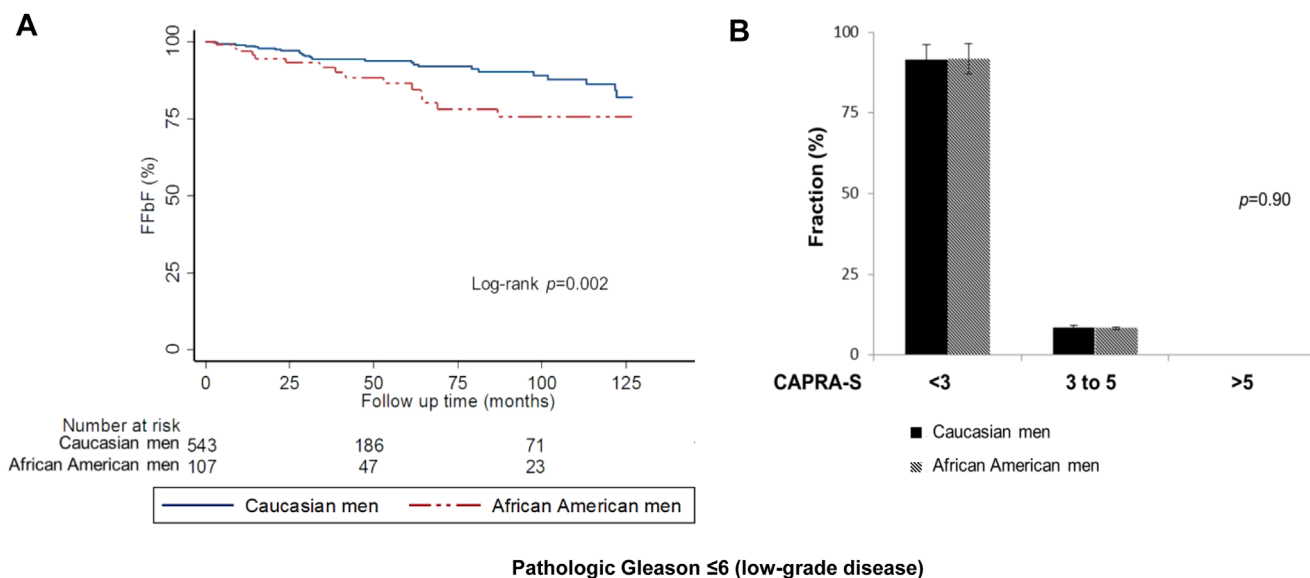
^b*P* value derived from the Person's chi-square test.

^cAdverse pathologic features: extraprostatic extension, seminal vesicle invasion, and positive surgical margin.

grade ≤ 6) disease. Nonetheless, these emerging data suggest that further study is needed to determine whether some AA men with low-grade disease and CAPRA-S score > 2 may derive benefit from additional/adjuvant therapy such as radiation or ADT. In light of these findings, AA men found to have biopsy GS ≤ 6 with clinically low-risk disease who choose AS should undergo more careful monitoring owing to the possibility of increased oncologic risk.

It is noteworthy that several studies have been conducted regarding the effect of race on FFbF after definitive PCA treatment with radical RP or radiotherapy. However, results from these studies have proven inconclusive [28–30]. These inconsistencies may be partly because of differences in the selection criteria and imbalances in the comparison groups.

The strength of our study is that it provides a stringent analysis of AA and CS men with similar adverse pathologic



Abbreviations: FFbF- Freedom From biochemical Failure, CAPRA-S- Cancer of the Prostate Risk Assessment Post-Surgical scoring system

Fig. 3. (A and B) The Kaplan-Meier curves for FFbF outcomes and CAPRA-S score grouping by race in men with pathologic Gleason ≤ 6 following radical prostatectomy at the University of Pennsylvania, 1990 to 2012. (Color version of figure is available online.)

features. Therefore, known socioeconomic factors such as inaccessibility to health care, late diagnosis, and suboptimal treatment are less likely to account for outcomes disparity in this cohort. Our data have major clinical implications for treatment recommendations, which includes potentially undertreating low-grade disease in AA men. Furthermore,

Table 4

Univariate and multivariate regression models of factors predicting FFbF in men with pathologic Gleason score ≤ 6 (low-grade disease) following radical prostatectomy at the University of Pennsylvania, 1990 to 2012

	HR	95% CI	<i>P</i> value
Univariate analysis			
Age	1.01	0.96–1.05	0.63
African American race	2.02	1.09–3.74	0.025
Serum PSA	1.22	1.06–1.41	0.005
T category	1.37	0.87–2.14	0.17
Clinical Gleason score	2.48	0.76–8.19	0.13
Year of prostatectomy	0.99	0.91–1.06	0.61
Extraprostatic spread	4.05	2.27–7.23	<0.001
Positive surgical margins	3.71	1.94–7.04	<0.001
Seminal vesicle invasion	8.1	2.87–22.8	<0.001
Multivariate analysis			
Age	1.02	0.97–1.06	0.44
Year of prostatectomy	0.99	0.92–1.07	0.81
Clinical Gleason score	1.23	0.35–4.41	0.74
Serum PSA	1.24	1.15–1.34	<0.001
Extraprostatic spread	3.77	1.79–7.95	<0.001
African American race	2.01	1.08–3.72	0.029
Seminal vesicle invasion	2.71	0.89–8.57	0.089
Positive surgical margins	1.83	0.81–4.12	0.15

Note: Boldfaced values represent statistically significant differences between groups.

P values derived from a Cox proportional hazards model.

AA men with low-grade disease need to be enrolled on clinical trials evaluating biomarker-driven risk-adapted treatment options to improve outcomes.

A major limitation to this study is that it has a relatively small number of AA men compared with CS men and represents the experience from a single tertiary center. Though the men in this study had identical adverse pathologic risk features, a randomized controlled trial is required to adequately answer the question of race and FFbF outcomes in men with low-grade disease. The outcomes were not adjusted for socioeconomic factors, diet, obesity, comorbid conditions, and adherence to treatment recommendations. Information on the tumor volume or the percentage of cores positive for tumor were inconsistently reported, and hence we could not adequately investigate outcomes in very low-risk patients who might have been eligible for AS.

5. Conclusion

AA race is a predictor of worse FFbF in patients with pathologic GS ≤ 6 or low-grade disease and favorable pathologic features. This highlights the need for clinically useful biomarkers that will enable us to identify AA men appropriate for AS vs. those harboring aggressive disease that may ultimately benefit from exploration of additional/adjuvant therapy such as radiation or ADT.

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