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TITLE: Do Black Men with Metastatic Castration-Resistant Prostate Cancer Have Worse Outcomes Than White Patients? A Nationwide VA Study

PRINCIPAL INVESTIGATOR: Adriana Vidal, PhD

CONTRACTING ORGANIZATION: Cedars-Sinai Medical Center

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Adriana Vidal, PhD

E-Mail: Adriana.Vidal@cshs.org

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Cedars-Sinai Medical Center
8700 Beverly Blvd, MOT
Los Angeles, CA 90048
USA

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14. ABSTRACT

Black men have a higher prostate cancer (PC) risk and mortality than white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. However, a few small studies suggested black men may actually have better outcomes than white men when treated with metastatic castration-resistant PC (mCRPC) drugs. We hypothesize that black men with mCRPC will have similar responses to modern mCRPC therapies but worse compliance; after accounting for poorer compliance, black men will actually have better responses to these therapies than white men. Our objective is, to create a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 46,535 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T). We will 1. Determine drug efficacy among black and white men with mCRPC; 2. Determine drug compliance among black and white men with mCRPC; and 3. Determine drug efficacy among black and white men with mCRPC after accounting for compliance.

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INTRODUCTION

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Black men have a higher prostate cancer (PC) risk and mortality vs. white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. In an equal access setting, we found black men had more PC, higher-grade PC, and more recurrences after surgery, arguing for more aggressive disease in black men. However, though we found recurrences after surgery were greater in black men, after adjusting for baseline disease differences, race was unrelated to recurrence or long-term outcomes (metastasis or PC death). Similarly, among men who failed surgery and received androgen deprivation therapy (ADT), long-term outcomes were unrelated to race (Vidal et al, Cancer 2019). This suggests, that when baseline differences are accounted for and men receive equal treatments, black men can experience similar outcomes as white men. Whether this is true for men with metastatic castration-resistant prostate cancer (mCRPC) receiving one of the new life-prolonging therapies is unknown. For the first time, we will test whether properly treated mCRPC black men have similar (or better) responses than white men. Importantly, understanding treatment patterns, efficacy, and adherence of life prolonging therapies for mCRPC by race is necessary not only to design rationale approaches to reducing PC health disparities, but also to help clinicians trying to decide the best drug to give to a man newly diagnosed with mCRPC based on race. To fulfill this goal, we are creating a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 39,925 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T).

KEYWORDS

Provide a brief list of keywords (limit to 20 words).

Prostate cancer; metastatic castration-resistant prostate cancer (mCRPC); race; Veterans

ACCOMPLISHMENTS

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

SOW Major Goals (as proposed in 2019):

STATEMENT OF WORK – 10/11/2018
PROPOSED START DATE October 1, 2019

Site 1: Cedars-Sinai Medical Ctr
8700 Beverly Blvd
Los Angeles 90048
Adriana Vidal

Site 2: Durham VA
Durham, NC 27707
PI: Adriana Vidal (AV)
Co-I: Stephen Freedland

Specific Aim 1: Determine drug efficacy among black and white men with mCRPC	Timeline	Site 1	Site 2
Major Task 1: Data Collection & Preparation	Months		
Subtask 1: Abstract data of all men with mCRPC	1-12	Dr. Vidal	Data technician, Meagan Foster, under AV supervision
Subtask 2: Create a SQL server database, managed using Microsoft SQL Management Studio	1-12	Dr. Vidal	Meagan Foster, under AV supervision
Milestone Achieved: Preparation of large dataset including drugs used	1-12		

Major Task 2: Statistical Analysis			
Subtask 1: Conduct statistical analyses	13-23	Dr. Vidal	Lauren Howard, under AV supervision
Subtask 2: Interpret results	13-23	Dr. Vidal Freedland	Drs. Freedland, Vidal
Subtask 3: Archive datasets for future analyses and future patient follow-up.	18-23	Dr. Vidal	Meagan Foster
Milestone Achieved: Create the largest dataset on mCRPC by race. Manuscript preparation			

Aim 1: Determine drug efficacy among black and white men with mCRPC. We will use the largest integrated health system in the US: The Veterans Health Administration. We will retrieve data on mCRPC therapies including Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide to compare drug efficacy among black and white men. Too few men were treated with Radium-223 or Sipuleucel-T for analysis. Drug efficacy will be measured as PSA maximum decline. We hypothesize black and white men have similar responses to mCRPC therapies.

Major Task 1: 1-12 First Months (First Year Progress Report): Data collection and Preparation.

Major Task 2: 13-23 Months (Second Year Progress Report): Statistical Analysis.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. **Major Activities – *Aim 1***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 1, please see SOW for Aim 1 above. As the SOW indicates, in the first 12 months of this study we conducted Data Collection and Preparation for the study, a major, time-consuming work. Below we expand on the work completed so far:

a) Local Durham VA Health Care system IRB approval, as well as VA Informatics and Computing Infrastructure (VINCI) approval, have been obtained so that we may proceed with all study activities, with all personnel required to complete these tasks.

b) Data collection has been completed as concerns for the objectives of Aim 1, as planned in the SOW.

	Table 1. Number of Patients with mCRPC treated at the VA			
	No record or other race	**Black**	**White**	**Total x Treat**
Distinct Patients x Race	5,727	7,737	26,461	39,925
Number of Patients (Patients can be counted multiple times)				
Cabazitaxel	60	215	484	759
Docetaxel	4008	2818	13205	20031
Abiraterone	1276	2822	9768	13866
Enzalutamide	812	2054	6812	9678

Table 1 shows the preliminary numbers of all men available to us within VINCI, reflecting treatment for mCRPC at National VA centers, since January 1, 2000. The data queries developed for mCRPC drugs resulted in a dataset of 39,925 men; of these, 11,474 received first treatment of Abiraterone; 20,201 with Docetaxel; and 5,136 with Enzalutamide. As we anticipate that the majority of mCRPC men receiving therapy within the VA system are regular users, these 39,925 men will be our analytic cohort and represents the largest cohort ever studied for mCRPC health disparities.

This cohort was initially identified using prostate cancer diagnosis ICD codes. Patients with a prostate cancer diagnosis code were then evaluated for metastatic, castrate-resistant disease based on a series of queries that classify a patient as (1) metastatic, (2) castrate, and/or (3) castrate resistant. Castrate resistance is determined by comprehensively evaluating hormone therapy treatment cycles and/or an orchiectomy procedure in conjunction with PSA lab results.

Patients who received abiraterone and/or enzalutamide treatments were classified as mCRPC patients. Patients identified as mCPRC were further evaluated for receipt of cabazitaxel and/or docetaxel treatments.

Treatments were identified using a combination of CPT codes and pharmacy data.

c) In addition to the queries developed to determine the data in Table 1, queries have been developed to determine information across a variety of our data elements of interest, notably for: demographic data, including race and age; and certain lab(s)/lab results, including prostate specific antigen (PSA), variables that will be used in the statistical analysis.

d) The NLP race model our team developed for this project, is a regular expression, race classifier paradigm utilizing a majority vote approach to output final results; this strategy has been adopted because within an individual patient there may exist n number of provider notes, each of which may have race reported differently, dependent upon a variety of factors. In addition to the race model, a prostate cancer metastasis model has also been generated, trained, and developed, and which employs a binomial (positive, negative) logistic regression paradigm. This logistic regression model uses keywords and keyword modifiers, extracted through provider and scan/radiology note sentence parsing to then assign a classification of “positive” or “negative” scan.

Site 1: Cedars-Sinai Medical Ctr
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PI: Adriana Vidal

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Durham, NC 27707
PI: Adriana Vidal (AV)
Co-I: Stephen Freedland

Specific Aim 2: Determine drug compliance among black and white men with mCRPC			
Major Task 1: Prepare data for analysis drug compliance by race			
Subtask 1: Retrieve data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men.	6-12	Dr. Vidal	Data technician, Meagan Foster, under AV supervision
Subtask 2: Analyze data on whether drug compliance differs by race	13-24	Dr. Vidal Freedland	Lauren Howard under, under AV supervision
Milestone(s) Achieved: Largest study ever to address drug compliance for mCRPC by race			
Specific Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance.			
Major Task 1: Prepare data for analysis			
Subtask 1: Ascertain response to drug, measured as PSA maximum decline, after accounting for compliance. Subtask 2: Analyze data and adjust for potential confounders including age, comorbidities, socioeconomic status, VA center, but also Gleason score, and primary treatment received	10-14 14-24	Dr. Vidal Freedland Dr. Vidal Freedland	Drs. Freedland, Vidal Lauren Howard, under Drs. Freedland, Vidal supervision
Milestone(s) Achieved: Determine drug efficacy for mCRPC by race in the largest dataset ever created.			

Aim 2: Determine drug compliance among black and white men with mCRPC. Among men given a mCRPC life-prolonging drug, we will determine compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men. We hypothesize black men have reduced compliance to mCRPC therapies vs. white men.

Major Task 1:
Subtask 1: 1-6 Months (First Year Progress Report): Prepare data for analysis on drug compliance by race
Subtask 2: 13-23 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 2:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed to conduct in the first year of the award for Aim 2, as detailed in SOW above. As the SOW indicates, in the first 6 months of this study we conducted Data Preparation for analysis on drug compliance by race, a major, time-consuming work. Below we expand on the work completed so far:

a) We have retrieved data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration.

b) We have calculated the duration of drug therapy and time until next therapy in each race group.

Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance. Among the men described in Aims 1 and 2, we will analyze response to drug, measured as PSA maximum decline, *after* accounting for compliance. We hypothesize response to therapy after accounting for compliance, is better in black men compared to white men.

Major Task 1:

Subtask 1: 10-14 Months (First Year Progress Report): Prepare data for analysis

Subtask 2: 14-24 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 3:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 3, as detailed in SOW for Aim 3 above. As the SOW indicates, in the first 14 months of this study we ascertained response to drug, measured as PSA maximum decline, after accounting for compliance. Below we expand on the work completed so far:

a) We determined the percent of patients experiencing a $\geq$ 30% maximum decline in PSA, a level that approaches surrogacy for explaining the survival benefits of androgen receptor (AR) targeted therapy and had a high degree of surrogacy for docetaxel treated patients.

2. **Specific Objectives – *Aims 1-3:***

The specific objectives for Aims 1-3 were to obtain all the data and create the database to conduct analysis. As described in Major Activities for Aim 1, we collected and prepared the data needed for the analysis of determining drug efficacy among black and white men with mCRPC; for Aim 2, we collected the data on compliance, the duration of drug therapy and time until next therapy in each race group; for Aim 3, we collected data on drug response by race group.

3. **Significant Results - *Aims 1-3:***

We have achieved significant results as scheduled in the SOW timeline, i.e. we have collected all data as expected. However, at this point, a comprehensive dataset has not been finalized. As stated in the SOW, we anticipate to conducting statistical analyses during the second year of this award.

4. **Other achievements:**

A new study coordinator and statistician have been on-boarded to the team at the Durham VA, to help us with this study and keep moving the project forward as planned.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

A new study coordinator, **Justin Waller**, has been on-boarded to the study team. He has been learning in-depth clinical prostate cancer knowledge and is learning about the VA's national data system (VINCI & CDW). He has received formal leadership coaching in his role.
Meagan Foster, our data operations manager, has been taking coursework towards a master's degree and has been learning about machine learning techniques that are being developed and applied as part of this project. In addition, she is doing an internship at a data science company where she is learning more about the agile development process.
Ruixin Yang, our data scientist, has been developing a manuscript for peer review describing one of the machine learning models being used in this study. He is working under the guidance of Dr. Klaassen, a VA urologist.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Our next step will be to apply the queries and NLP models above-mentioned to the study cohort, to develop a comprehensive dataset. This is a computationally intensive process given the size of the cohort (~40,000 men) and complexity of the data returned, which will require considerable quality assurance. Once the dataset is generated, the PI and statistician will perform quality assurance measures and begin analysis. We anticipate the statistical analysis will be conducted well before the end of Year 2 of this grant.

IMPACT

D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

As we have not finished analyzing the data, no impact on society has yet been achieved. However, we expect our results will impact the treatment of late stage prostate cancer, specifically mCRPC for black Veterans.

Thus, nothing to report at this time.

CHANGES/PROBLEMS

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

N/A

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

PRODUCTS

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

The manuscripts listed below are related to this project, however, not directly funded with this DoD award. These studies, from our group, helped move the field forward in terms of mCRPC and racial disparities, the main topic of this award. Thus, this is why I have decided to include them in this report.

1. Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting. Howard LE, Zhang J, Fishbane N, Hoedt AM, Klaassen Z, Spratt DE, **Vidal AC**, Lin D, Hitchins MP, You S, Freeman MR, Yamoah K, Davicioni E, **Freedland SJ**. Prostate Cancer Prostatic Dis. 2019 Dec 16. doi: 10.1038/s41391-019-0197-3. Online ahead of print. PMID: 31844180.
2. Racial Discrepancies in Overall Survival among Men Treated with ^{223}Radium. Zhao H, Howard LE, De Hoedt A, Terris MK, Amling CL, Kane CJ, Cooperberg MR, Aronson WJ, Klaassen Z, Polascik TJ, **Vidal AC, Freedland SJ.** J Urol. 2020 Feb;203(2):331-337. doi: 10.1097/JU.0000000000000524. Epub 2019 Sep 3. PMID: 31479407

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

N/A

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

N/A

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

N/A

- **Technologies or techniques**
  N/A

- **Inventions, patent applications, and/or licenses**
  N/A

- **Other Products**
  N/A

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? Site I

No change

Name:	*Adriana Vidal*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	***3.6***
Contribution to Project:	*Leads the project*
Funding Support:	
Name:	*Marcio Diniz*
Project Role:	*Biostatistician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	***0.24***
Contribution to Project:	*Power calculations*
Funding Support:	
Name:	*Stephen Freedland*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	***0.60***
Contribution to Project:	*Guidance and expertise*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners? (Subcontract, Site 2)

Organization Name: Durham VA Health Care System (DVAHCS)/Institute for Medical Research (IMR)
Location of Organization: Durham, North Carolina
Partner's contribution to the project: The team at DVAHCS/IMR provides database development, protocol/regulatory, and data analysis support.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

APPENDICES

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Prostate Cancer and Prostatic Diseases
https://doi.org/10.1038/s41391-019-0197-3

ARTICLE

Clinical Research

Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting

Lauren E. Howard[1,2] · Jingbin Zhang[3] · Nick Fishbane[3] · Amanda M. De Hoedt[2] · Zachary Klaassen[4] · Daniel E. Spratt[5] · Adriana C. Vidal[6] · Dechen Lin[7,8] · Megan P. Hitchins[7,8] · Sungyong You[6,9] · Michael R. Freeman[6,9] · Kosj Yamoah[10] · Elai Davicioni[3] · Stephen J. Freedland[2,6]

Received: 6 September 2019 / Revised: 20 November 2019 / Accepted: 2 December 2019

Abstract

Background The Decipher 22-gene genomic classifier (GC) may help in post-radical prostatectomy (RP) decision making given its superior prognostic performance over clinicopathologic variables alone. However, most studies evaluating the GC have had a modest representation of African-American men (AAM). We evaluated the GC within a large Veteran Affairs cohort and compared its performance to CAPRA-S for predicting outcomes in AAM and non-AAM after RP.

Methods GC scores were generated for 548 prostate cancer (PC) patients, who underwent RP at the Durham Veteran Affairs Medical Center between 1989 and 2016. This was a clinically high-risk cohort and was selected to have either pT3a, positive margins, seminal vesicle invasion, or received post-RP radiotherapy. Multivariable Cox models and survival C-indices were used to compare the performance of GC and CAPRA-S for predicting the risk of metastasis and PC-specific mortality (PCSM).

Results Median follow-up was 9 years, during which 37 developed metastasis and 20 died from PC. Overall, 55% ($n = 301$) of patients were AAM. In multivariable analyses, GC (high vs. intermediate and intermediate vs. low) was a significant predictor of metastasis in all men (all $p < 0.001$). Consistent with prior studies, relative to CAPRA-S, GC had a higher C-index for 5-year metastasis (0.78 vs. 0.72) and 10-year PCSM (0.85 vs. 0.81). There was a suggestion GC was a stronger predictor in AAM than non-AAM. Specifically, the 5-year metastasis risk C-index was 0.86 in AAM vs. 0.69 in non-AAM and the 10-year PCSM risk C-index was 0.91 in AAM vs. 0.78 in non-AAM. However, the test for interaction of race and the performance of the GC in the Cox model was not significant for either metastasis or PCSM (both $p \geq 0.3$).

Conclusions GC was a very strong predictor of poor outcome and performed well in both AAM and non-AAM. Our data support the use of GC for risk stratification in AAM post-RP. While our data suggest that GC may actually work better in AAM, given the limited number of events, further validation is needed.

Introduction

Accurate assessment of disease aggressiveness is crucial for appropriate management of prostate cancer (PC) patients. Traditional risk factors include PSA, stage, and grade [1]. After a patient undergoes a radical prostatectomy (RP) the above-mentioned factors and other clinicopathologic variables are used to risk-stratify patients. The variables have been combined into a variety of multivariable models, such as Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) [2]. CAPRA-S is superior to any individual clinicopathologic variable, but there remains significant room for further improvement.

Toward this effort, there has been growing interest in genomics as a means to risk-stratify patients [3]. There are three readily available clinical genomic tests to predict oncological outcomes (e.g., adverse pathology, metastasis, cancer-specific death) in PC patients: Decipher (Decipher

Supplementary information The online version of this article (https://doi.org/10.1038/s41391-019-0197-3) contains supplementary material, which is available to authorized users.

✉ Stephen J. Freedland
stephen.freedland@cshs.org

Extended author information available on the last page of the article.

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Biosciences), Oncotype Dx (Genomic Health), and Prolaris (Myriad Genetics). While all have been well-validated, in general, the cohorts used to derive and validate these tests are comprised of mostly European-American men (EAM). Thus, whether these tests apply as well, better, or worse to African-American men (AAM) is largely untested.

PC incidence is higher in AAM, and on a population level AAM die from PC more often than EAM [4]. Thus, AAM suffer a disproportionately higher burden of PC than EAM. We recently demonstrated that differing long-term outcomes for AAM can be explained by differences in equal access and standardized treatment [5, 6]. However, data have demonstrated that AAM have tumors enriched for differing biologic phenotypes, and most relevant to the current study, different gene expression profiles [7–9]. Given the reliance of all of the three commercial classifiers on gene expression, it is critical to evaluate if these tests perform similarly in AAM. Previous studies have demonstrated that the omission of AAM in genomic research as a whole could, in fact, widen the already pervasive disparity. Furthermore, if these commercial tests are to be used clinically irrespective of race, it is imperative to determine whether the Decipher genomic classifier (GC) works in AAM.

Hence, we tested the accuracy of the Decipher 22-gene GC to predict metastases and PC-specific mortality (PCSM) after RP in a diverse high-risk equal access cohort. Specifically, we tested whether GC worked better, worse, or the same in AAM as in non-AAM. To do this, we studied men treated with RP at the Durham Veterans Affairs Medical Center (DVAMC).

Materials and methods

Study cohort

The study cohort consisted of men treated with RP for clinically localized PC between 1989 and 2016 at the DVAMC. A subset of patients from this cohort was used in prior multicenter studies evaluating GC [10–12], though the current analysis represents the first report of the entire cohort. Our goal was to select men at high risk for metastases – i.e., those most likely to benefit from additional risk stratification. As such, our inclusion criteria were pathologic stage pT2 with positive surgical margins, or pT3/4 disease, or received postoperative radiation for biochemical recurrence after RP. Biochemical recurrence was defined as one PSA value above 0.2 ng/mL or two PSA values of 0.2 ng/mL after RP. Patients with positive lymph nodes from RP were excluded. In addition, selected patients had to have available tumor tissue blocks and at least 2 post-RP PSA measurements. Patients with nodal or distant metastasis pre- or peri-operatively or who received any neo-adjuvant hormone or radiation therapy were excluded. Self-reported race was abstracted from the electronic medical records. The study followed PRoBE and NCI-REMARK design and reporting guidelines for prospective blinded validation of prognostic tumor biomarkers [13, 14]. The DVAMC Institutional Review Board reviewed and approved the research protocol under which this study was conducted.

Tumor sampling and genomic data

Central pathological review of formalin-fixed paraffin-embedded (FFPE) RP tumor specimens from each eligible patient was conducted to re-grade tumors (according to ISUP 2005 criteria) and to select the index lesion with highest grade group and tumor volume for the GC assay. We selected tumor samples with >60% tumor cellularity by area to minimize benign contamination from the region with the highest grade group and if present, extraprostatic extension (EPE) or seminal vesicle invasion. Tumor was sampled using a 1.0-mm biopsy punch tool (Miltex, York, PA, USA). RNA extraction, cDNA amplification, and microarray hybridization were performed as previously described (Decipher Biosciences, Inc, San Diego, CA, USA) [15]. Microarray quality control was applied using Affymetrix Power Tools packages [16] and probeset summarization and normalization were performed using the single-channel array normalization (SCAN) algorithm [17].

Risk models

GC [18, 19] and CAPRA-S [2] scores were calculated as previously described. GC and CAPRA-S risk groups for categorical analyses were determined using established cut-points [20, 21]. As there were few CAPRA-S low-risk cases in this cohort of men who were all selected to have intermediate-risk disease, these were combined with the CAPRA-S intermediate-risk group of patients for the survival analyses.

Statistical analyses

Patient characteristics were summarized overall and stratified by race. Differences between races were tested using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

The endpoints assessed were metastasis (regional or distant, detected via computed tomography and/or a bone scan) and PCSM. In time-to-event analyses, event times were defined as time from RP to metastases or PCSM, or date of the last follow-up.

The prognostic accuracies of CAPRA-S, GC, and the combined models were established based on time-dependent receiver operating characteristic (ROC) curves for survival data using the nearest neighbor estimator [22].

95% confidence intervals (CIs) for time-dependent C-indices were computed via bootstrap resampling. Optimism correction was done for the C-indices of the combined models using bootstrap with 500 resamples. Survival C-indices were considered statistically significant if the lower and higher bound of the 95% CI did not cross 0.50. Cumulative incidence curves for metastasis and PCSM risk were constructed accounting for other-cause death as the competing risk [23]. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) for both endpoints, and Firth's penalized bias reduction method was applied for low event models. Variables included in the multivariable model were age at RP, race, and CAPRA-S. The use of hormone therapy was correlated with disease progression, and therefore it was not included in the multivariable analysis due to multicollinearity. An analysis was performed to evaluate GC and clinicopathologic risk models stratified by race. Tests of interaction were performed to determine if race impacted the performance of GC to predict metastasis or PCSM. Statistical analyses were performed in R V3.5 (R Foundation, Vienna, Austria) and all statistical tests were two-sided using a 5% significance level.

Results

Study cohort and patient characteristics

A total of 622 men treated with RP between 1989 and 2016 were eligible for the study and had available FFPE tissue blocks for central pathology review and re-grading (Fig. 1). After excluding ineligible patients, those with missing information or that failed microarray quality control, the final analytic cohort consisted of 548 men. The median follow-up of the analytic cohort was 9 years. The median age and PSA levels before surgery were 62 years and 7.1 ng/mL (Table 1). The majority (55%, $n = 301$) were AAM. Caucasian men (43%, $n = 235$) and men of other races (2%, $n = 11$) were grouped as non-AAM. One patient with race unavailable was excluded from race-stratified analyses. AAM were younger at RP, had higher pathological stage, and had a lower rate of EPE (all $p < 0.05$).

The CAPRA-S clinical risk model classified 10, 62, and 28% as low, intermediate, and high risk for recurrence, respectively. GC classified 51, 24, and 25% as low, intermediate, and high risk for metastasis, respectively. A total of 37 men developed metastasis and 20 died of PC within the follow-up period.

Risk models as predictors of clinical outcomes

In the multivariable analysis, both GC intermediate- and high-risk groups (HR 6.51, 95% CI 2.33–21.8 and HR 9.60, 95% CI 3.51–32.0, respectively) were significantly associated with higher risk of metastasis even after adjusting for CAPRA-S. GC intermediate- and high-risk groups were also associated with increased risk of PCSM (HR 25.5, 95% CI 2.84–3365 and HR 56.0, 95% CI 6.82–7297, respectively). CAPRA-S was not associated with higher risk of metastasis nor PCSM (HR 1.93, 95% CI 0.95–3.92 and HR 2.48, 95% CI 0.93–7.16, respectively) (Table 2). A sensitivity analysis was performed adjusting for year of RP and adjuvant radiotherapy and similar results were observed.

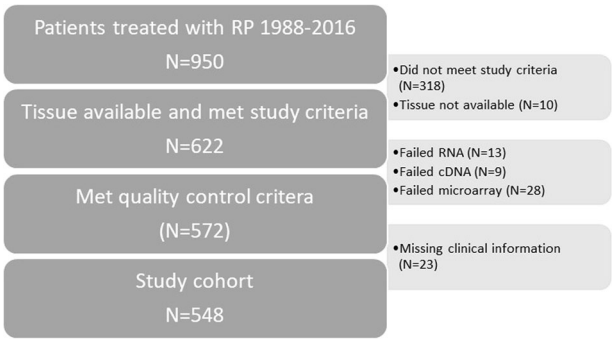

Fig. 1 Consort diagram showing the cohort selection. RP radical prostatectomy.

The prognostic value of GC was additionally reflected using C-indices for 5-year metastasis and 10-year PCSM (Supplementary Fig. 1). The C-index for 5-year risk of metastasis by GC (0.78) was higher than that of CAPRA-S (0.72), and the combination of the two (0.77) was no higher than by GC alone. For 10-year PCSM, similar results were seen in that the C-index by GC (0.85) was higher than for CAPRA-S (0.81), with their combination (0.86) slightly higher than GC alone. The cumulative incidence of metastases and PCSM is shown in Fig. 2.

Risk prediction and outcomes by race

When stratified by race, in multivariable analysis, CAPRA-S was not associated with metastasis nor PCSM in either non-AAM or AAM (Table 2). In contrast, GC intermediate- and high-risk groups were significantly associated with higher risk of metastasis in both non-AAM (HR 4.03, 95% CI 0.88–23.3 and HR 4.87, 95% CI 1.23–27.2, respectively) and AAM (HR 9.09, 95% CI 2.43–49.0 and HR 14.5, 95% CI 3.86–78.9, respectively), although the association in the intermediate group did not reach statistical significance in non-AAM. Similarly, GC intermediate- and high-risk groups were significantly associated with higher risk of PCSM in both non-AAM (HR 14.5, 95% CI 1.39–1968 and HR 16.6, 95% CI 1.70–2249, respectively) and AAM (HR 12.8, 95% CI 0.99–1796 and HR 49.4, 95% CI 5.13–6647, respectively), although the association in the intermediate

Table 1 Patient characteristics, overall and stratified by race.

Variables	Study cohort	Non-AAM	AAM	*p* value[a]
No. patients (%)	548 (100)	246 (45)	301 (55)	
Age at surgery	62 (57, 65)	63 (59, 67)	60 (56, 64)	<0.001
Race				
African-American	301 (55)	–	–	
Caucasian	235 (43)	–	–	
Other	11 (2)	–	–	
Unavailable	1 (<1)	–	–	
Preoperative PSA (ng/ml)	7.1 (5.1, 10.8) NA = 17	7.0 (5.0, 10.3) NA = 13	7.2 (5.2, 11.3) NA = 4	0.178
Pathological grade group				0.277
1	67 (12)	37 (15)	29 (10)	
2	333 (61)	142 (58)	191 (64)	
3	84 (15)	36 (15)	48 (16)	
4	28 (5)	12 (5)	16 (5)	
5	36 (7)	19 (8)	17 (6)	
Pathological stage				0.008
pT2	307 (56)	124 (50)	182 (61)	
pT3a	101 (18)	59 (24)	42 (14)	
pT3b	98 (18)	48 (20)	50 (17)	
pT4	42 (8)	15 (6)	27 (9)	
Positive surgical margins	472 (86)	215 (87)	256 (85)	0.458
Extraprostatic extension	188 (34)	106 (43)	82 (27)	<0.001
Seminal vesicle invasion	113 (21)	55 (22)	58 (19)	0.397
Pre-SRT PSA (ng/ml)	0.12 (0.04, 0.4) NA = 289	0.11 (0.03, 0.39) NA = 139	0.14 (0.07, 0.4) NA = 150	0.349
Any RT	263 (48)	108 (44)	154 (51)	0.102
Adjuvant RT	261 (48)	107 (44)	153 (51)	0.086
Any ADT	128 (23)	52 (21)	76 (25)	0.265
Follow-up for censored patients, months	113 (67, 166) NA = 37	123 (77, 172) NA = 16	104 (65, 158) NA = 21	0.006

[a]Calculated using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables

Table 2 Multivariable hazard ratios for metastasis and prostate cancer-specific mortality, among all patients and stratified by race.

	Full Cohort			Non-African-American			African-American			P-interaction race X GC
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	
Metastasis										
Age at RP	0.97	0.92–1.03	0.315	0.99	0.91–1.09	0.884	0.96	0.90–1.04	0.297	0.297
AAM vs. non-AAM	1.29	0.65–2.64	0.475	–	–	–	–	–	–	
CAPRA-S high vs. low/ intermediate	1.93	0.95–3.92	0.067	2.60	0.88–8.07	0.084	1.41	0.55–3.62	0.474	
GC intermediate vs. low	6.51	2.33–21.8	<0.001	4.03	0.88–23.3	0.072	9.09	2.43–49.0	<0.001	
GC high vs. low	9.60	3.51–32.0	<0.001	4.87	1.23–27.2	0.023	14.5	3.86–78.9	<0.001	
PCSM										
Age at RP	0.94	0.87–1.02	0.116	0.96	0.85–1.07	0.449	0.93	0.83–1.04	0.237	0.397
AAM vs. non-AAM	1.10	0.42–2.97	0.847	–	–	–	–	–	–	
CAPRA-S high vs. low/ intermediate	2.48	0.93–7.16	0.069	2.83	0.72–12.8	0.136	1.66	0.39–8.13	0.498	
GC intermediate vs. low	25.5	2.84–3365	0.002	14.5	1.39–1968	0.023	12.8	0.99–1796	0.051	
GC high vs. low	56.0	6.82–7297	<0.001	16.6	1.70–2249	0.012	49.4	5.13–6647	<0.001	

RP radical prostatectomy, *AAM* African-American men, *EAM* European-American men, *GC* genomic classifier

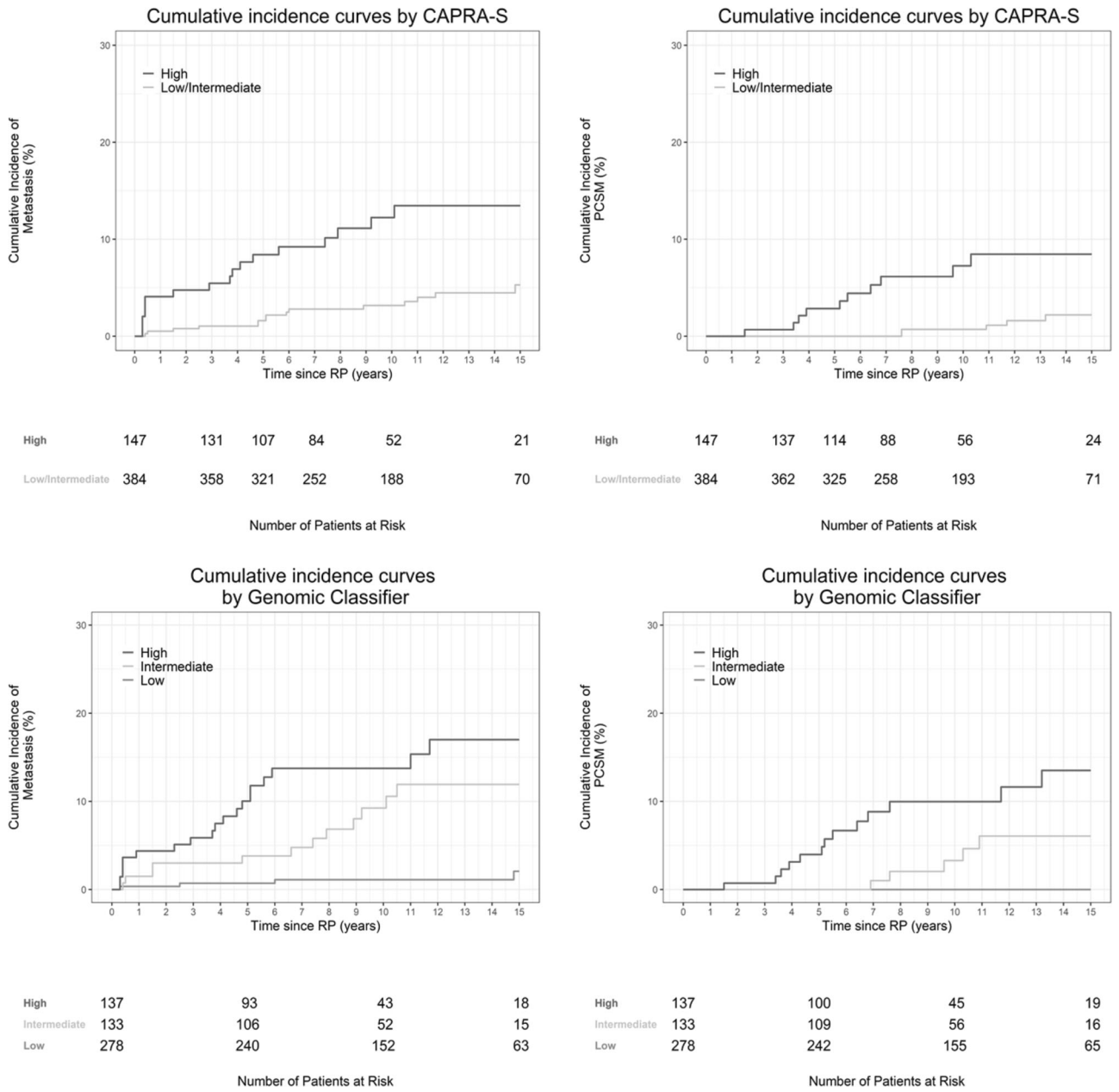

Fig. 2 Cumulative incidence of metastasis and prostate cancer-specific mortality, stratified by CAPRA-S and the Decipher genomic classifier. PCSM prostate cancer-specific mortality.

group did not reach statistical significance in AAM. The test for an interaction between GC and race was not significant for either metastasis ($p = 0.297$) or PCSM ($p = 0.397$).

For predicting 5-year metastasis, the C-index for CAPRA-S was similar in AAM (0.69) and non-AAM (0.73) whereas for GC, the C-index was markedly higher in AAM (0.86) compared with non-AAM (0.69) (Fig. 3). Similar to the results among all men, the C-indices for the combined models (0.83 for AAM and 0.68 for non-AAM) were similar to the C-index of GC alone. For predicting 10-year PCSM, the C-indices for CAPRA-S were higher in non-AAM (0.86) vs. AAM (0.75). In contrast, the C-indices for GC were higher among AAM (0.91) than non-AAM (0.78). Again, the C-indices for the combined models were similar to GC alone in both AAM (0.92) and non-AAM (0.80). The cumulative incidence curves for metastases and PCSM are shown in Fig. 4.

Discussion

Accurate risk stratification is crucial for PC management. While gene expression tests can provide valuable information, their performance in AAM has not been thoroughly

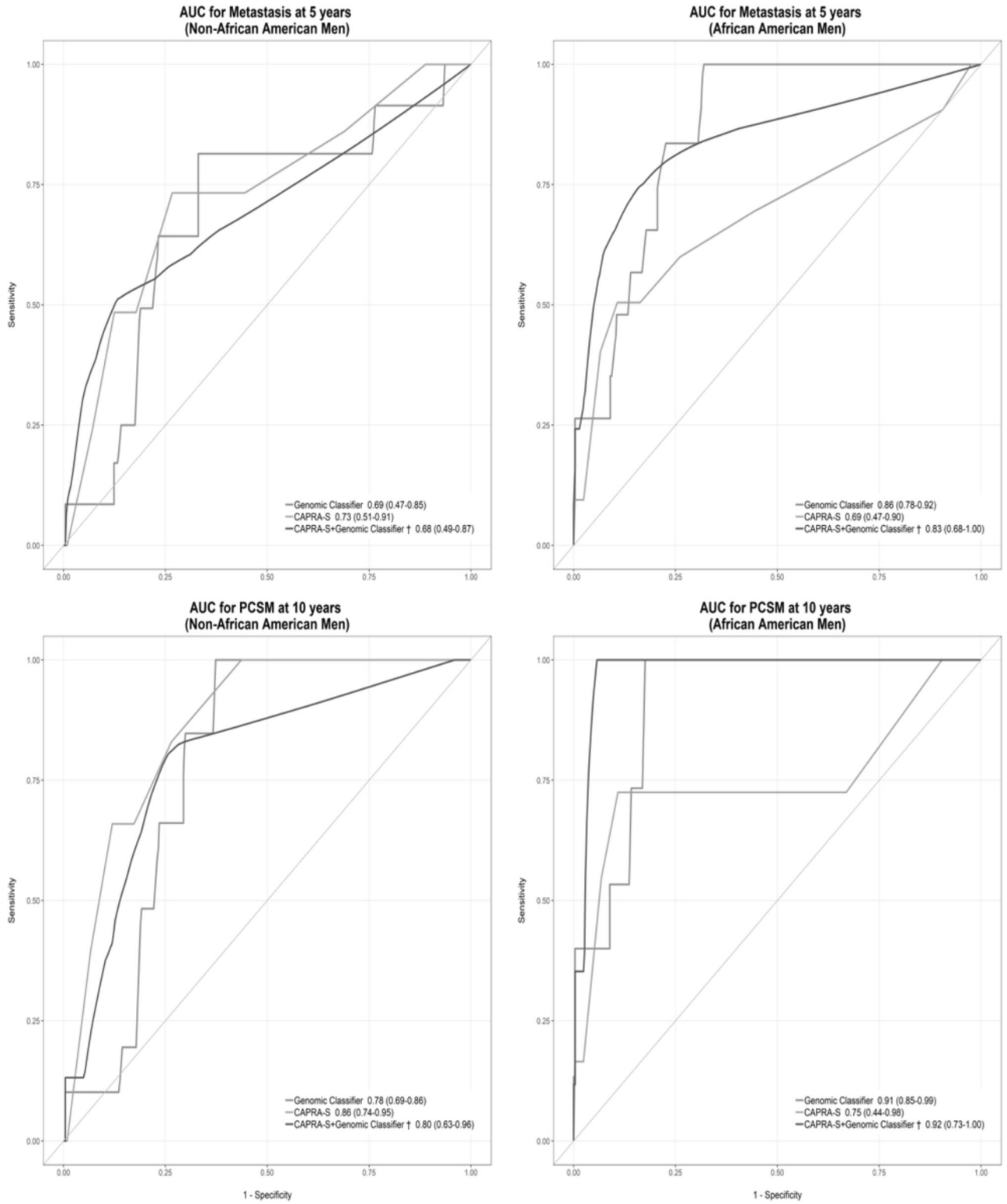

Fig. 3 Receiver operating characteristic (ROC) curve for CAPRA-S and genomic classifier predicting 5-year metastasis and 10-year prostate cancer-specific mortality, stratified by race. AUC area under the curve, PCSM prostate cancer-specific mortality.

studied. To our knowledge, we performed the largest study of PC gene expression testing in AAM, analyzing data from 548 men treated by RP, of which 55% were AAM. We found, consistent with prior studies, that GC was a strong predictor of clinical outcomes. Importantly, we found that GC has similar, if not better, performance among AAM.

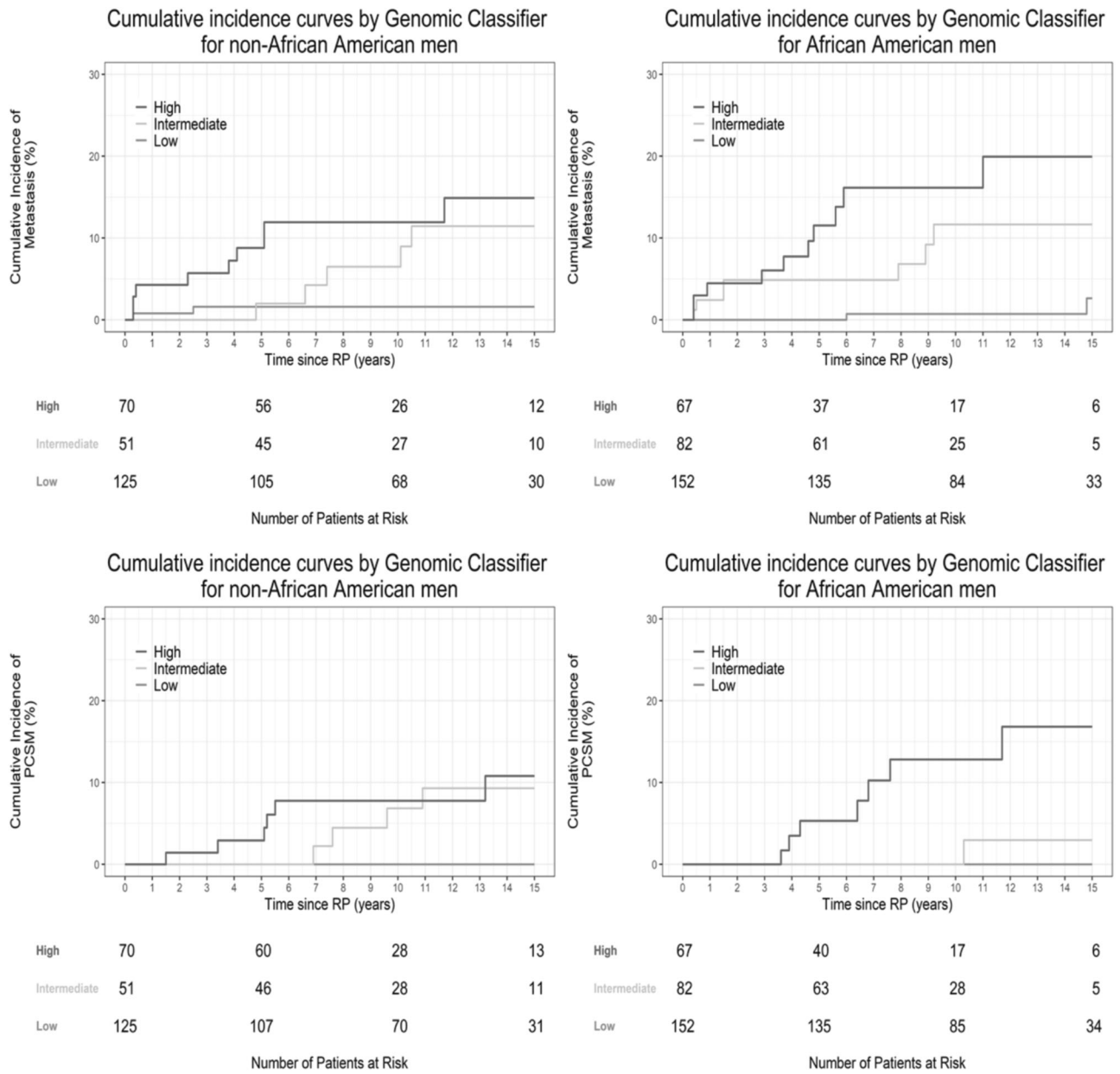

Fig. 4 Cumulative incidence of metastasis and prostate cancer-specific mortality by race, stratified by the Decipher genomic classifier. PCSM prostate cancer-specific mortality.

This suggests that GC can be confidently used in PC patients regardless of race. Whether GC consistently performs better in AAM requires further evaluation.

There are currently three commercially available genomic tests for men diagnosed with PC. While all three have been validated for use at the time of initial biopsy and after surgery to predict clinical outcomes [18, 24–28], little data exist regarding their value in AAM. In a study of 402 men (82 AAM) undergoing RP, Cullen et al. showed that OncotypeDx worked similarly in AAM and EAM to predict adverse pathology and biochemical recurrence [29]. However, metastasis was not assessed. In a small cohort of 141 men (81 AAM) undergoing radiation therapy, we previously showed that Prolaris predicted metastasis with no evidence of difference in performance by race [30]. A large individual patient-level meta-analysis ($n = 855$) of the performance of Decipher post-RP included 106 AAM [11]. The HR per 0.1 unit of the GC score was very similar for EAM and AAM, suggesting no interaction by race. As such, our current study with 302 AAM is nearly threefold larger than any prior study assessing the prognostic value of gene expression testing in AAM. Consistent with the prior and much smaller studies, we saw no evidence that GC performed worse in AAM. As such, though the data are

limited, given that all three genomic tests have shown similar prognostic ability in AAM, it seems reasonable to conclude that the currently available commercial genomic tests work at least as well in AAM as non-AAM [31]. Our data provide robust support for the Decipher classifier in AAM, given its extremely strong performance in risk stratifying men post-RP.

Recent data suggest that PC can be subdivided into various molecular subtypes [32–34]. Importantly, data also suggest that while AAM's tumors can be categorized into the same subtypes, the distribution of tumors differs between AAM and EAM [35]. Whether this alone explains prior studies finding differences in gene expression between AAM and EAM is not clear [7, 36]. However, given the differences in subtype distribution between AAM and EAM it stands to reason that certain genes may be more predictive of outcome in one race than another. Indeed, a prior study suggests exactly this – that certain biomarkers can predict outcome in an ethnicity-dependent manner [37]. As such, in the future, it is likely that either race or molecular subtyping (which is correlated to race) will be done first and a specific signature for that subtype (or race) can be applied to generate an even more accurate risk classifier than what is currently used. However, until that time, our data suggest that currently available commercial tests can be used regardless of race.

Of note, when we compared GC against CAPRA-S, a commonly used tool for risk assessment in RP patients, CAPRA-S categorized 10% of patients as low-risk, whereas GC categorized 51% as low-risk. The low-risk GC group did indeed have very low incidence of metastasis and PCSM. Thus, GC was better able to identify a larger low-risk group in this clinically high-risk cohort, regardless of race. GC also had superior discriminatory capability compared with CAPRA-S, and in AAM, the C-index for 10-year PCSM exceeded 0.90. Furthermore, GC was an independent predictor of metastasis and PCSM after adjusting for CAPRA-S in our cohort, signifying that it adds more prognostic information than clinical/pathological characteristics alone.

Our study is not without limitations. First, we examined men at high risk for metastases. Whether GC works as well in AAM as non-AAM across the full spectrum of PC risk requires further study. Second, though our study was the largest study of AAM to date, with nearly threefold more AAM than prior studies, the overall number of events was modest, especially for PCSM which resulted in wide CIs and limited power for interaction testing by race. As such, we cannot confidently exclude the possibility, as suggested by higher C-indices, that GC works better in AAM, though this requires further testing in other cohorts. Third, our study was focused on veterans. Whether similar results would be seen in other populations requires further study. We used CAPRA-S as the comparison for risk stratification after RP, but this tool is optimized to predict recurrence and not metastases, which was our primary outcome. Whether GC would perform better than other clinical tools optimized to predict metastases is unknown.

Conclusion

In summary, in a validation cohort including a large number of AAM, we found that GC accurately predicted metastases and PCSM risk, regardless of race. Given similar results in other studies validating other genomic tests in AAM, albeit smaller studies, the totality of the literature to date suggests that gene expression testing performs similarly regardless of race, and the Decipher GC has an excellent ability to risk-stratify AAM post-RP.

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Compliance with ethical standards

Conflict of interest JZ, NF, and ED are employees of Decipher Biosciences.

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Affiliations

Lauren E. Howard[1,2] · Jingbin Zhang[3] · Nick Fishbane[3] · Amanda M. De Hoedt[2] · Zachary Klaassen[4] · Daniel E. Spratt[5] · Adriana C. Vidal[6] · Dechen Lin[7,8] · Megan P. Hitchins[7,8] · Sungyong You[6,9] · Michael R. Freeman[6,9] · Kosj Yamoah[10] · Elai Davicioni[3] · Stephen J. Freedland[2,6]

1 Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA

2 Department of Surgery, Division of Urology, Veteran Affairs Healthcare System, Durham, NC, USA

3 Decipher Biosciences, Inc, Vancouver, BC, Canada

4 Department of Surgery, Section of Urology, Augusta University - Medical College of Georgia, Augusta, GA, USA

5 Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

6 Department of Surgery, Division of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

7 Department of Medicine, Cedars-Sinai, Los Angeles, CA, USA

8 Center for Bioinformatics and Functional Genomics, Cedars-Sinai, Los Angeles, CA, USA

9 Department of Biomedical Sciences, Cedars-Sinai, Los Angeles, CA, USA

10 Section of Genitourinary Radiation Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Racial Discrepancies in Overall Survival among Men Treated with ^{223}Radium

Hanson Zhao, Lauren E. Howard, Amanda De Hoedt,* Martha K. Terris, Christopher L. Amling, Christopher J. Kane, Matthew R. Cooperberg, William J. Aronson,* Zachary Klaassen, Thomas J. Polascik, Adriana C. Vidal and Stephen J. Freedland*,†

From the Division of Urology, Department of Surgery, Cedars-Sinai Medical Center (HZ, ACV, SJF), Department of Urology, UCLA School of Medicine and Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles, Los Angeles (WJA), Urology Department, University of California San Diego Health System (CJK), San Diego and Department of Urology, University of California-San Francisco Helen Diller Family Comprehensive Cancer Center (MRC), San Francisco, California, Duke Cancer Institute, Duke University School of Medicine (LEH, TJP) and Division of Urology, Durham Veterans Affairs Health Care System (LEH, ADH, ZK, TJP, SJF), Durham, North Carolina, Section of Urology, Veterans Affairs Medical Center and Section of Urology (ZK), Augusta University-Medical College of Georgia, Augusta (MKT, ZK), Georgia, and Division of Urology, Department of Surgery, Oregon Health and Science University (CLA), Portland, Oregon

Purpose: Several recent studies on metastatic castration resistant prostate cancer demonstrated improved overall survival in black vs white men. ^{223}Radium is Food and Drug Administration approved for metastatic castration resistant prostate cancer based on a survival benefit in the ALSYMPCA (A Phase III Study of Radium-223 Dichloride in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases) trial, in which 94% of participants were white. We identified a real world population of patients with metastatic castration resistant prostate cancer who received ^{223}radium to compare differences in baseline characteristics and outcomes in black vs nonblack men.

Materials and Methods: We reviewed the charts of all men who received ^{223}radium in the entire Veterans Affairs system. We compared treatment patterns and baseline characteristics between black and nonblack men. We used Cox models to analyze predictors of time from ^{223}radium start to overall survival and time to skeletal related events.

Results: We identified 318 patients treated with ^{223}radium, including 87 (27%) who were black. Median followup after ^{223}radium initiation was 25.3 months (IQR 13.8–37.1). Black men were younger than nonblack men when starting ^{223}radium (median age 67 vs 70 years, $p < 0.001$) and they had higher prostate specific antigen (median 159.9 vs 90.2 ng/ml, $p = 0.014$) and alkaline phosphatase (median 163 vs 135 IU/l, $p = 0.017$). A greater proportion of black men received docetaxel prior to ^{223}radium (77% vs 55%, $p < 0.001$). On multivariable analysis black race was associated with a decreased risk of mortality from the time of ^{223}radium initiation (HR 0.75, 95% CI 0.57–0.99, $p = 0.045$).

Abbreviations and Acronyms

ALP = alkaline phosphatase

ALSYMPCA = A Phase III Study of Radium-223 Dichloride in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases

CRPC = castration resistant prostate cancer

FDA = Food and Drug Administration

mCRPC = metastatic CRPC

OS = overall survival

PSA = prostate specific antigen

PSADT = PSA doubling time

SRE = skeletal related event

VA = Veterans Affairs

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† Correspondence: 8635 West 3rd St., Suite 1070W, Los Angeles, California 90048 (telephone: 310-423-4700; FAX: 310-423-1886; e-mail: stephen.freedland@cshs.org).

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Conclusions: Black men had longer overall survival than nonblack men, although they appeared to receive radium later in the disease course. Further studies are required to verify our findings and explore biological differences between black and nonblack men with metastatic castration resistant prostate cancer.

Key Words: prostatic neoplasms, mortality, African continental ancestry group, European continental ancestry group, neoplasm metastasis

RACIAL disparities in prostate cancer are well described but not precisely understood. Black men are more likely to be diagnosed with prostate cancer and they are at a higher risk for prostate cancer mortality than white men.[1,2] The etiology of this discrepancy is likely multifactorial and thought to be related to differences in tumor genetics and biology, screening rates, treatment options and access to care.[3–5] While much prior work has focused on men with localized disease, little is known about differences between black and nonblack men with advanced prostate cancer.

In the last several years new treatment options for mCRPC have emerged.[6] One such therapy, ^{223}radium, is a bone seeking α particle emitter which preferentially targets areas of osteoblastic or sclerotic metastasis.[7–9] In 2013 ^{223}radium was FDA approved to treat mCRPC based on the ALSYMPCA trial.[10] In that phase III, randomized, double-blind study ^{223}radium showed an OS benefit compared to placebo (median OS 14.9 vs 11.3 months, HR 0.70, 95% CI 0.58–0.83, p <0.001). Notably 94% of the ALSYMPCA participants were white. As such, the effect of ^{223}radium in black men has been unclear.

Interestingly, several recent analyses pooling clinical trial data have demonstrated an OS benefit in black men with mCRPC who were treated with docetaxel or sipuleucel-T.[11,12] In addition, black men with mCRPC may also have a better response to abiraterone and enzalutamide.[13,14]

In the current study we identified a heterogeneous population of men in the entire VA system with mCRPC who were treated with ^{223}radium. Using this cohort we compared differences in baseline characteristics and outcomes between black and nonblack men treated with ^{223}radium. Given the results of other studies, we hypothesized that black men treated with ^{223}radium would have similar or better OS than nonblack men.[11–14]

PATIENTS AND METHODS

Data Source and Ascertainment of Study Cohort

This study was approved by the Durham VA Medical Center Institutional Review Board (IRB No. 00340). We identified data on all men in the entire nationwide VA health care system who received ^{223}radium through September 2017 and were alive as of January 1, 2013. To achieve this, we created a VA database of men with a radiotherapy CPT code (A9606, A9699 or 79101) and also had "Xofigo," "Zofigo," "Ra-223" or "223radium" as key words in progress notes. As there was no specific code for ^{223}radium prior to 2015, we also included men with 2 or more progress notes 28 days apart with the same key words. This identified 318 men. The medical record of each patient was reviewed to confirm treatment with ^{223}radium along with treatment dates.

All patients were confirmed to have metastatic bone CRPC at the time of ^{223}radium initiation. CRPC status was determined using the PCWG2 (Prostate Cancer Working Group 2) criteria, including a 25% or greater increase in PSA and an absolute increase of 2 ng/ml or greater above the PSA nadir while castrate.[15] Castration was defined as testosterone less than 50 ng/dl, bilateral orchiectomy or continuous receipt of a luteinizing hormone-releasing hormone agonist or antagonist. After confirming that all men treated with ^{223}radium had CRPC, we then individually reviewed imaging reports and progress notes to identify prostate cancer metastasis to bone, lungs, liver, nonpelvic lymph nodes and other visceral tissues. Bone pain was abstracted from the medical notes within 2 months before or after bone metastasis developed.

Patients were followed until the date of death as determined from the electronic medical records or to the last followup date. SREs were defined as pathological fracture, spinal cord compression, or radiation or surgery to bone. Using imaging reports and medical records, we abstracted the first incidence of a SRE after the development of bone metastasis. To ensure the accuracy of data collection, we randomly selected 10% of all collected data for secondary review.

Statistical Analysis

PSADT was calculated by the natural log of 2 divided by the slope of the linear regression of the natural log of PSA with time in months. All available PSA values within 2 years prior to the first diagnosis of bone metastasis but after the CRPC diagnosis were used to calculate PSADT, which required 2 or more PSA values during a period of 3 months or more.

Kaplan-Meier curves were used to compare OS and time to SREs in black and nonblack men after ^{223}radium initiation with differences tested by the log rank test. OS was considered the primary outcome and SREs were a secondary outcome. Cox proportional hazards models were used to test the association between race and OS, and race and SREs. Time zero was considered the initiation of ^{223}radium. Patients in whom a SRE developed before the initiation of ^{223}radium were excluded from the time to SRE model.

Covariates of each outcome were chosen using backward stepwise selection with $\alpha = 0.05$ for entry and 0.1 for removal. However, race was forced into the model.

Candidate covariates included patient age at ^{223}radium treatment (continuous), year of ^{223}radium treatment (continuous), biopsy grade group (1 vs 2-3 vs 4-5 vs unknown), primary localized treatment (none vs radical prostatectomy and/or radiation vs radiation alone), PSA at ^{223}radium (continuous and log transformed), PSADT at metastasis (less than 9 months vs 9 or longer vs not calculable), months from ADT to CRPC (continuous), months from CRPC to first bone metastasis (continuous), bone pain at the metastasis diagnosis (no vs yes vs unknown), a SRE before ^{223}radium (no vs yes in the OS model only) and the number of bone metastases at the initial diagnosis of bone metastasis (1 vs 2 vs 3-9 vs 10 or more vs unknown). After the covariates were chosen the models were stratified by race to test whether predictors of time to a SRE or OS varied by race. For any significant variable in either model we checked for interactions with race by including a cross product term in the model and applying the Wald test.

RESULTS

We identified 318 patients in the entire VA system who received ^{223}radium, of whom all had bone mCRPC (supplementary table, https://www.jurology.com). Of the patients 87 (27%) were black. A total of 223 white men and 3 men of other races were grouped into a nonblack category. Median followup after ^{223}radium initiation was 25.3 months (IQR 13.8–37.1 months). A SRE developed in 217 patients (68%) at some point, including in 41 (19%) after ^{223}radium initiation. A total of 277 patients (87%) died during the study period.

Black men were younger than nonblack men when ^{223}radium treatment began (median age 67 vs 70 years, $p < 0.001$). There was no difference in prostate cancer grade at diagnosis, primary localized treatment or the number of bone metastases. Black men had higher PSA (median 159.9 vs 90.2 ng/ml, $p = 0.014$) and ALP (median 163 vs 135 IU/l, $p = 0.017$) when ^{223}radium was initiated. A greater proportion of black men received docetaxel prior to ^{223}radium therapy (77% vs 55%, $p < 0.001$). There was no difference in the number of ^{223}radium injections received or the proportion of men with PSADT less than 9 months between the 2 groups.

Median survival was 11 months (95% CI 9.7–12.5). The Kaplan-Meier curves showed similar OS in black and white men ($p = 0.16$, fig. 1). Median survival was 10.9 (95% CI 9.5–12.5) vs 11.5 months (95% CI 8.9–15.6) in nonblack vs black men. On multivariable analysis black race was associated with decreased OS from the time of ^{223}radium initiation (HR 0.75, 95% CI 0.57–0.99, $p = 0.045$, see table). A SRE before ^{223}radium and higher PSA at ^{223}radium were associated with worse OS (all $p < 0.05$). Bone pain at metastasis entered the model but did not reach statistical significance ($p = 0.067$). There was no significant interaction between race and any predictor of mortality (all $p > 0.50$), suggesting all risk factors were associated with OS regardless of race.

A total of 229, 292, 259 and 9 patients were treated with docetaxel, abiraterone, enzalutamide and sipuleucel-T, respectively. When we further controlled for treatments received prior to ^{223}radium, the HR for race was slightly weaker and the results, while no longer statistically significant, remained similar since black men had improved OS (HR 0.77, 95% CI 0.58–1.02, $p = 0.064$).

Of the 142 men without a SRE prior to ^{223}radium initiation time to a SRE was similar between races (fig. 2, $p = 0.97$). Race was not associated with the SRE risk on multivariable analysis (HR 0.71, 95%

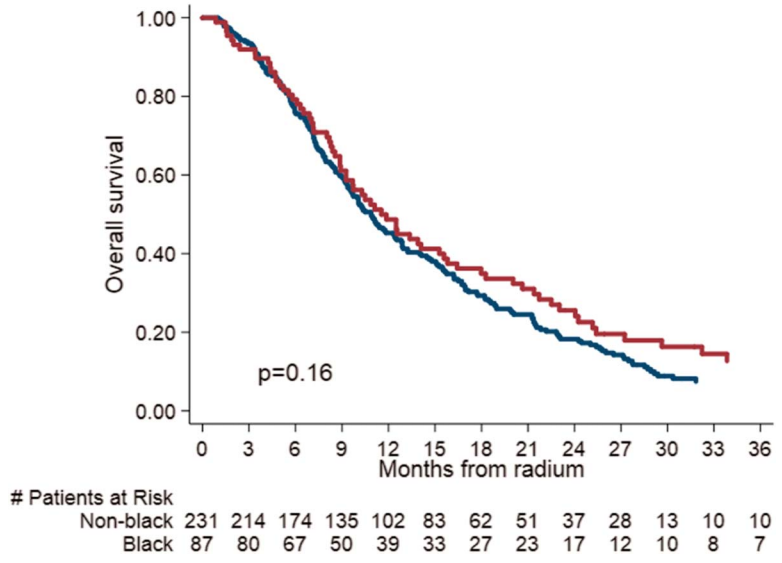

Figure 1. Kaplan-Meier curve of OS after ^{223}radium initiation by nonblack (blue curve) and black (red curve) race

HR of predictors of time from ^{223}radium initiation to all cause mortality in 314 patients and skeletal related event in 140 by race

	Overall		Nonblack		Black	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
			*All cause mortality**			
Race:		0.045		—		—
Nonblack	Referent		—		—	
Black	0.75 (0.57–0.99)					
Bone pain at metastasis:		0.067	0.11	0.32		0.11
No	Referent		Referent		Referent	
Yes	1.30 (0.99–1.70)		1.20 (0.88–1.64)		1.63 (0.95–2.80)	
Unknown	0.90 (0.59–1.39)		0.90 (0.55–1.48)		0.85 (0.34–2.12)	
Skeletal related event before ^{223}radium		0.028		0.12		0.10
No	Referent		Referent		Referent	
Yes	1.32 (1.03–1.70)		1.26 (0.94–1.68)		1.64 (0.98–2.74)	
Log transformed PSA at ^{223}radium	1.18 (1.11–1.26)	<0.001	1.15 (1.06–1.25)	0.001	1.26 (1.11–1.43)	<0.001
			Skeletal related event†			
Race:		0.36		—		—
Nonblack	Referent		—		—	
Black	0.71 (0.34–1.48)					
Age at ^{223}radium	0.94 (0.90–0.98)	0.008	0.93 (0.88–0.99)	0.013	0.95 (0.86–1.04)	0.24
Log transformed PSA at ^{223}radium	1.19 (1.01–1.41)	0.040	1.25 (1.00–1.55)	0.048	1.28 (0.90–1.82)	0.18
No. bone metastases:		0.033		0.015	Did not converge‡	—
1	Referent		Referent			
2	3.90 (1.19–12.8)		3.23 (0.99–10.8)			
3–9	1.62 (0.55–4.81)		0.90 (0.28–2.85)			
10 or More	1.03 (0.28–3.73)		0.52 (0.10–2.59)			

* All p interactions >0.50.
† All p interactions >0.55.
‡ Not enough events.

CI 0.34–1.48, p=0.36, see table). However, younger age at ^{223}radium, higher PSA at ^{223}radium and more bone metastases were associated with an increased SRE risk. There was no interaction of race with age, PSA or the number of bone metastases (all p >0.55).

DISCUSSION

While there has been tremendous growth in the number of mCRPC therapies, racial discrepancies in the treatment and outcomes of this disease state have not been well described except in a few recent studies.[11–14] In this study we identified all men with mCRPC in the national VA system who received ^{223}radium, a mCRPC treatment which was FDA approved in 2013. We compared differences in patient characteristics, treatment patterns and outcomes between black and nonblack men. On multivariable analysis black race was associated with a 25% decreased risk of mortality from the time

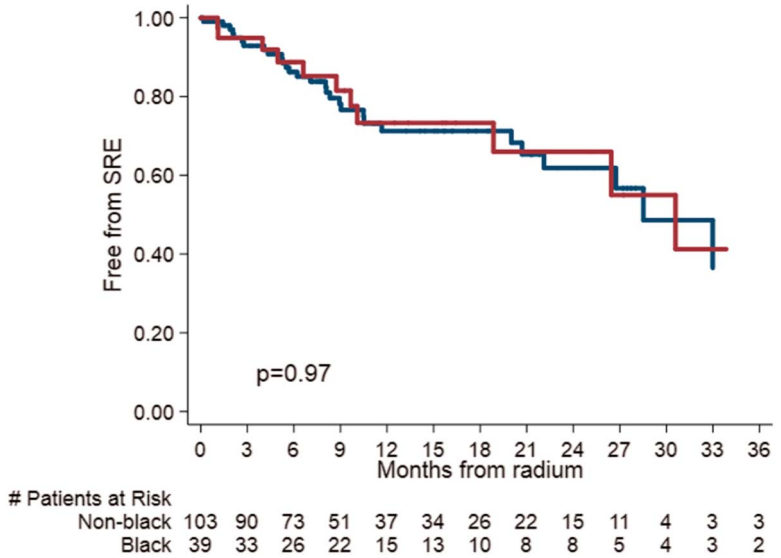

Figure 2. Kaplan-Meier curve of time to SRE after ^{223}radium initiation by nonblack (blue curve) and black (red curve) race

of ^{223}radium initiation vs that in nonblack men. If confirmed in future studies, this suggests that among men treated with ^{223}radium, black men have a better outcome. Whether this is due to ^{223}radium being more effective in black men requires further study.

Previous studies pooling data from large clinical trials in men with mCRPC likewise revealed improved OS among black men.[11,12,16,17] In an earlier analysis of 8 phase II and III trials Halabi et al found that black men with mCRPC were at lower risk for death than white men (HR 0.77, 95% CI 0.65–0.92, p = 0.004).[16] This association held true in black men with mCRPC treated with docetaxel in a recent pooled analysis of 9 phase III trials (HR 0.81, 95% CI 0.72–0.91, p <0.001).[11] Quinn et al also found a survival benefit in black men compared to matched white men in 3 pooled trials of sipuleucel-T (HR 0.49, 95% CI 0.26–0.91, p = 0.02).[12] On the other hand, Spratt et al noted no difference in OS and a trend toward an increased risk of progression in black men in an analysis of 5 mCRPC clinical trials, although these results were based on only 77 black men.[17] Indeed, the lack of black men in mCRPC clinical trials is a pervasive problem contributing to our poor understanding of how agents work in this population.[18]

There are inherent biases in patients enrolled in clinical trials. Patients are carefully selected because of the disease state, prior treatments, access to health care, financial status and comorbidities. Additionally, black men have been notoriously underrepresented in large prostate cancer trials.[19] In the discussed studies the percent of black men ranged from 4.7% to 14%.

Outside the context of clinical trials, real world data on racial disparities in men with mCRPC has been limited and follows a similar trend.[14,20] Sartor et al reported better survival for black men compared to white men when treated with sipuleucel-T from the PROCEED (Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer) Registry (HR 0.67, 95% CI 0.53–0.84 p <0.001).[20] Recently a retrospective analysis at the VA by McNamara et al in 2,910 chemotherapy naïve patients with mCRPC treated with abiraterone or enzalutamide also demonstrated improved OS in black men compared to white men (HR 0.826, 95% CI 0.732–0.933).[14] Each study had the benefit of higher enrollment of black patients (33% and 27%, respectively).[14,20] However, to our knowledge no study to date has analyzed whether similar trends occur in men treated with ^{223}radium.

In our cohort 27% of men treated with ^{223}radium were black. While most baseline characteristics were similar in black and nonblack men, the black men had higher PSA and ALP, and were more likely to be treated with docetaxel prior to ^{223}radium, suggesting a possible ^{223}radium treatment delay. There may be bias among providers for treating black men who have mCRPC with a more aggressive regimen first, such as chemotherapy. However, as this was an observational study, the reasons for this apparent treatment delay require further study. Notably the survival benefit in black men with mCRPC is now seen across an entire spectrum of life prolonging therapies including docetaxel, sipuleucel-T, abiraterone/enzalutamide and now ^{223}radium.

The racial disparity in survival between men with localized and advanced prostate cancer is not well understood. Of men with localized disease black men are thought to have worse outcomes due to differences in screening, access to care, diet, genetics and cancer treatment.[21] In men with advanced disease the outcomes appear to be reversed. Given the preponderance of data suggesting improved outcomes in black men with mCRPC, further studies are needed to understand whether they are due to inherent biological differences or other causes. Specifically, differences in prostate cancer genetics, the castration response, hormone levels, drug pharmacokinetics and pharmacodynamics need to be further investigated.

Our study has several limitations. This is a retrospective study with inherent selection bias since the primary physician determined the treatments offered to patients. In this cohort many patients were diagnosed with mCRPC prior to FDA approval of ^{223}radium and they may have received various therapies or combinations of therapies before ^{223}radium. Thus, the fact that they were still alive to receive ^{223}radium suggests that they had more indolent disease, although how this would have affected our findings regarding race is unclear. We aim to explore these treatment patterns with ^{223}radium in a future study.

Further, some patients may not have been captured in this study if they received ^{223}radium treatment outside the VA system. In addition, some variables were not readily available at the time of ^{223}radium initiation (eg PSADT and lactate dehydrogenase) and they may have been confounded by prior therapies.

Finally, SREs were determined based on a retrospective chart review. Although this approach may have underestimated the SRE rate, in prior studies using this approach the SRE rate closely mirrored data from phase III trials, which gives some level of validity to our approach. Nevertheless, this study is more representative of a diverse, real world clinical cohort of patients and the results have

important implications in the expanding field of mCRPC. Further studies are required to verify our findings.

CONCLUSIONS

Of men with mCRPC in the national VA system who received ^{223}radium we found that black men had longer survival than nonblack men. These findings persisted despite black men receiving ^{223}radium later in the disease course, as evidenced by higher PSA and ALP levels at the time of ^{223}radium initiation and black men being more likely to receive docetaxel prior to ^{223}radium. As this is now the fourth study to show that black men with mCRPC treated with new life extending treatments have better survival than nonblack men, further studies are required to investigate racial differences in the biology of mCRPC.

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EDITORIAL COMMENTS

In demonstrating that ^{223}radium administered for metastatic CRPC in the equal access VA Health System results in longer survival of black men the authors perpetuate broad themes in prostate cancer biology, cancer therapeutic delivery and the personal, economic and societal value of equal access to health services across disparate groups. We know that black men have higher rates of prostate cancer diagnosis and death from prostate cancer but if provided with access to mCRPC therapy such as docetaxel, particularly through NCI (National Cancer Institute) sponsored cooperative group trials, they actually have better outcomes (reference 11 in article). Black men with mCRPC also appear to have better survival when given sipuleucel-T.[1] Based on the data presented in this report we can add ^{223}radium to the list of agents with which black men with access actually do better than the general population.

What are some barriers to getting black men and other disparately impacted groups with prostate

cancer, such as those in rural communities, access to life prolonging agents for advanced prostate cancer? We know that expanding health insurance coverage can neutralize preexisting racial disparities in access to treatment.[2] Delivery is also important since ^{223}radium and sipuleucel-T are logistically complicated therapies administered at a limited number of centers and they may not be accessible to those who are uninsured or underinsured, or geographically isolated.

Practical solutions to access and delivery challenges are critical if we are to improve outcomes in disproportionately affected men with prostate cancer. The biology of risk, response and outcome represents fertile ground for further research.

Anishka A. D'Souza and David I. Quinn
Section of Genitourinary Medical Oncology
Norris Comprehensive Cancer Center
University of Southern California
Los Angeles, California

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Racial disparities in the treatment of prostate cancer are an important focus to improve patient care and reduce cancer mortality. Studies have shown that black men are more likely to have delayed diagnosis and treatment of more advanced disease. Treatment of advanced prostate cancer has recently undergone rapid progression following the results of several landmark clinical trials. Unfortunately, prostate cancer clinical trials have suffered from underrepresentation of minorities in the United States (reference 19 in article). Determining the impact of racial differences in prostate cancer outcomes requires untangling a complex relationship between biological and social factors which may also be related to each other. Along with tumor characteristics, differences in access to care and social equality may have significant contributions to cancer survival.[1]

This group evaluated outcomes in men with mCRPC undergoing treatment with ^{223}radium in the VA Health System. By its nature this group represents a diverse group of men with similar potential access to health care. As opposed to the ALSYMPCA trial, which included predominately white patients (reference 10 in article), this real world experience included a cohort of which more than a quarter were black men. Although black men had higher PSA and alkaline phosphatase prior to starting treatment, the results show a significant reduction in mortality compared to that in nonblack patients.

The results of this study and others suggesting better advanced prostate cancer outcomes in minority patients provide a basis for studies examining the cause of these findings. As efforts to improve metastatic prostate cancer treatment by identifying targeted treatments and actionable alterations expand, racial disparities in care will remain an important consideration.

Kelly L. Stratton
Department of Urology
Stephenson Cancer Center
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

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