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TITLE: Treatment Options and Survival of Metastatic Prostate Cancer Patients

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CONTRACTING ORGANIZATION: Washington University, St. Louis, MO

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Treatment Options and Survival of Metastatic Prostate Cancer Patients

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In this proposal, we will utilize a prostate cancer cohort from the VA hospitals to explore the survival benefit among men diagnosed with metastatic prostate cancer who receive definitive treatment (alone or with adjuvant therapies) compared to men who receive non-definitive treatment; and we will assess the treatment related side effects that affect quality of life among men diagnosed with metastatic prostate cancer who receive definitive vs. non-definitive treatment. The specific aims are:

Aim 1: To examine the survival benefit among men diagnosed with metastatic prostate cancer that receive definitive treatment compared to men that receive non-definitive treatment.

Aim 2: To examine treatment-related side effects that affect quality of life (impotence, incontinence and pain) among men diagnosed with metastatic prostate cancer that receive definitive treatment compared to men that receive non-definitive treatment.

15. SUBJECT TERMS

Prostate cancer, disparities, treatment, VHA, VACCR, survival, mortality, recurrence

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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1. **INTRODUCTION:**
The objective of this study is to build on the comprehensive data that has been cultivated through the Health Disparity award and expand it to explore survival and quality of life benefits of definitive and non-definitive treatment combinations. In the study proposed here, we will abstract additional individual-level data on all treatments received including dates to assess timing of treatment, clinical assessment and/or diagnoses of treatment-related side effects that affect quality of life such as impotence, incontinence and pain. The additional data abstraction will also allow for the creation of comprehensive covariates including co-morbidity scores that contribute to survival in a metastatic prostate cancer population.

2. **KEYWORDS:**
Prostate cancer, disparities, treatment, VHA, VACCR, survival, mortality, recurrence

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

1. Team Meeting
   i. Review grant and progress of recruitment in parent study – Year 1, Month 1 – 100%
   ii. Team Meetings will occur monthly throughout the award – Year 1-3, Monthly – 100%
   iii. Interview and hire staff – Year 1, Month 2 – 100%
2. Regulatory review and IRB
   i. Complete and submit forms for regulatory review – Year 1, Months 1-2 – 100%
   ii. Complete and submit IRB forms for review – Year 1, Months 2-3 – 100%
   iii. Obtain approval for regulatory and IRB forms – Year 1, Month 4 – 100%
3. Study team will abstract and clean data
   i. Develop data abstraction form – Year 1, Months 3-5 – 100%
   ii. Abstract data – Year 1, Month 4-6 – 100%
   iii. Run frequencies, report, and correct any errors found – Year 1, Month 4-6 – 100%
4. Perform analyses
   i. Finalize data analysis plans – Year 1, Months 7-10 – 100%
   ii. AIM 1 – Yr 1: 10-12 – Yr 2: 1-2 – 100%
   iii. AIM 2 – Year 2, Months 3-6 – 100%
5. Manuscript Development
   i. AIM 1 –Year 2, Months 3-8 – 100%
   ii. AIM 2 – Year 2, Months 9-12; Year 3, Months 1-3 – 100%
   iii. Additional analyses– Year 3, Months 3-6 – 100%
6. Presentations – Years 2-3 – completed
7. Community Input/Feedback – Years 1-3 – completed
8. Planning for next study – Year 3, Months 6-12 – completed

What was accomplished under these goals?

1. Major activities: Data activities included: established regular team meetings, hired statistician, achieved IRB approval, updated data with an additional year of diagnoses and vital status data, developed data abstraction form, ran frequencies and corrected errors, finalized variable definitions. We completed data analyses for each of the aims and published one manuscript, one under review and two additional manuscripts in progress.

2. Specific objectives to be completed this year: Complete manuscripts for aim 3 and additional analyses. We are continuing to review results with community partners and share the research results through conference presentations. In addition, we are planning for subsequent research projects based on the study results. The proposal currently in development will focus on an intervention to address quality of life outcomes among prostate cancer survivors. We will complete the project in a 1 year no cost extension.

3. Significant results or key outcomes: Four significant manuscripts are published or under review.

Schoen M, Carson, K, Eisen, S, Bennett, Luo S, Reimers M, Knoche E, Whitmer A, Yan Y, Drake B, Sanfilippo K. *Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases*. Prostate Cancer and Prostatic Diseases. . 2022 Sep 14. doi: 10.1038/s41391-022-00588-5. PMID: 36104504

Abstract:
Background: Comorbid diseases influence patient outcomes, yet little is known about how comorbidities interact with treatments for metastatic castrate-resistant prostate cancer (mCRPC). No head-to-head trials have compared the efficacy of abiraterone and enzalutamide - oral androgen-receptor targeted agents (ARTAs) for mCRPC. In patients with comorbid disease, outcomes with ARTAs may differ due to disparate mechanisms of action, adverse events, and drug interactions.
Methods: Retrospective observational study of US veterans starting treatment for mCRPC with abiraterone or enzalutamide between 9/2014 and 6/2017 to compare treatment duration and survival based on age and comorbid diseases. The association between treatment and overall survival (OS) was assessed using Cox proportional hazards and propensity-score matched modeling while adjusting for potential confounders. Sensitivity analyses were performed based on patient age, comorbidities, and subsequent treatments for mCRPC.
Results: Of 5822 veterans treated for mCRPC, 43.0% initially received enzalutamide and 57.0% abiraterone. Veterans initially treated with enzalutamide versus abiraterone were older (mean 75.8 vs. 75.0 years) with higher mean Charlson comorbidity index (4.4 vs. 4.1), and higher rates of cardiovascular disease or diabetes (74.2% vs. 70.6%). In the entire population, veterans initially treated with enzalutamide had longer median OS compared to those initially treated with abiraterone (24.2 vs. 22.1 months, $p = 0.001$). In veterans with cardiovascular disease or diabetes, median treatment duration with enzalutamide was longer (11.4 vs. 8.6 months, $p < 0.001$) with longer median OS compared to abiraterone (23.2 vs. 20.5 months, $p < 0.001$). In a propensity score matched cohort, enzalutamide was associated with decreased mortality compared to abiraterone (HR 0.90, 95% CI 0.84–0.96).
Conclusions: Veterans with cardiovascular disease or diabetes had longer treatment duration and OS with enzalutamide compared to abiraterone. Further study of ARTA selection could benefit men with metastatic castrate resistant prostate cancer and likely hormone sensitive prostate cancer, especially among patients with comorbid diseases.

Drake BF, Khan S, Hicks V, Nichols K, Taylor M. *Definitive treatment and risk of death among men diagnosed with metastatic prostate cancer at the Veterans Health Administration*. 2023 Mar; Vol 79: 24-31. https://doi.org/10.1016/j.annepidem.2023.01.004.

Abstract:
Background: The majority of men with metastatic prostate cancer are treated with hormone therapy alone. However, definitive treatment (radical prostatectomy or radiation) of the primary tumor may provide a clinical benefit by reducing the tumor burden, potentially improving survival. Here we assess the potential survival benefit associated with receipt of definitive treatment among men diagnosed with metastatic prostate cancer.
Methods: We conducted a retrospective cohort study of men diagnosed with metastatic prostate cancer at the Veterans Health Administration between 1997-2009. Men were identified using two definitions of metastatic prostate cancer: those diagnosed withT4/M1/N1 disease (n=3716) or those diagnosed with T4/M1 disease only (n=2330). The association of definitive treatment and both all-cause and prostate cancer-specific mortality was assessed using Cox Proportional Hazards with adjustment for potential confounders.
Results: Receipt of definitive treatment was associated with a reduced risk of all-cause(Hazard Ratio (HR): 0.36; 95% Confidence Interval (CI): 0.32, 0.41)and prostate cancer-specific mortality (HR: 0.29; 95% CI: 0.25, 0.35) among men diagnosed with T4/M1/N1 metastatic disease. Definitive treatment was similarly associated with a reduced risk of all-cause (HR: 0.46; 95% CI: 0.39, 0.53) and prostate cancer-specific (HR: 0.38; 95% CI: 0.31, 0.47) mortality among men diagnosed with T4/M1 only metastatic disease.
Conclusion: Definitive treatment may improve survival in men diagnosed with metastatic prostate cancer.

Khan S, Chang SH, Seyerle AA, Wang M, Hicks V, Drake BF. Post-diagnostic metformin and statin use and risk of biochemical recurrence in Veterans diagnosed with prostate cancer. Prostate. 2023 Sep;83(12):1150-1157. doi: 10.1002/pros.24557. Epub 2023 May 16.

Abstract:

Objective: To evaluate the impact of post-diagnostic metformin or statin use and duration on risk of biochemical recurrence in a racially-diverse cohort of Veterans.

Methods: The population consisted of men diagnosed with prostate cancer in the Veterans Health Administration and treated with either radical prostatectomy or radiation (Full cohort n = 65,759, Black men n = 18,817, White men n = 46,631, Other = 311). The association between post-diagnostic (1) metformin and (2) statin use with biochemical recurrence was assessed using multivariable, time-varying Cox Proportional Hazard Models for the overall cohort and by race. In a secondary analysis, metformin and statin duration were evaluated.

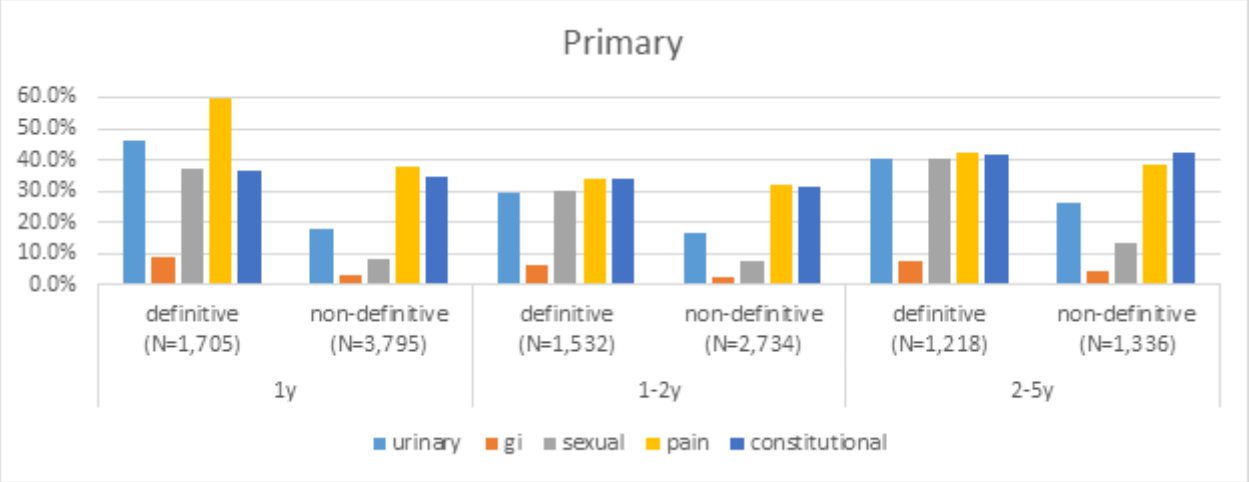
Results: Post-diagnostic metformin use was not associated with biochemical recurrence (multivariable-adjusted hazard ratio [aHR]: 1.01; 95% confidence interval [CI]: 0.94, 1.09), with similar results observed for both Black and White men. However, duration of metformin use was associated with a reduced risk of biochemical recurrence in the cohort overall (HR: 0.94; 95% CI: 0.92, 0.95) as well as both Black and White men. By contrast, statin use was associated with a reduced risk of biochemical recurrence (HR: 0.83; 95% CI: 0.79, 0.88) in the overall cohort as well as both White and Black men. Duration of statin use was also inversely associated with biochemical recurrence in all groups.

Conclusion: Post-diagnostic metformin and statin use have the potential to prevent biochemical recurrence in men diagnosed with prostate cancer.

Drake BF, Khan S, Wang M, Kim E, Chang S, Schoen M. *Quality of Life among Prostate Cancer Patients with Metastatic Disease, Comparing Definitive and non-Definitive treatment.* Under Review.

Men identified from the VACCR as being diagnosed with prostate cancer between the years 1997 and 2013						
		Metastatic Cancer: T4, M1, or N1				
	Non-definitive treatment		**Definitive treatment**		**Total**	
N	3,797		1,705		5,502	
%	69.0		31.0		100.0	
	N	%	N	%		p-value
Age (year)						<.0001
<50	35	0.9	51	3.0		
50-<60	517	13.6	485	28.5		
60-<70	1,137	29.9	837	49.1		
70+	2,108	55.5	332	19.5		
Race						0.7269
White	2,599	68.5	1,179	69.2		
Black	1,090	28.7	476	27.9		
Other	22	0.6	7	0.4		
Unknown	86	2.3	43	2.5		
BMI (kg/m2)						<.0001
<18.5	101	2.7	21	1.2		
18.5-<25	1,262	33.2	447	26.2		
25-<30	1,429	37.6	677	39.7		
30+	1,005	26.5	560	32.8		
Stage						<.0001
Missing	69	1.8	156	9.2		
1	1	0.0	10	0.6		
2	59	1.6	744	43.6		

3	7	0.2	32	1.9		
4	3,661	96.4	763	44.8		
Grade						<.0001
Missing	539	14.2	95	5.6		
1	18	0.5	6	0.4		
2	454	12.0	271	15.9		
3	2,650	69.8	1,292	75.8		
4	136	3.6	41	2.4		
Location						<.0001
Urban	2,767	72.9	1,197	70.2		
Rural	900	23.7	485	28.5		
Unknown	130	3.4	23	1.4		
Academic						0.4338
Academic	1,076	28.3	511	30.0		
Non-academic	775	20.4	333	19.5		
Unknown	1,946	51.3	861	50.5		
Family history of any reportable malignancy						<.0001
Yes	1,068	28.1	640	37.5		
No	1,545	40.7	696	40.8		
Unknown	1,184	31.2	369	21.6		
QOL measure for yr1 - urinary						<.0001
Yes	689	18.2	792	46.5		
No	3,108	81.9	913	53.6		
QOL measure for yr1 - GI						<.0001
Yes	118	3.1	150	8.8		
No	3,679	96.9	1,555	91.2		
QOL measure for yr1 - sexual						<.0001
Yes	308	8.1	629	36.9		
No	3,489	91.9	1,076	63.1		
QOL measure for yr1 - pain						<.0001
Yes	1,443	38.0	1,020	59.8		
No	2,354	62.0	685	40.2		
QOL measure for yr1 - constitutional						0.1187
Yes	1,305	34.4	623	36.5		
No	2,492	65.6	1,082	63.5		
Survived for >= 1 yr after Pca dx						0.3432
Yes	3,795	100.0	1,705	100.0		
No	2	0.1	0	0.0		
Survived for >= 2 yr after Pca dx						<.0001
Yes	2,736	72.1	1,530	89.7		
No	1,061	27.9	175	10.3		
Survived for >= 5 yr after Pca dx						<.0001
Yes	1,336	35.2	1,218	71.4		
No	2,461	64.8	487	28.6		



Time	Primary	Any	urinary	gi	sexual	pain	constitutional
1y	definitive (N=1,705)	78.1%	46.5%	8.8%	36.9%	59.8%	36.5%
	non-definitive (N=3,795)	61.2%	18.2%	3.1%	8.1%	38.0%	34.4%
1-2y	definitive (N=1,532)	67.2%	29.5%	6.5%	29.8%	33.6%	33.9%
	non-definitive (N=2,734)	54.6%	16.6%	2.7%	7.6%	32.0%	31.6%
2-5y	definitive (N=1,218)	75.2%	40.5%	7.8%	40.1%	42.0%	42.0%
	non-definitive (N=1,336)	67.1%	26.0%	4.2%	13.1%	38.6%	42.4%

4. Other achievements: The stated goals for the SOW have been met.
It took a little longer than expected to hire a biostatistician; however, we were able to add Mei Wang to the team who started with experience and access to analyze VA data. Analysis paused in March 2020 when the institution instituted work from home. However, we were able to set up and utilize remote access to the VA server. Response times to data requests remain longer than usual; however, we are able to continue our monthly meetings, contribute data abstraction, data analyses and draft manuscripts.

What opportunities for training and professional development has the project provided?
Through this project we have provided training on data abstraction and coding assistance to other VA cancer investigators conducting research using VAMC clinical data.

How were the results disseminated to communities of interest?
Dr. Drake presented an update of the data analyses from this project to the Epidemiology and Clinical Research group at the VA Medical Center. Dr. Saira Khan presented results from this research at the American Society of Preventive Oncology (ASPO) conference.

What do you plan to do during the next reporting period to accomplish the goals?
This grant has ended. However, we are continuing to meet monthly as a team to collaborate on future research projects.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?
Nothing to report

5. **CHANGES/PROBLEMS:**

Changes in approach and reasons for change
Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Problem: Work from home order to due COVID-19 leads to slower response times and virtual team meetings.
Solution: All of our data requests have been submitted and our team will continue to meet via Zoom, virtually, to keep the project moving forward.

Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals
Nothing to report

Significant changes in use of biohazards and/or select agents
Nothing to report

6. **PRODUCTS:**

Publications, conference papers, and presentations

- **Journal publications.**

Khan S, Chang SH, Hicks V, Wang M, Grub RL, Drake BF. Improved survival with post-diagnostic metformin and statin use in a racially diverse cohort of US Veterans with advanced prostate cancer. Prostate Cancer and Prostatic Diseases. 2021 Nov 22. doi: 10.1038/s41391-021-00475-5. Online ahead of print. PMID: 34811499

Schoen MW, Carson KR, Eisen SA, Bennett CL, Luo S, Reimers MA, Knoche EM, Whitmer AL, Yan Y, Drake, BF, Sanfilippo KM. Survival of veterans' treatment with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases. Prostate Cancer Prostatic Dis. 2022 Sep 14. doi: 10.1038/s41391-022-00588-5. PMID: 36104504.

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Drake BF, Khan S, Wang M, Kim E, Chang S, Schoen M. *Quality of Life among Prostate Cancer Patients with Metastatic Disease, Comparing Definitive and non-Definitive treatment.* Under Review.

- **Books or other non-periodical, one-time publications.**
  Nothing to report

- **Other publications, conference papers, and presentations.**
  Nothing to report

Website(s) or other Internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

Name:	Bettina F. Drake, PhD, MPH
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-9340-5848
Nearest person month worked:	5
Contribution to Project:	Dr. Drake is the lead investigator on this study
Funding Support:	DOD grant
Name:	Su-Hsin Chang, PhD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	0000-0001-5872-9556
Nearest person month worked:	4
Contribution to Project:	Dr. Chang has expertise in treatment effect evaluation and extensive experience using data from the Veterans Health Administration (VHA) to study obesity and cancer.
Funding Support:	DOD grant
Name:	Eric Kim, MD
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Dr. Kim will provide prostate cancer clinical expertise to the study team.
Funding Support:	DOD grant
Name:	Mei Wang, MS
Project Role:	Statistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Ms. Wang will perform all data cleaning and statistical analysis for the project
Funding Support:	DOD grant

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

None

What other organizations were involved as partners?
Nothing to report

8. **SPECIAL REPORTING REQUIREMENTS**
   COLLABORATIVE AWARDS:
   N/A

   QUAD CHARTS:
   N/A

9. **APPENDICES:**
   None