3-1-2023

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Annals of Epidemiology 79 (2023) 24–31

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: sciencedirect.com/journal/annals-of-epidemiology

Original article

# Definitive treatment and risk of death among men diagnosed with metastatic prostate cancer at the Veterans Health Administration

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ARTICLE INFO

*Article history:*
Received 21 July 2022
Revised 29 December 2022
Accepted 5 January 2023
Available online 11 January 2023

*Keywords:*
Prostate cancer
Mortality
Survival
Definitive treatment
Veterans health administration

ABSTRACT

*Purpose:* To assess the potential survival benefit associated with receipt of definitive treatment (radical prostatectomy or radiation), compared to non-definitive treatment (hormonal therapy or chemotherapy) among men with metastatic prostate cancer.

*Methods:* A cohort of men diagnosed with metastatic (T4/M1/N1 or T4/M1) prostate cancer from 1999 to 2013 in the Veterans Health Administration were identified and followed to December 28, 2014. All-cause and prostate cancer-specific mortality were evaluated at 10 years for the T4/M1/N1 cohort and 8 years for the T4/M1/ cohort. The association of definitive treatment (radical prostatectomy or radiation), compared to non-definitive (hormonal therapy or chemotherapy) with both all-cause and prostate cancer-specific mortality was assessed using inverse probability of treatment weighted (IPTW) multivariable survival analyses.

*Results:* The cohort included 2919 with T4/M1/N1 disease and 1479 men with T4/M1 disease. Receipt of definitive treatment was associated with a reduced risk of 10-year all-cause (Hazard Ratio (HR): 0.61; 95% Confidence Interval (CI): 0.57–0.65) and prostate cancer-specific mortality (HR: 0.50; 95% CI: 0.46-0.55) among men diagnosed with T4/M1/N1 met–astatic disease. Definitive treatment was similarly associated with a reduced risk of all-cause (HR: 0.84; 95% CI: 0.77–0.91) and prostate cancer-specific (HR: 0.81; 95% CI: 0.73–0.90) mortality among men diagnosed with T4/M1 only metastatic disease.

*Conclusions:* Definitive treatment may improve survival in men diagnosed with metastatic prostate cancer.



## Introduction

In the U.S., an estimated 34,130 deaths were attributable to prostate cancer (PCa) in 2021 [1]. For men diagnosed with localized or regional disease (stages I-III), the 5-year relative survival rate is nearly 100% [1]. However, men who are diagnosed with metastatic disease (stage IV) only have a 30.6% 5-year relative survival rate [1].

With emerging novel therapeutic strategies, men diagnosed with PCa have more treatment options now than ever before. Broadly, treatment types can be categorized into: (1) definitive therapy including radical prostatectomy (surgery) or radiation, and

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.annepidem.2023.01.004

(2) non-definitive therapy, including chemotherapy or hormonal therapies, such as androgen deprivation therapy (ADT) [2]. Treatment options differ depending on the extent of the disease, patient's risk of recurrence, and patient characteristics such as age, comorbidity, and personal preference [2].

Currently, there is no standard treatment for high risk or newly diagnosed metastatic PCa. The National Comprehensive Cancer Network (NCCN) does provide guidelines for treatment for newly diagnosed high risk and metastatic PCa that include definitive therapies, non-definitive therapies, or a combination of both [3]. The guidelines for patients who are classified as very high risk (clinical stage T3b, primary Gleason pattern 5 or ≥4 cores with Gleason score 8–10) include external beam radiation (EBRT) plus ADT, EBRT plus brachytherapy plus ADT, radical prostatectomy plus pelvic lymph node dissection, or ADT alone in select patients that are not candidates for radical prostatectomy [3]. For men with regional spread of disease (i.e., Any T, N1, M0), the NCCN guidelines recommend EBRT plus ADT or ADT alone [3]. Finally, for men with M1 metastatic PCa, the current guidelines recommend primary therapy with ADT only [3].

Although the majority of men with metastatic PCa are treated with non-definitive therapy alone, there is limited evidence that definitive treatment with either radical prostatectomy or radiation can improve both PCa-specific or all-cause survival among men diagnosed with metastatic PCa [4–15]. To date, the STAMPEDE clinical trial observed that radiation in addition to standard therapy improves failure-free survival, but not all-cause mortality in men with newly diagnosed metastatic PCa [16]. However, this trial is limited to evaluation of radiation and might not be generalizable to men in the U.S., as recruitment was limited to the U.K. and Switzerland [16]. Most observational studies utilize the Surveillance, Epidemiology, and End Results (SEER) [4,6,7,10,15] and the National Cancer Database (NCDB) [13,14]. The remaining evidence comes from small institutional studies [9,12,17], a retrospective case-series [18], and one study utilizing the Munich Cancer Registry [8].

The objective of our study is to assess the potential survival benefit associated with receipt of definitive treatment (radical prostatectomy or radiation), compared to non-definitive treatment (hormonal therapy or chemotherapy) among men diagnosed with metastatic prostate cancer at the Veterans Health Administration (VHA).

## Methods

### *Data sources*

The cohort for this study was retrieved from The Veterans Affairs Central Cancer Registry (VACCR). The VACCR collects and stores data on veterans diagnosed with cancer and receiving treatment at a VHA medical center. These data include patient demographics, cancer identification, stage, grade, and treatment [19]. Additional clinical data, such as prostate-specific antigen (PSA) values and comorbid conditions, were retrieved from the Corporate Data Warehouse (CDW), which stores data entered by medical staff during patient visits.

This study received the approval from the St. Louis VA Medical Center, Washington University in St. Louis, and Department of Defense (DOD) Institutional Review Boards. A waiver of informed consent was received.

### *Study population*

From the VACCR, we identified men that were diagnosed with metastatic PCa between 1999 and 2013 with known clinical severity (i.e., grade and PSA), and utilized two definitions of metastatic disease: a comprehensive definition that included men diagnosed with T4, M1, or N1 PCa and a more restrictive definition of metastatic disease that only included men diagnosed with T4 or M1 disease. This cohort (T4/M1) excludes patients who only had node positivity at the time of diagnosis. The T4/M1/N1 cohort includes all patients with any evidence of disease outside of the prostate at the time of diagnosis. Clinical severity was missing for 42.7% and 52.3% of the T4/M1/N1 and T4/M1 cohorts, respectively. This resulted in 3277 men with T4/M1/N1 disease and 1712 men with T4/M1 disease, with known clinical severity. We then limited our analytic cohort to men with known exposure, outcome, and covariate status. Men that received no PCa treatment were excluded. Our final analytic cohorts consisted of 2919 (T4/M1/N1) and 1479 men (T4/M1), respectively.

### *Outcomes*

Our primary outcomes were all-cause death and PCa-specific death. Death status was determined from VA Vital Status data, which captures approximately 97% of all deaths [20,21]. PCa-specific deaths were identified if the cause of death was recorded as ICD-9 code C61, malignant neoplasm of the prostate. Final death status was determined on December 28, 2014, the last date for which death status was available. Follow-up time began on date of diagnosis and continued until death or censoring.

### *Exposure*

Our primary exposure was receipt of definitive treatment. Definitive treatment was defined as radical prostatectomy (surgery), radiation, surgery with adjuvant radiation, or surgery/radiation with chemotherapy or hormone therapy. Non-definitive treatment was defined as receipt of hormone therapy, chemotherapy, or a combination of hormone therapy and chemotherapy

### *Covariates*

Model covariates included: years from PCa diagnosis to first treatment (≤median, >median), grade (1, 2, 3, and 4), age at diagnosis (<50, ≥50-<60, ≥60-<70, and ≥70), race (White, African American, and Other), PSA at diagnosis (0–20, >20), location (urban, rural) and Charlson comorbidity index without malignancy at diagnosis**.**

### *Statistical analysis*

Inverse probability of treatment weighted (IPTW) survival analyses were utilized to reduce the bias resulting from the assignment of definitive treatment [22,23]. Generalized boosted regression was used to model a patient's likelihood of receiving definitive or non-definitive treatment [24] with model covariates. We used Kolmogorov-Smirnov statistics to assess covariates balances until all of the covariates were balanced [25]. Using the estimated model, we obtained the propensity scores for definitive treatment status, which were then used to compute the weights for the IPTW-adjusted survival analyses [26].

Survival (all-cause and PCa-specific) by definitive treatment status was compared using IPTW-adjusted Kaplan-Meir plots and the log-rank test. For all survival models follow-up began at time of first treatment. Since the covariates used in generalized boosted model can influence both treatment assignment and outcomes, we included the same covariates in our IPTW-adjusted time-to-event models [27]. Proportionality was assessed by examining the IPTW-adjusted Kaplan-Meir plots for violations of the proportional hazards assumption. To account for non-proportionality in survival analysis, we used a step function for the time-dependent covariate

and determined the change point that yielded the largest log partial likelihood [28]. All survival analyses were limited to ≤10 years due to sparse data after 10 years. For the T4/M1 analytic cohort, there was a violation of the proportional hazards assumption at 8 years. To account for this, results were stratified by ≤8 years versus >8∼10 years for both all-cause and PCa-specific survival. Number of patients censored and 8 and 10 years is available in supplementary material. In a sensitivity analysis, we repeated the analysis, and stratified by race.

All tests were two-sided. Statistical significance was evaluated at $\alpha = 0.05$ level. All statistical analyses were performed using SAS statistical software version 9.4 and R version 3.6.0 (R Core Team, 2019).

## Results

### *Characteristics of study population*

#### *T4/M1/N1*

Among men identified as metastatic using our comprehensive definition, there were a median of 55 days (mean: 212.4 days) from diagnosis to treatment (Table 1). The majority of men were diagnosed with Grade 3 (88.8%) cancer and were older than 60 years of age at time of diagnosis (78.8%). White men made up the majority of cohort (71.3%) followed by African American men (27.9%). Just over half the cohort was diagnosed with a PSA ≥20 (54.4%). Most men resided in an urban area at time of diagnosis (74.2%). 34.1% of the men received definitive treatment.

Among the men that received definitive treatment, surgery was most prevalent treatment type (64.8%), followed by radiation (43.7%), with 8% of men receiving both surgery and radiation. Among men that received non-definitive treatment, hormone therapy was by far the predominant treatment type (99.7%); the remaining 0.3% of men received either chemotherapy or chemotherapy with hormone therapy. Men that received definitive treatment had a significantly shorter time from diagnosis to treatment, were younger at age of diagnosis, had a lower PSA at diagnosis, a lower Charlson Comorbidity score, and were less likely to die over follow-up as compared to men that received non-definitive treatment.

#### *T4/M1*

Overall, demographic characteristics were similar among the cohort of men identified as metastatic using our more restrictive definition of metastatic disease. However, this more restrictively defined cohort was more likely to receive definitive treatment (34.1%) as compared to the T4/M1/N1 cohort (16.2%). Men that received definitive treatment were significantly younger at diagnosis, had a lower PSA, a lower Charlson Comorbidity score, and were less likely to die over follow-up as compared to men that received non-definitive treatment.

### *Definitive treatment and mortality*

#### *T4/M1/N1*

During follow-up there were 1909 deaths from any-cause, 1281 (67.1%) of these deaths were attributable to PCa. IPTW-adjusted Kaplan-Meier plots for all-cause and PCa-specific mortality by receipt of definitive treatment (Fig. 1) indicated that receipt of definitive treatment was associated with a significantly longer all-cause mortality-free survival: median survival 5.83 years for the definitive treatment group versus 3.69 years for the non-definitive treatment group (log-rank test *P*-value: <.0001) and PCa-specific mortality-free survival: median survival 8.78 years for the definitive treatment group versus 4.72 years for the non-definitive treatment group (log-rank test *P*-value: <.0001).

IPTW-adjusted multivariable time-to-event analysis results show that receipt of definitive treatment was associated with a decreased risk of all-cause mortality (HR: 0.61; 95% CI: 0.57–0.65) up to 10 years after diagnosis (Table 2). Our results suggest that after 10 years post-diagnosis the survival benefit of definitive treatment diminishes. Receipt of definitive treatment was also associated with a significantly reduced risk of PCa-specific mortality (HR: 0.50; 95% CI: 0.46–0.55) up to 10-year post diagnosis, with no survival benefit observed after 10 years.

#### *T4/M1*

During follow-up there were 1170 death from any-cause, 809 (69.1%) of these deaths were attributable to PCa. IPTW-adjusted Kaplan-Meier plots for all-cause and PCa-specific mortality by definitive treatment status (Fig. 2) indicated that receipt of definitive treatment was associated with a significantly longer all-cause mortality-free survival: median survival 3.86 years for the definitive treatment group versus 3.23 years for the non-definitive treatment group (log-rank test *P*-value: <.0001) and PCa-specific mortality-free survival: median survival 4.62 years for the definitive treatment group versus 4.28 years for the non-definitive treatment group (log-rank test *P*-value: <.0001).

IPTW-adjusted multivariable time-to-event analysis results for the more restrictive cohort (T4/M1) were consistent with the larger T4/M1/N1 cohort, but somewhat attenuated. Receipt of definitive treatment was associated with a decreased risk of all-cause mortality (HR: 0.84; 95% CI: 0.77–0.91) up to 8 years after diagnosis. Our findings suggest that 8–10 years after diagnosis, the survival benefit of definitive treatment diminishes. Definitive treatment was similarly associated with a significantly reduced risk of PCa-specific mortality (HR: 0.81; 95% CI: 0.73–0.90) up to 8 years after diagnosis, after which there was no survival benefit.

### *Race-stratification*

In a sensitivity analysis, where we stratified by race, we observed a similar survival benefit for both all-cause and PCa-specific mortality in the T4/M1/N1 cohort for both Black and White men (Supplemental Material). No significant associations were observed for either Black or White men in the T4/M1 cohort.

## Discussion

In this large, national study of U.S. Veterans diagnosed with the metastatic PCa, we observed that definitive treatment with either radical prostatectomy and/or radiation was associated with a significantly lower risk of both all-cause and PCa-specific mortality. To our knowledge, this is the first study to examine the association between the receipt of definitive treatment and survival among men diagnosed with metastatic PCa within the VHA.

Our findings are consistent with the previous findings of definitive treatment among men diagnosed with metastatic PCa, including two meta-analyses [29,30] Most of this prior evidence comes from studies that utilized either SEER or the NCDB databases [4,6,7,10,11,13–15]. Specifically, a meta-analysis of five studies by Carneiro et al. indicated that receipt of local treatment (i.e., radical prostatectomy and/or radiation) was associated with a significantly longer overall survival (Risk Difference (RD): 0.19; 95% CI: 0.17–0.21) [29] and cancer-specific survival (two studies), (RD: 0.16; 95% CI: 0.16–0.29) [29]. The second meta-analysis of nine studies by Wang et al. was more consistent with our analytic approach using hazard ratios instead of risk differences; however, it chiefly examined radical prostatectomy as the primary definitive treatment type [30]. Similarly, this study reported that radical prostatectomy (vs. non-local therapy) was associated with a reduced risk of all-cause (HR: 0.49; 95% CI: 0.44–0.46) and cancer-specific (HR: 0.36;

**Table 1**
Patients characteristics of men diagnosed with metastatic* prostate cancer at the Veterans Health Administration between 1999 and 2013, by receipt of definitive prostate cancer treatment.

| | Metastatic Cancer: T4, M1, or N1 | | | | Metastatic Cancer: T4 or M1 | | | |
|---|---|---|---|---|---|---|---|---|
| | Cohort | Non-definitive Treatment † | Definitive Treatment ‡ | | Cohort | Non-definitive Treatment † | Definitive Treatment ‡ | |
| | N = 2919<br>N (%) | N = 1925<br>N (%) | N = 994<br>N (%) | *P*-value § | N = 1479<br>N (%) | N = 1240<br>N (%) | N = 239<br>N (%) | *P*-value § |
| **Days from diagnosis to first treatment**, | | | | <.0001 | | | | .0604 |
| <= Median | 1461 (50.05) | 1024 (53.19) | 437 (43.96) | | 747 (50.51) | 613 (49.44) | 134 (56.07) | |
| > Median | 1458 (49.95) | 901 (46.81) | 557 (56.04) | | 732 (49.49) | 627 (50.56) | 105 (43.93) | |
| **Grade** | | | | .0097 | | | | .4068 |
| 1 | 7 (0.24) | 6 (0.31) | 1 (0.10) | | 6 (0.41) | 6 (0.48) | 0 (0) | |
| 2 | 214 (7.33) | 153 (7.95) | 61 (6.14) | | 130 (8.79) | 109 (8.79) | 21 (8.79) | |
| 3 | 2592 (88.80) | 1684 (87.48) | 908 (91.35) | | 1276 (86.27) | 1065 (85.89) | 211 (88.29) | |
| 4 | 106 (3.63) | 82 (4.26) | 24 (2.41) | | 67 (4.53) | 60 (4.84) | 7 (2.93) | |
| **Age** | | | | <.0001 | | | | <.0001 |
| <50 | 48 (1.64) | 19 (0.99) | 29 (2.92) | | 16 (1.08) | 9 (0.73) | 7 (2.93) | |
| ≥50- <60 | 570 (19.53) | 294 (15.27) | 276 (27.77) | | 228 (15.42) | 171 (13.79) | 57 (23.85) | |
| ≥60-<70 | 1203 (41.21) | 678 (35.22) | 525 (52.82) | | 522 (35.29) | 413 (33.31) | 109 (45.61) | |
| ≥70 | 1098 (37.62) | 934 (48.52) | 164 (16.50) | | 713 (48.21) | 647 (52.18) | 66 (27.62) | |
| **Race** | | | | .2187 | | | | .714 |
| White | 2082 (71.33) | 1354 (70.34) | 728 (73.24) | | 1032 (69.78) | 860 (69.35) | 172 (71.97) | |
| Black | 814 (27.89) | 554 (28.78) | 260 (26.16) | | 435(29.41) | 370 (29.84) | 65 (27.20) | |
| Other | 23 (0.79) | 17 (0.88) | 6 (0.60) | | 12 (0.81) | 10 (0.81) | 2 (0.84) | |
| **PSA** | | | | <.0001 | | | | <.0001 |
| 0-<20 | 1332 (45.63) | 635 (32.99) | 697 (70.12) | | 532 (35.97) | 398 (32.10) | 134 (56.07) | |
| ≥20 | 1587 (54.37) | 1290 (67.01) | 297 (29.88) | | 947 (64.03) | 842 (67.90) | 105 (43.93) | |
| **Location** | | | | .0017 | | | | .2983 |
| Urban | 2165 (74.17) | 1463 (76.00) | 702 (70.62) | | 1110 (75.05) | 937 (75.56) | 173 (72.38) | |
| Rural | 754 (25.83) | 462 (24.00) | 292 (29.38) | | 369 (24.95) | 303 (24.44) | 66 (27.62) | |
| **Definitive Treatment Type** | | | | | | | | |
| Surgery ‖ | – | 0 | 644 (64.79) | – | – | 0 | 95 (39.75) | – |
| Radiation ¶ | – | 0 | 415 (41.75) | | – | 0 | 190 (79.50) | |
| **Pca-Death (censored at 10 yr)** | | | | <.0001 | | | | .0033 |
| Yes | 1281 (43.88) | 1041 (54.08) | 240 (24.14) | | 809 (54.70) | 699 (59.37) | 110 (46.03) | |
| No | 1638 (56.12) | 884 (45.92) | 754 (75.86) | | 670 (45.30) | 541 (43.63) | 129 (53.97) | |
| **All death (censored at 10 yr)** | | | | <.0001 | | | | <.0001 |
| Yes | 1909 (65.40) | 1500 (77.92) | 409 (41.15) | | 1170 (79.11) | 1013 (81.69) | 157 (65.69) | |
| No | 1010 (34.60) | 425 (22.08) | 585 (58.85) | | 309 (20.89) | 227 (18.31) | 81 (34.31) | |
| **Charlson comorbidity index** | 1.39 (1.71) | 1.55 (1.82) | 1.09 (1.44) | <.0001 | 1.50 (1.77) | 1.56 (1.79) | 1.22 (1.63) | .0077 |

* Metastatic cancer was defined in two ways: (1) Men diagnosed with T4, M1, or N1 prostate cancer or (2) men diagnosed with T4 or M1 prostate cancer.
† Non-definitive treatment was defined as receipt of any other therapy other than surgery (radical prostatectomy or radiation).
‡ Definitive treatment is defined as receipt of surgery (radical prostatectomy) or radiation, either alone or adjuvantly with other therapies.
§ *P*-value determined using chi-square test for categorical variables and *t*-test for continuous variables.
‖ receipt of surgery (radical prostatectomy), either alone or adjuvantly with other therapies; percentages sum to over 100% as some men received both radiation and surgery.
¶ receipt of radiation, either alone or adjuvantly with other therapies; percentages sum to over 100% as some men received both radiation and surgery.

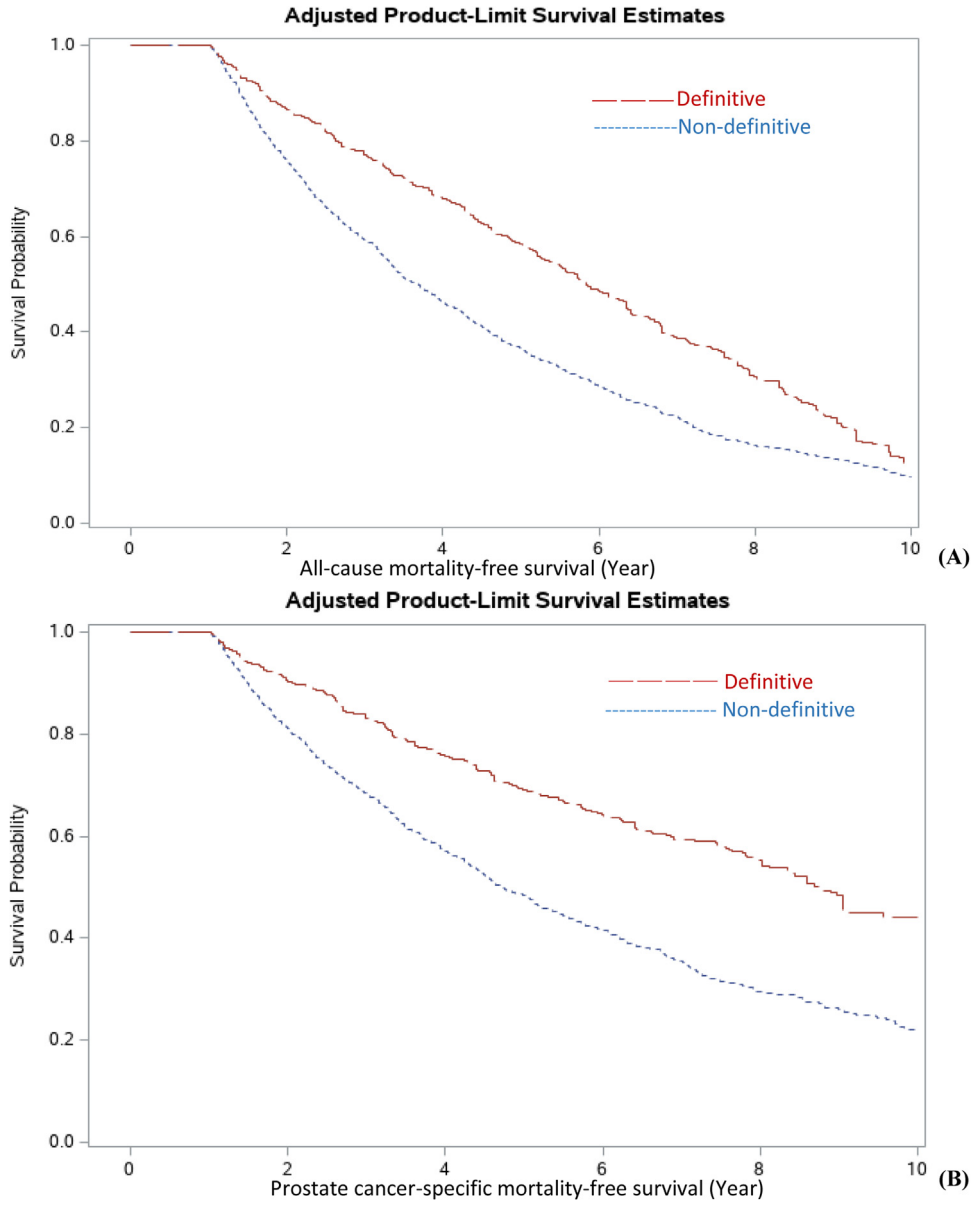


**Fig. 1.** Kaplan Meir survival plots by receipt of definitive treatment for (A) all-cause mortality-free survival and (B) prostate cancer-specific mortality-free survival in men diagnosed with T4/M1/N1 prostate cancer.

**Table 2**
Inverse probability of definitive treatment weighted survival analyses: overall mortality and prostate cancer-specific mortality among men diagnosed with metastatic prostate cancer at the Veterans Health Administration between 1999 and 2013.

| Outcome | Follow-up | Definitive vs. Non-Definitive HR (95% CI) |
|---|---|---|
| | | **T4M1N1 (n = 2919)** |
| All-cause mortality | **≤10 years** | 0.61 (0.57, 0.65) |
| Pca-specific mortality | **≤10 years** | 0.50 (0.46, 0.55) |
| | | **T4M1 (n = 1479)** |
| All-cause mortality | **≤8 years** | 0.84 (0.77, 0.91) |
| | **>8~10 years** | 3.33 (2.19, 5.05) |
| Pca-specific mortality | **≤8 years** | 0.81 (0.73, 0.90) |
| | **>8~10 years** | 3.05 (1.73, 5.35) |

Inverse probability of treatment weighted survival analyses adjusting for years from prostate cancer diagnosis to first treatment (<= median and > median), Grade (1,2,3,4), age at diagnosis (<50, ≥50-<60, ≥60-<70, ≥70), race (White, Black, Other), PSA at diagnosis (0–20, >20), and location (urban, rural) and comorbidity index without malignancy.

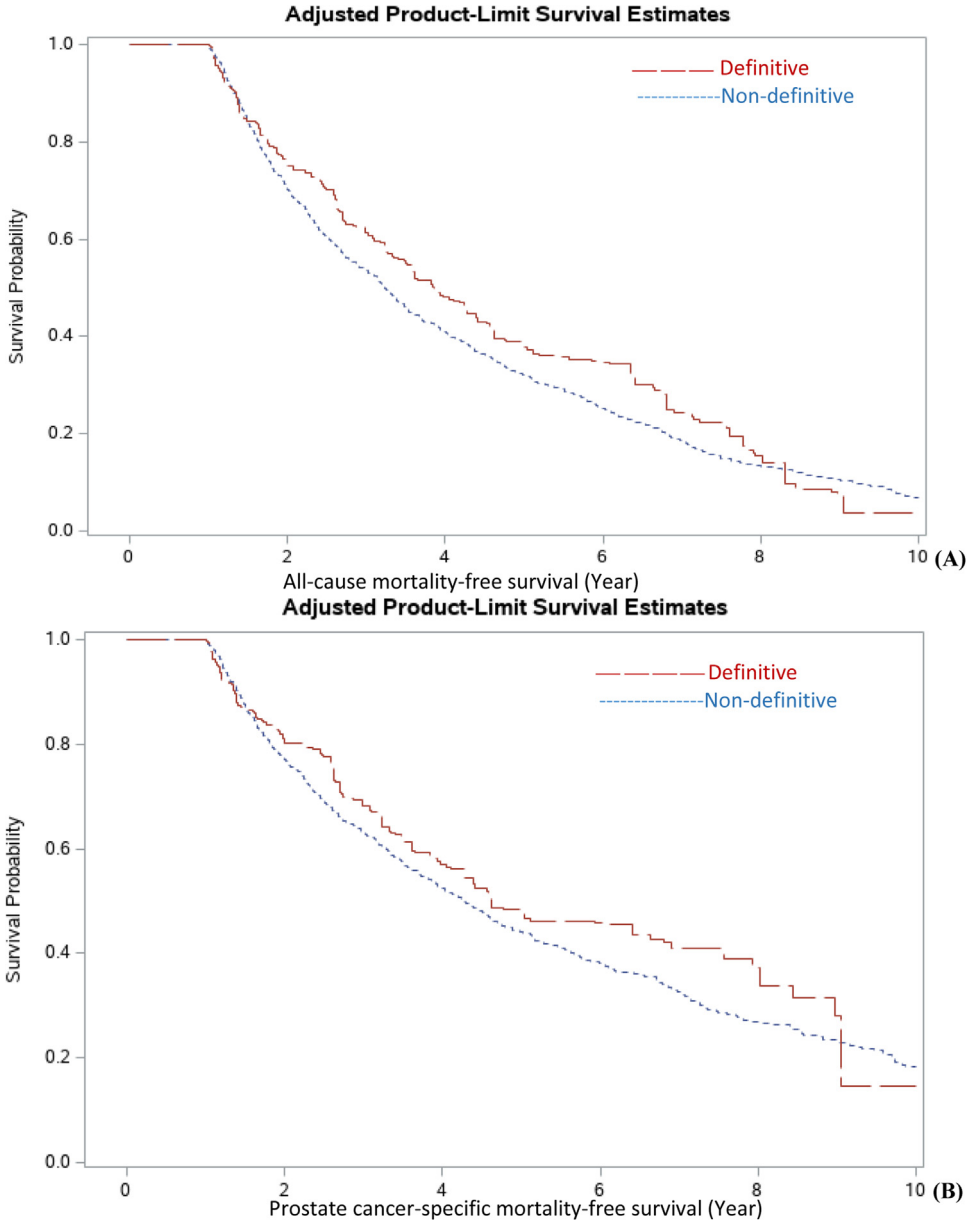


**Fig. 2.** Kaplan Meir survival plots by receipt of definitive treatment for (A) all-cause mortality-free survival and (B) prostate cancer-specific mortality-free survival in men diagnosed with T4/M1 prostate cancer.

0.30–0.43) mortality [30]. Our study builds on these previous findings in a large, ethnically-diverse, national cohort of men treated at the VHA.

These observational findings are supported by biological evidence. Radical prostatectomy reduces the primary tumor burden, as even aggressive systematic therapy with ADT and/or chemotherapy insufficiently treats the primary tumor [31]. Removal of the primary tumor can potentially interrupt Src signaling, eliminate the "source" for other metastases, and reduce chemokines [31]. Specifically, Src signaling is associated with tumor proliferation, angiogenesis, and invasion; thus removal of the primary tumor can interrupt Src signaling and subsequent disease progression [31]. In addition, the primary tumor may also serve as a source of metastatic cells throughout the body ("self-seeding"), and thus removal of the primary tumor is hypothesized to prevent new metastases [31,32]. Finally, the primary tumor can produce chemokines that can direct tumor cells to specific organ sites, and therefore removing the primary tumor can inhibit the trafficking of circulating tumor cells [31]. Prostate directed radiation therapy is hypothesized to work through similar biological mechanisms [32,33]. Radiation also reduces and potentially eliminates primary tumor burden. Additionally, there is some evidence that radiation can also have an "abscopal effect" [33]. The abscopal effect is a radiation-induced immunological response that results in a regression of distant disease after local treatment of the primary tumor with radiation, primarily through activation of antitumor cellular immunity [33].

Despite this evidence, in both our study and nationally, ADT monotherapy remains the primary treatment type for men with metastatic PCa [34]. In our study, the vast majority of men (T4/M1/N1: 64.4%; T4/M1: 81.7%) diagnosed with PCa received ADT only. Moving forward, appropriately identifying the men that could most benefit from definitive treatment after a diagnosis of metastatic disease is of vital importance. In our study, we observed that men that received definitive treatment were, on average, younger, had a lower PSA at diagnosis, and, had a lower

Charlson Comorbidity score. This observation is consistent with Parikh et al., where younger patients with less aggressive tumor characteristics were more likely to receive definitive treatment in the context of metastatic disease [13]. A SEER-based study suggested that among men with metastatic PCa, only those with a *predicted* cancer-specific mortality risk (based on tumor characteristics) less than 40% experience a survival benefit with receipt of definitive treatment [7]. Correctly identifying the men that could most benefit from definitive treatment could enhance survival among men metastatic disease and could potentially also help reduce the disparities characteristic of PCa [1].

Our study demonstrates that 35.0% of White men received definitive treatment compared to 31.9% of African American men in the T4/M1/N1 cohort. However, this potential disparity is likely minimized in our study population as all men have equivalent access to care through the VA health system. Indeed, previous research has indicated that receipt of definitive treatment among men with metastatic disease is associated with higher incomes, private insurance, Medicare, and treatment at a comprehensive or an academic medical center [13]. Thus, it is possible that in other populations there is a greater disparity in receipt of definitive treatment associated with race. Lack of definitive treatment for African American men with advanced PCa has the potential to exacerbate existing disparities, particularly considering that African American men are more likely to present with aggressive disease and should thus be considered for multimodality treatment.

Currently, specific recommendations regarding definitive treatment in men diagnosed with metastatic PCa are lacking. Although our study and others suggest a survival benefit for definitive treatment for metastatic PCa, clear guidelines do not exist, especially for men with M1 disease. Clearer guidelines could help ensure that all men with metastatic disease are at least considered for definitive treatment, especially given the low survival rates for metastatic PCa and disparities in survival across races [1]. Ongoing clinical trials (NCT03678025, NCT02454543, and NCT01751438) that are examining standard-of-care systematic therapy with or without definitive treatment in men with metastatic PCa are necessary next steps in establishing clearer guidelines [35–37].

Our study is limited by the lack of randomization of treatment assignment. As such, receipt of definitive treatment was based on individual and clinician choice. Many factors contribute to treatment choice, and it likely that healthier, more compliant patients were more likely to receive definitive treatment. We are unable to account for all the factors that may have contributed to receipt of definitive treatment. This could have resulted in a selection bias where clinicians selectively offered definitive treatment to “healthier” patients. This could have biased our results if the survival benefit observed in these patients was not due to definitive therapy, but rather due to a selection of healthier patients to receive such treatment. However, with additional adjustment for frailty, we still observed a survival benefit associated with definitive treatment (data not shown). Nonetheless, it is possible that the observed benefit of definitive treatment is at least partially attributable to selection bias. It is also important to note that newer types of ADT have been introduced since the start of our study and we do not have information on modality of radical prostatectomy (i.e., robotic or laparoscopic), both of which could have impacted survival outcomes. Finally, our study may only be generalizable to male Veterans rather than all U.S. males.

Despite these limitations, our study had several strengths. To our knowledge, this is the first study to examine the receipt of definitive treatment in men with metastatic PCa in a large, nationally representative, ethnically-diverse, cohort of U.S. Veterans. Our study includes *all* men diagnosed with metastatic PCa at *any* VA hospital across the U.S., over a 14-year period between 1999 and 2013. Our cohort is ethnically diverse, with approximately 30% of the cohort consisting of African American men. Finally, because the VHA provides care regardless of insurance status or ability to pay, our study is able to control for healthcare access. This is in contrast to the previously published literature, where receipt of definitive treatment may have been influenced by socioeconomic factors such as income or insurance status.

## Conclusion

Receipt of definitive treatment in men with metastatic PCa is associated with reduced mortality. Clinicians and patients should carefully consider definitive treatment as a part of their multimodality approach to metastatic disease. In addition to ongoing clinical trials, future studies among men with metastatic PCa are needed to examine the impact of definitive treatment on the quality of life metrics and patient-reported outcomes.

## Author contributions

**BFD:** conceptualization, funding acquisition, writing-reviewing and editing; **SK:** data curation, data-interpretation, writing-original draft; **MW:** formal analysis, project administration, writing-review and editing; **VH:** data curation, formal analysis, writing-review and editing; **KN:** project administration, writing-original draft; **MT:** project administration, writing-original draft; **EHK:** clinical expertise, data-interpretation, writing-review and editing; **S-HC:** methodology, data-interpretation, writing-review and editing

## Acknowledgments

BFD, S-HC, MW, and EHK are supported by the Department of Defense (DOD) grants W81XWH-19–1–0214 and W81XWH-14–1–0503. SK was supported by the DOD grant W81XWH-18–1–0168 (PC170130). BFD and S-HC are supported by the Foundation of Barnes-Jewish Hospital and Siteman Cancer Center.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2023.01.004.

## References

[1] Surveillance epiedmiology, and end results program (SEER). Cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html. Accessed February 28, 2019.
[2] American Society of Clinical Oncology. Treatment: prostate cancer. https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Accessed February 28, 2019.
[3] Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate cancer, version 1.2016. J Natl Compr Canc Netw 2016;14(1):19–30.
[4] Antwi S, Everson TM. Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. Cancer Epidemiol 2014;38(4):435–41. doi:10.1016/j.canep.2014.1004.1002.
[5] Cho Y, Chang JS, Rha KH, et al. Does radiotherapy for the primary tumor benefit prostate cancer patients with distant metastasis at initial diagnosis? PLoS ONE 2016;11(1):e0147191 eCollection 0142016. doi:10.0141371/journal.pone.0147191.
[6] Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? a SEER-based study. Eur Urol 2014;65(6):1058–66 Epub 2013 Nov 1020. doi:10.1016/j.eururo.2013.1011.1012.
[7] Fossati N, Trinh QD, Sammon J, et al. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. Eur Urol 2015;67(1):3–6 Epub 2014 Sep 1010. doi:10.1016/j.eururo.2014.1008.1056.
[8] Gratzke C, Engel J, Stief CG. Role of radical prostatectomy in metastatic prostate cancer: data from the munich cancer registry. Eur Urol 2014;66(3):602–3 Epub 2014 May 1010. doi:10.1016/j.eururo.2014.1004.1009.

[9] Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 2015;193(3):832–8 Epub 2014 Sep 1022. doi:10.1016/j.juro.2014.1009.1089.
[10] Leyh-Bannurah SR, Gazdovich S, Budaus L, et al. Local therapy improves survival in metastatic prostate cancer. Eur Urol 2017;72(1):118–24 Epub 2017 Apr 1013. doi:10.1016/j.eururo.2017.1003.1020.
[11] Loppenberg B, Dalela D, Karabon P, et al. The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis. Eur Urol 2017;72(1):14–19 Epub 2016 May 1019. doi:10.1016/j.eururo.2016.1004.1031.
[12] Moschini M, Morlacco A, Kwon E, Rangel LJ, Karnes RJ. Treatment of M1a/M1b prostate cancer with or without radical prostatectomy at diagnosis. Prostate Cancer Prostatic Dis. 2017;20(1):117–21 Epub 2017 Jan 1033. doi:10.1038/pcan.2016.1063.
[13] Parikh RR, Byun J, Goyal S, Kim IY. Local therapy improves overall survival in patients with newly diagnosed metastatic prostate cancer. Prostate 2017;77(6):559–72 Epub 22017 Jan 23217. doi:10.1002/pros.23294.
[14] Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. J Clin Oncol 2016;34(24):2835–42 Epub 2016 Jun 2820. doi:10.1200/JCO.2016.2867.4788.
[15] Satkunasivam R, Kim AE, Desai M, et al. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-Medicare analysis. J Urol 2015;194(2):378–85 Epub 2015 Feb 1021. doi:10.1016/j.juro.2015.1002.1084.
[16] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet North Am Ed 2018;392(10162):2353–66.
[17] Gandaglia G, Fossati N, Stabile A, et al. Radical prostatectomy in men with oligometastatic prostate cancer: results of a single-institution series with long-term follow-up. Eur Urol 2017;72(2):289–92.
[18] Sooriakumaran P, Karnes J, Stief C, et al. A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical prostatectomy for distant metastatic prostate cancer at presentation. Eur Urol 2016;69(5):788–94.
[19] Department of Veterans Affairs. Veterans Affairs Central Cancer Registry (VACCR). https://catalog.data.gov/dataset/veterans-administration-central-cancer-registry-vaccr. Accessed December 20 2018,.
[20] Savas LS, del Junco DJ, Bastian LA, Vernon SW. Mortality ascertainment of women veterans: a comparison of sources of vital status information, 1979-2002. Med Care 2009;47(1):125–8. doi:10.1097/MLR.1090b1013e3181809125.
[21] Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the department of veterans affairs. Popul Health Metr 2006;4(2). doi:10.1186/1478-7954-1184-1182.
[22] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
[23] Imbens GW. The role of the propensity score in estimating dose-response functions. Biometrika 2000;87(3):706–10.
[24] McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods 2004;9(4):403.
[25] Ridgeway G, McCaffrey D, Morral A, Burgette L, Griffin BA. Toolkit for weighting and analysis of nonequivalent groups: a tutorial for the twang package. Santa Monica, CA: RAND Corporation; 2017.
[26] Xie J, Liu C. Adjusted kaplan–meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med 2005;24(20):3089–110.
[27] Karwa V, Slavković AB, Donnell ET. Causal inference in transportation safety studies: comparison of potential outcomes and causal diagrams. Ann Appl Stat 2011:1428–55.
[28] Klein JP, Moeschberger ML. *Survival analysis: techniques for censored and truncated data.* vol 1230. New York: Springer; 2003.
[29] Carneiro A, Baccaglini W, Glina FPA, et al. Impact of local treatment on overall survival of patients with metastatic prostate cancer: systematic review and meta-analysis. Int Braz J Urol 2017;43(4):588–99. doi:10.1590/S1677-5538.IBJU.2016.0483.
[30] Wang Y, Qin Z, Wang Y, et al. The role of radical prostatectomy for the treatment of metastatic prostate cancer: a systematic review and meta-analysis. Biosci Rep 2018;38(1). doi:10.20171042/BSR20171379.
[31] Metcalfe MJ, Smaldone MC, Lin DW, Aparicio AM, Chapin BF. Role of radical prostatectomy in metastatic prostate cancer: a review. Urol Oncol 2017;35(4):125–34 Epub 2017 Feb 1019. doi:10.1016/j.urolonc.2017.1001.1001.
[32] Blanchard P, Bossi A, Fizazi K. Radiation therapy to the primary in metastatic prostate cancer: palliation only or altering tumor biology? Curr Opin Urol 2017;27(6):580–6. doi:10.1097/MOU.0000000000000444.
[33] Arcangeli S, Zilli T, De Bari B, Alongi F. Hit the primary": a paradigm shift in the treatment of metastatic prostate cancer? Crit Rev Oncol Hematol 2016;97:231–7 Epub 2015 Aug 1029. doi:10.1016/j.critrevonc.2015.1008.1023.
[34] Litwin MS, Tan HJ. The diagnosis and treatment of prostate cancer: a review. JAMA 2017;317(24):2532–42. doi:10.1001/jama.2017.7248.
[35] Standard systematic therapy with of without definitive treatment in treating participants with metastatic prostate cance https://clinicaltrials.gov/ct2/show/study/NCT03678025?show_desc=Y#desc. Accessed March 25, 2019.
[36] Impact of radical prostatectomy as primary treatment in patients with prostate cancer with limited bone metastases (g-RAMPP). https://clinicaltrials.gov/ct2/show/NCT02454543. Accessed October 8 2021,.
[37] Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery). Best systemic therapy or best systemic therapy (BST) plus definitive treatment (Radiation or surgery). https://clinicaltrials.gov/ct2/show/NCT01751438. Accessed October 8 2021,.