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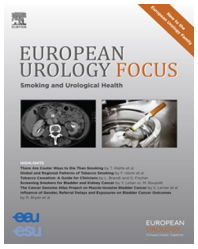

Prostate Cancer

In Men with Castration-Resistant Prostate Cancer, Visceral Metastases Predict Shorter Overall Survival: What Predicts Visceral Metastases? Results from the SEARCH Database

Colette A. Whitney [a], *Lauren E. Howard* [a,b], *Edwin M. Posadas* [c], *Christopher L. Amling* [d], *William J. Aronson* [e,f], *Matthew R. Cooperberg* [g], *Christopher J. Kane* [h], *Martha K. Terris* [i], *Stephen J. Freedland* [a,j,*]

[a] *Urology Section, Veterans Affairs Medical Center, Durham, NC, USA;* [b] *Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC, USA;* [c] *Cedars-Sinai Medical Center, Division of Hematology/Oncology, Los Angeles, CA, USA;* [d] *Division of Urology, Department of Surgery, Oregon Health & Science University, Portland, OR, USA;* [e] *Urology Section, Department of Surgery, Veterans Affairs Medical Center, Greater Los Angeles, Los Angeles, CA, USA;* [f] *Department of Urology, University of California at Los Angeles Medical Center, Los Angeles, CA, USA;* [g] *Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA;* [h] *Division of Urology, Department of Surgery, University of California at San Diego Medical Center, San Diego, CA, USA;* [i] *Urology Section, Division of Surgery, Veterans Affairs Medical Center and Division of Urologic Surgery, Department of Surgery, Medical College of Georgia, Augusta, GA, USA;* [j] *Department of Surgery, Division of Urology and Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA*

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Abstract

Background: Although visceral metastases (VMs) are widely recognized to portend worse prognoses compared with bone and lymph metastases in men with metastatic castration-resistant prostate cancer (mCRPC), little is known about what predicts VMs and the extent to which men with VMs do worse.
Objective: To determine whether men with VMs at initial mCRPC diagnosis have worse overall survival (OS) and identify predictors of VMs.
Design, setting, and participants: We analyzed 494 men diagnosed with castration-resistant prostate cancer post-1999 and no known metastases from five Veterans Affairs hospitals of the Shared Equal Access Regional Cancer Hospital (SEARCH) database who later developed metastases. Radiology scans within 30 d of initial metastasis diagnosis were reviewed to collect information on bone, visceral, and lymph node metastases. We analyzed the 236 men who had a computed tomography scan performed.
Outcome measurements and statistical analysis: Predictors of VMs and OS were evaluated using logistic regression and Cox models, respectively.
Results and limitations: Of the 236 mCRPC patients, 38 (16%) had VMs. Regarding VMs, 19 patients (50%), 8 patients (21%), and 16 patients (42%) had metastases in the liver, lungs, and other locations, respectively. VMs were a predictor of OS on crude analysis (hazard ratio [HR]: 1.88; 95% confidence interval [CI], 1.30–2.72; $p = 0.001$) and after risk adjustment (HR: 1.84; 95% CI, 1.24–2.72; $p = 0.002$). Age, year, treatment center, prostate-specific antigen (PSA), and time from CRPC to metastases were significant in predicting OS (all $p < 0.05$). None of the variables tested were associated with having VMs (all $p > 0.09$). Prospective studies and larger cohorts are needed to validate our findings.
Conclusions: Demographic, tumor, and PSA kinetic characteristics were not predictive of having VMs, but VMs predicted worse OS.
Patient summary: Because patients with VMs have worse overall survival, further research is needed to develop better biomarkers and thus diagnose those with VMs at earlier stages in their disease course.

* Corresponding author. Division of Urology, Department of Surgery, Cedars-Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048, USA. Tel. +1 310 423 3497; Fax: +1 310 4234711.
E-mail address: stephen.freedland@cshs.org (S.J. Freedland).

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1. Introduction

When prostate cancer (PCa) becomes metastatic, it has a strong predilection for the bone. However, metastases to other sites can occur including lymph nodes and visceral metastases (VMs). Historically, these other sites were often combined under the category soft tissue metastases. More recently, there has been increasing recognition that VMs, commonly including liver and lung metastases, are a poor prognostic sign conveying a different prognosis than lymph node–only involvement [1–3]. As a result, the Prostate Cancer Working Group 2 (PCWG2) recommendations now state that baseline characteristics and posttreatment outcomes should be reported separately for those with lymph node metastases versus VMs [4].

Despite the general acceptance that VMs are a poor prognostic sign, two key questions remain. First, what is the prognosis for men with VMs at the time of initial diagnosis of metastatic castration-resistant prostate cancer (mCRPC)? Many of the studies showing that men with VMs have poor outcomes looked at men with either hormone-naive metastases [1] or more advanced mCRPC (ie, those starting chemotherapy or progressing postchemotherapy) [3,5,6]. Thus the impact of VMs at the time of initial diagnosis of mCRPC is unclear. Second, what predicts the development of VMs? Currently, there are no known prognostic factors for the diagnosis of VMs. For instance, they can develop in the absence of prostate-specific antigen (PSA) progression [7]. Thus identifying men at greatest risk of VMs remains challenging.

To address these gaps in the literature, we studied men with CRPC and no known metastases (M0/Mx) who later developed metastases to determine which factors predicted having VMs at the time of initial metastasis diagnosis. To the best of our knowledge, this is the first study comparing those with VMs to those without VMs at the time of initial mCRPC diagnosis in a multiethnic cohort. We then examined overall survival (OS) as a function of VMs.

2. Material and methods

2.1. Study cohort

After obtaining institutional review board approval, we identified 494 men from five Veterans Affairs (VA) medical centers (Durham, NC; West Los Angeles, San Francisco, and San Diego, CA; Augusta, GA, USA) of the Shared Equal Access Regional Cancer Hospital (SEARCH) database who had no known metastases at the time of CRPC diagnosis but who were later diagnosed with metastases. M0/Mx was defined as the absence of a positive imaging test for distant metastases before CRPC diagnosis. Imaging prior to and after CRPC diagnosis including at the time of initial PCa diagnosis was at provider discretion. Data on all imaging tests (bone scan, magnetic resonance imaging [MRI], computed tomography [CT], x-ray) after CRPC diagnosis were collected including date, type, and outcome. Outcome was based on specific and consistent terminology used in the radiology report to classify the imaging test as positive, negative, or equivocal. Metastases in the bone, viscera, and lymph nodes were based on imaging at the time of mCRPC diagnosis. Men with brain metastases were considered to have VMs in "other location." Castration was defined as a bilateral orchiectomy, testosterone <50 ng/dl, or, in the absence of testosterone data, receipt of continuous androgen-deprivation therapy (ADT). CRPC was defined as per the PCWG2: a 2 ng/ml and 25% increase from the post-ADT PSA nadir [8]. Radiology scans (bone scan, MRI, CT, x-ray) within 30 d of the initial diagnosis of metastasis were reviewed to collect information on bone, visceral, and lymph node metastases. We limited our cohort to 236 men who had a CT as part of their metastatic work-up that found the initial metastasis to ensure all men had equal opportunities to have their VMs detected, if present.

2.2. Statistical analyses

Characteristics captured at the time of mCRPC diagnosis included age, year, race, treatment center, initial biopsy Gleason score, primary localized treatment (yes/no), metastases in lymph nodes (yes/no), PSA, PSA doubling time (PSA DT), time from ADT to CRPC, and time from CRPC to metastases. These were compared between M0/Mx CRPC men who had VMs and those who did not using rank sum tests for continuous variables and a chi-square or Fisher exact test for categorical variables. Predictors of VMs were tested using logistic regression, and predictors of OS were tested using Cox models among men with mCRPC with the time of initial mCRPC diagnosis as time zero. We performed a 10-fold cross-validation to calculate the area under the curve (AUC) of the multivariable logistic regression model. Multivariable models were adjusted for age and year of metastases (continuous), race (black vs nonblack), treatment center (categorical), biopsy Gleason score (2–6, 7, 8–10 vs unknown/no biopsy), primary local treatment (none vs radical prostatectomy and/or radiation), metastases in lymph nodes (yes vs no), PSA at metastases (continuous), PSA DT at metastases (<9, ≥9 vs missing), months from ADT to CRPC (continuous), and months from CRPC to metastases (continuous). Kaplan-Meier curves were created for nonvisceral and visceral disease and compared using the log-rank test.

Stata v.14.0 (StataCorp, College Station, TX, USA) was used for all statistical analyses. A $p < 0.05$ was the threshold for statistical significance.

3. Results

3.1. Baseline characteristics

Of the 236 patients, 38 (16%) were found to have VMs at the time of initial mCRPC diagnosis. Regarding VMs, 19 patients (50%), 8 patients (21%), and 16 patients (42%) had metastases in the liver, lungs, and other locations, respectively. Overall, a third of the patients were black, and about 20% did not receive any local therapy. At the time of metastases diagnosis, the median age was >74 yr, the median PSA was >40 ng/ml, and about 50% of the patients had a PSA DT <9 mo. The average time from ADT to CRPC was >30 mo and from CRPC to metastases was >15 mo. There were no significant differences between men who did and did not have VMs in age, year of metastases, treatment center, biopsy Gleason score, primary local treatment, metastases in lymph nodes, PSA at metastases, PSA DT at metastases, months from ADT to CRPC, months from CRPC to metastases, and total follow-up (Table 1).

3.2. Predictors of visceral metastases among men with metastatic castration-resistant prostate cancer

We examined the various factors related to having VMs at the time of initial mCRPC diagnosis. On univariable analysis,

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