Estimating high-risk castration resistant prostate cancer (CRPC) using electronic health records

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Introduction: *Canadian guidelines define castration-resistant prostate cancer (CRPC) at high risk of developing metastases using PSA doubling time (PSADT) < 8 months, whereby men may be offered more frequent bone scans/imaging. We evaluated PSA data from nonmetastatic (M0) prostate cancer patients treated at urology and oncology clinics across the United States (US) to describe the proportion and characteristics of patients who met CRPC and high-risk criteria.*

Materials and methods: *We identified M0 prostate cancer patients aged ≥ 18 years receiving androgen deprivation therapy (ADT) in 2011 from electronic health records (EHR), covering 129 urology and 64 oncology practices across the US. We estimated the proportion of prostate cancer patients with evidence of CRPC (consecutive rising PSAs) and subsets that may be at high risk (using several PSA and PSADT cut-points).*

Results: *Among 3121 M0 prostate cancer patients actively treated with ADT, 1188 (38%) had evidence of CRPC. Of these, 712 (60%) qualified as high risk in 2011 based on PSADT < 8 months (equivalent to ≤ 8 months in these data). Men ≥ 65 years were more likely to have evidence of CRPC than younger men, although younger men were more likely to have evidence of high-risk disease. CRPC was more common among men receiving ADT in the oncology setting than the urology setting (48% versus 37%).*

Conclusions: *In this large EHR study with patient-level PSA data, 38% of men with M0 prostate cancer treated with ADT had CRPC. Approximately 60% of M0 CRPC patients may experience a PSADT of < 8 months. These findings require validation in a Canadian patient population.*

Key Words: castration-resistant prostate cancer, high risk for bone metastases, CUA guidelines, PSA doubling time, real-world data

Introduction

Canadian guidelines for the management of castration-resistant prostate cancer (CRPC) were recently updated in 2015 by the Canadian Urological Association (CUA) and the Canadian Urological Oncology Group (CUOG).[1] The guidelines provide recommendations for the scheduling of bone scans and additional imaging modalities (x-ray radiography and computerized tomography [CT] scans) according to PSA doubling time (PSADT) to screen for development of metastases in men with nonmetastatic (M0) CRPC. In the last update published in 2013,[2] clear guidance was introduced for the management of patients with a rapid PSADT (< 8 months) who may be at risk for developing earlier metastases and therefore eligible for more frequent imaging every 3 to 6 months, as well as incorporating newly available agents into the treatment algorithms (abiraterone acetate, cabazitaxel, enzalutamide, radium 223, denosumab). The recommendations represent a number of significant

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therapeutic clinical programs culminating over the short period of time since 2010 resulting in new drugs, and an improved understanding of the disease including how PSA kinetics are predictive of risk of bone metastases. It remains unclear how many patients fit into the high-risk category of PSADT of < 8 months that requires more frequent surveillance.

Clinical trials have used PSA kinetics to define high risk of bone metastases among M0 CRPC patients.[3,4] Insights into the role of PSA and PSA kinetics in the natural history of M0 CRPC were gleaned specifically from the data collected for the placebo arms of these trials. In one failed randomized, controlled phase 3 trial,[3] analysis of the placebo group determined that baseline PSA > 10 ng/mL and PSA velocity independently predicted shorter time to bone metastasis. Similarly, a more recent randomized, controlled phase 3 clinical trial that used PSA kinetics as part of the inclusion criteria (PSA > 8 ng/mL or PSADT ≤ 10 months), found differences in time to bone metastasis or death among subsets of patients defined using different PSA kinetics (PSADT of ≤ 10, ≤ 6, and ≤ 4 months).[4]

Outside of clinical trials, where patients encountered are more representative of the general prostate cancer population,[5] the CRPC disease state has not been adequately characterized or quantified. Part of the difficulty in studying this patient population relates to the lack of a standard definition for CRPC. Typically, CRPC is determined by sequential rises in PSA levels despite ongoing androgen deprivation therapy (ADT), although precise definitions vary from study to study.[2,6-10] There are also no specific criteria for identifying M0 CRPC patients who may be at highest risk for developing bone metastases, although higher baseline PSA and PSA velocity have consistently been associated with a greater risk of bone metastasis after ADT.[4,11,12] Perhaps most importantly, however, the majority of large population-based sources of data commonly used for research purposes lack serial PSA measures, which limits the ability to identify CRPC patients in general and CRPC patient subgroups that may be at highest risk for developing bone metastases.

In the United States (US), the rapid adoption of electronic health records (EHR) for the clinical management of patients among community urology and oncology practices largely due to the extensive use of pharmacotherapy and laboratory testing for cancer patients, makes EHR a valuable tool for studies in urologic oncology.[13] We therefore conducted an analysis of EHR from M0 prostate cancer patients treated in urology and oncology clinics across the US to estimate the proportion of M0 prostate cancer patients with evidence of CRPC who meet definitions of high risk in a given year.

Materials and methods

Study population

The source data was an EHR database (OSCER; Oncology Services Comprehensive Electronic Records)[14] covering 129 urology (273 clinical sites) and 64 oncology (442 clinical sites) practices from across the 50 US states. OSCER utilizes encryption software so that individual patient-level data are anonymous, and protected consistent with the final Health Insurance Portability and Accountability Act (HIPAA) Security Rule from the US Department of Health and Human Services.[13,15]

The study cohort included men with confirmed M0 prostate cancer diagnosis (International Classification of Diseases, 9th Revision [ICD-9] diagnosis code 185), aged ≥ 18 years, and receiving ADT in a 1 year period (January 1, 2011 to December 31, 2011).

Excluded were patients with evidence of metastatic involvement of distant organs at any time in their record using ICD-9 codes for metastases to specific sites or systems and/or recorded cancer stage information. Because bone is the most common site of distant metastases in prostate cancer patients, the definition of bone metastasis was expanded by excluding men who had any evidence of intravenous bisphosphonate therapy (zoledronic acid, pamidronate), consistent with the approach used to estimate prevalence of bone metastases in the US population.[16]

ADT was defined as either: 1) receipt of bilateral orchiectomy in the current year or any prior year; and/or 2) at least two administrations of gonadotropin releasing hormone (GnRH) antagonists/agonists, one in the current year (2011) and at least one additional GnRH treatment in the current year or prior year (2010 or 2011). At least 6 months of GnRH treatment was required. GnRH antagonists/agonists included degarelix, goserelin acetate implant, leuprolide acetate, leuprolide acetate implant, and triptorelin.

From this cohort of patients treated with ADT in 2011, we identified patients with evidence of CRPC using an a priori definition found in clinical trials[4,17] of three consecutive rising PSA values: PSA1 < PSA2 < PSA3 where the last two values are required to be above 1.0 ng/mL, and PSA results were required to be at least 2 weeks apart and may have occurred any time in the patient's record (i.e., CRPC was identified in 2011 or any time prior).

Because there is no clear definition of what constitutes high risk, various combinations of the following cut-points for absolute PSA value and PSADT were explored: PSA absolute values in ng/mL (8 and 20) and PSA-DT in months (4, 6, 8, 10). Calculation of PSADT was consistent with the commonly used Memorial Sloan-Kettering

Cancer Center nomogram, and utilized all PSA values for subjects who had least one value during the 1 year study time frame. A minimum of two recorded PSA lab tests were required in the formula: (ln 2 × t) /(ln [PSA_t] – ln [$PSA_{initial}$]), where $PSA_{initial}$ and PSA_t are any two successive PSA values and t is the time interval between the two PSA values.[18,19]

Results

M0 prostate cancer patients on ADT

Of 48,916 patients with prostate cancer identified in the OSCER database, we excluded 4726 patients who did not have valid PSA values recorded during the 1 year study time frame, 6 patients who were less than 18 years old in 2011, 3220 patients with diagnosed metastases, and 24 patients with prior intravenous bisphosphonate use. The vast majority of patients (n = 37,819) were excluded for no evidence of receipt of ADT (either bilateral orchiectomy or GnRH treatment).

The study cohort comprised 3121 men representing adult M0 prostate cancer patients on ADT in 2011. This included 129 men who had undergone bilateral orchiectomy (4%) and 2992 GnRH agonist patients (96%). Nearly 90% of these men were 65 years or older (n = 2806), and the majority received treatment in a urology clinic (87%), Table 1. There was a median of 596 days between patients' first record in OSCER and first ADT administration in 2011.

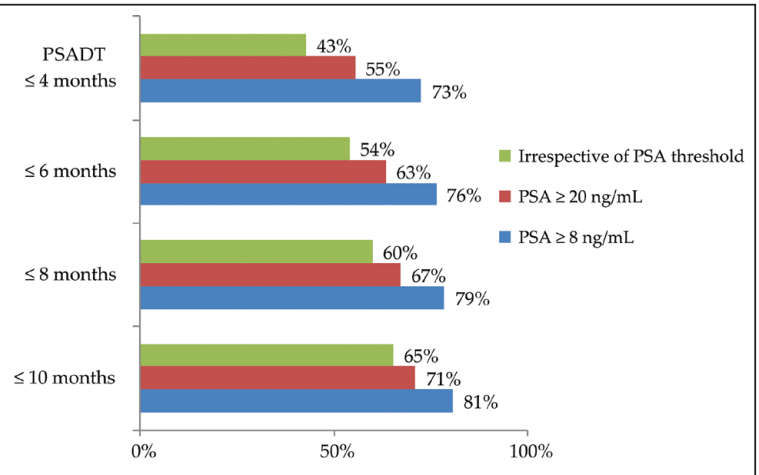
CRPC and high-risk CRPC

Among the study cohort, 1188 (38%) met the CRPC definition. Most patients fulfilled the CRPC criteria in 2009 (21%), 2010 (31%), or 2011 (28%), with the remaining patients meeting the CRPC definition in 2006 (2.2%), 2007 (6.5%), or 2008 (11%). Multiple definitions of high-risk disease were evaluated based on varying combinations of absolute PSA and PSADT from 2011, Figure 1. Sixty percent of CRPC patients met the definition of PSADT ≤ 8 months. Examining a range of PSADT values (≤ 4, 6, 8, and 10 months), the prevalence proportion ranged from 43% (≤ 4 months) to 65% (≤ 10 months). When the definition of high risk was an absolute PSA value of ≥ 20 ng/mL (irrespective of PSADT), the lowest proportion of patients met high-risk criteria (36%). PSA value of ≥ 8 ng/mL, regardless of PSADT, resulted in a subset of 785 (66%) high-risk patients. Examining the high risk definition PSA kinetics (PSA > 8 ng/mL or PSADT ≤ 10 months) used in a large phase 3 clinical trial[17] yielded 959 (81%) high-risk patients.

Men aged 65 years or older were more likely to have evidence of CRPC than younger men (39% versus 30%), but among those with CRPC they were slightly less likely to have evidence of high-risk disease than younger men (54% versus 57%). Although CRPC was more common among men receiving ADT in the oncology setting versus those being treated in the urology setting (48% versus 37%), over half of men with CRPC in both settings demonstrated signs of high-risk disease (oncology: 58%, urology: 53%).

Characteristics of the ADT and CRPC cohorts

Table 1 summarizes characteristics of the entire cohort as well as the characteristics of the subset of CRPC patients. Mean body mass index (BMI) was similar



CRPC Subsets*	Irrespective of PSA threshold *n* (%)	PSA ≥ 20 ng/mL *n* (%)	PSA ≥ 8 ng/mL *n* (%)
PSADT ≤ 4 months	509 (43)	659 (56)	863 (73)
PSADT ≤ 6 months	642 (54)	753 (63)	908 (76)
PSADT ≤ 8 months	712 (60)	799 (67)	934 (79)
PSADT ≤ 10 months	776 (65)	845 (71)	959 (81)
Irrespective of PSADT	—	405 (34)	785 (66)

CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; DT = doubling time
*CRPC subset is the population satisfying either or both of the criteria in the row or column heading. For example, of 1188 patients with CRPC, 959 had either a PSA ≥ 8 ng/mL or PSADT ≤ 10 months. Of these, 785 had a PSA ≥ 8 ng/mL and 776 had PSADT ≤ 10 months.

Figure 1. Size of subsets considered to be at high risk of bone metastases using varying combinations of criteria satisfying thresholds for either an absolute PSA level and/or a PSADT among patients with M0 CRPC (n = 1188).

TABLE 1. **Descriptive characteristics of ADT-treated M0 prostate cancer, and CRPC patients**

	ADT-treated patients (n = 3121) No. (%)	**CRPC patients (n = 1188) No. (%)**
Treatment setting		
Clinic region		
Northeast	597 (19)	179 (15)
South	1774 (57)	718 (60)
Midwest	349 (11)	110 (9)
West	385 (12)	177 (15)
Other/unknown	16 (1)	4 (0.3)
Clinic type		
Urology	2721 (87)	996 (84)
Oncology	400 (13)	192 (16)
Demographics		
Age on January 1, 2011		
< 45	1 (0.03)	0
45-< 55	37 (1)	13 (1)
55-< 65	277 (9)	82 (7)
65-< 75	806 (26)	262 (22)
≥ 75	2000 (64)	831 (70)
Race		
White	912 (29)	425 (36)
African American	65 (2)	30 (3)
Hispanic	20 (1)	4 (0.3)
Asian / Pacific Islander	6 (0.2)	4 (0.3)
Other	14 (0.4)	4 (0.3)
Unknown	2104 (67)	721 (61)
No. patients with BMI	2403	949
Mean BMI most recent (kg m^{-2})	28.1	28.0
Treatment history		
Anti-androgen therapy within prior 3 years	552 (18)	274 (23)
Chemotherapy within prior 3 years	9 (0)	3 (0)
Orchiectomy (ever)	15 (0)	6 (1)
Comorbidities		
Chronic obstructive pulmonary disease	656 (21)	231 (19)
Diabetes	921 (30)	326 (27)
Heart disease	579 (19)	226 (19)
Liver disease/insufficiency	68 (2)	21 (2)
Renal disease/insufficiency	360 (12)	140 (12)
PSA metrics		
Median number of PSA tests received in prior 3 years	5.0	8.0
Median value of PSA tests received in prior 3 years	0.8	2.6
Number of patients with a PSA test at first ADT treatment in all history (up to within 1 month prior to the treatment)	1422	703
Median value of PSA at first ADT treatment in all history (up to within 1 month prior to the treatment)	1.9	4.3

ADT = androgen deprivation therapy; M0 = nonmetastatic; CRPC = castration-resistant prostate cancer; BMI = body mass index; PSA = prostate-specific antigen

across the groups, and for high-risk CRPC subsets (approximately 28 kg/m^2). Additionally, patients with CRPC (and high-risk CRPC subsets) were more likely to have received anti-androgen therapy (flutamide or nilutamide) within the prior 3 years. There appeared to be no major differences in the presence of comorbidities between the cohorts.

As expected from our cohort selection, compared to the ADT cohort overall, the CRPC (and high-risk CRPC subsets) had a history of more PSA testing and higher median PSA levels in the 3 years prior to the first ADT received in 2011. Furthermore, patients with CRPC (or high-risk CRPC subgroups) had higher median PSA values at the first sign of ADT use in their entire patient record, measured within 1 month prior to the treatment (1.9 ng/mL; 4.3 ng/mL; 4.9 ng/mL for the entire ADT cohort, the CRPC subset, and high-risk CRPC subset [PSADT ≤ 6 months], respectively).

Discussion

In this study, real-world data from urology and oncology clinics across the United States were used to identify a large cohort (n = 3121) of M0 prostate cancer patients actively receiving ADT in 2011. We found that 38% of M0 prostate cancer patients demonstrated evidence of CRPC in their patient record, as defined by two consecutive rises in levels of PSA. Exploring different combinations of PSA thresholds and doubling times to define high risk led to a range of estimates. The lowest prevalence proportion being 34% based on an absolute PSA threshold of ≥ 20 ng/mL, regardless of doubling time, and the highest being 81% for PSA ≥ 8 ng/mL or PSADT ≤ 10 months used in a recent trial.[17] Of relevance to the Canadian guidelines, we found that approximately 60% of M0 CRPC patients may experience a PSADT of ≤ 8 months. We note that although the Canadian guidelines defined PSADT as < 8 months, and we defined PSADT as ≤ 8 months, there were no patients in our sample with a PSADT = 8.0 months and therefore the two metrics are equivalent.

We found that 38% of M0 prostate cancer patients actively receiving ADT demonstrated evidence of CRPC. It is important to note that this estimate may in fact be an underestimate as it relies on patients coming to clinic regularly to be screened for rising PSA. Men aged ≥ 65 years were more likely to have evidence of CRPC than younger men, although younger men were more likely to have evidence of high-risk disease. CRPC was more common among men receiving ADT in the oncology setting than the urology setting (48% versus 37%). Estimates in the literature of PSA relapse rates range from 12% to 59% in studies following newly diagnosed patients from 5 to 15 years primarily after radical prostatectomy or radiotherapy.[18,20-33] A systematic literature review of studies characterizing CRPC by Kirby et al[34] found four of five studies examining progression from prostate cancer diagnosis to CRPC (including metastatic CRPC) supported that 10%-20% of prostate cancer patients develop CRPC (a fifth study reported that 53% of patients developed CRPC) in approximately 5 years of follow up. It should be noted that these estimates are not specific to a population of M0 prostate cancer patients actively treated with ADT.

The recent observational study by Banefelt et al[35] of EHR from urology clinics across Sweden examined M0 prostate cancer patients actively receiving ADT (n = 446), as in our study, and found that a similar proportion of men had evidence of CRPC (42%), and 50% developed CRPC after 5 years, reaching close to 80% after 8 years of follow up. Among 148 patients who developed CRPC before bone metastases, 59 (40%) met the primary definition of high-risk disease using a PSADT of ≤ 6 months that was associated with a 2-fold increased risk of bone metastasis or death.[17]

This is the first observational study to examine different definitions of high-risk disease based on PSA data. PSA-based definitions offer a more practical clinical approach for identifying high-risk CRPC patients than some predictive nomograms of prostate cancer disease recurrence based on characteristics at prostate cancer diagnosis.[36,37] Of the 1188 CRPC patients, between 43% and 65% were high risk based on PSA kinetics depending on the PSADT cut-point used to define high risk. However, to properly assess the clinical utility of these PSA-based criteria, an important next step would be to measure the absolute risk of bone metastases in these patient subsets in a real-world setting, with careful control for any differing treatment patterns. PSA levels and kinetics as predictors of clinical outcomes were assessed in a time-varying manner during ADT treatment (compared to previous work using PSADT only at diagnosis, or at randomization) in the Banefelt et al[35] study of EHR from urology clinics in Sweden. PSA and PSADT were confirmed as strong predictors of bone metastasis, any metastasis, and death; specifically, PSADT ≤ 6 months and PSA ≥ 20 ng/mL were associated with highest adjusted hazard ratios of 6.9 (95% CI: 4.7-10.1) and 7.4 (95% CI: 5.1-10.7), respectively, for risk of bone metastasis or death.

In the exploratory analysis of the placebo arm of a randomized, controlled trial, Smith et al[4] demonstrated that men who had no evidence of metastases at study entry were at particularly high risk of bone metastasis or death if they experienced a shorter PSADT with

an apparent relative risk increase at approximately PSADT ≤ 6 months. The proportions of CRPC patients who had a PSADT in our study versus Smith et al[4] placebo data are as follows: 65% versus 81% (580/716) of M0 CRPC patients had PSADT ≤ 10 months, 60% versus 72% (517/716) PSADT ≤ 8, 54% versus 60% (427/716) PSADT ≤ 6, 43% versus 40% (289/716) PSADT ≤ 4 months, respectively. Because patients in the trial were preselected using high-risk criteria, the proportions reported from real-world evidence in our analysis are slightly lower, but relatively consistent, than the clinical trial population. Although we excluded metastatic patients from the underlying cohort and therefore did not evaluate CRPC and high-risk CRPC among patients who developed bone metastases, Smith et al[17] reported that more than half (529/1031) of the potentially eligible high-risk CRPC patients were excluded from the clinical trial before randomization because bone metastases were found upon bone scans at baseline. Future work is needed to evaluate optimal screening for detection of bone metastases in the high-risk CRPC population.

This study emphasizes the value of EHR in urology and oncology observational research. Although cross-sectional in nature in our estimation of prevalence proportions during 2011, we did have a median of 1.6 years of history in the patient record in OSCER. EHR data are particularly advantageous for studies that rely on laboratory tests as these results are typically entered directly into the EHR system by the laboratory, and include the name and date of the test, result, applicable units, and the normal reference range, which reflects the real-world needs of the clinical practice for routine management and treatment planning of patients. This type of analysis would not have been possible in other large population-based sources of data that lack patient serum PSA values over time, critical to identifying CRPC and high-risk CRPC patients.

Despite the strengths in richness of EHR data and PSA values available for analysis, these findings will not be entirely applicable to the Canadian population. Serum testosterone data were not routinely available for the study cohort at time of ADT administration or at the time of PSA testing to confirm castration levels. The frequency of PSA testing in the US during the study period was likely higher than in other countries (CRPC patients had a median of 8 tests over 3 years).[35] We conclude that approximately 60% of patients with M0 CRPC will be in the high-risk category of PSADT < 8 months according to Canadian CRPC treatment guidelines,[1] which warrant more frequent bone scans. Further work is needed to validate these prevalence proportions in a Canadian CRPC population. □

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