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Survival and clinical metastases among prostate cancer patients treated with androgen deprivation therapy in Sweden

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ABSTRACT

Objectives: To examine the incidence of metastases and clinical course of prostate cancer patients who are without confirmed metastasis when initiating androgen deprivation therapy (ADT).
Methods: Retrospective cohort study conducted using electronic medical records from Swedish outpatient urology clinics linked to national mandatory registries to capture medical and demographic data. Prostate cancer patients initiating ADT between 2000 and 2010 were followed from initiation of ADT to metastasis, death, and/or end of follow-up.
Results: The 5-year cumulative incidence (CI) of metastasis was 18%. Survival was 60% after 5 years; results were similar for bone metastasis-free survival. The 5-year CI of castration-resistant prostate cancer (CRPC) was 50% and the median survival from CRPC development was 2.7 years. Serum prostate-specific antigen (PSA) levels and PSA doubling time were strong predictors of bone metastasis, any metastasis, and death.
Conclusion: This study provides understanding of the clinical course of prostate cancer patients without confirmed metastasis treated with ADT in Sweden. Greater PSA values and shorter PSA doubling time (particularly $\leq$ 6 months) were associated with increased risk of bone metastasis, any metastasis, and death.

1. Introduction

Internationally, prostate cancer is the second most common cancer diagnosed among men, and the sixth most common cause of cancer death among men [1]. Despite efforts at better screening and treatment, prostate cancer continues to be a major public health burden. In Sweden, prostate cancer is the most common cancer in men with an average annual increase in incidence of 2.7% over the last 20 years and 0.8% over the last 10 years [2]. The increased incidence of prostate cancer is attributed to widespread serum prostate-specific antigen (PSA) testing in the population and the majority of new cases are diagnosed with non-metastatic disease. Approximately 15–40% of men diagnosed with prostate cancer who undergo therapy with curative intent will develop recurrent disease. The initial presentation of recurrence is most frequently evidenced by an increase in serum PSA in the absence of metastases [3–5]. Androgen deprivation therapy (ADT) has become the standard of care for men with PSA recurrence after primary therapy [6–8]. ADT includes gonadotropin-releasing hormone (GnRH) analog therapy and, to a much less frequent extent, bilateral orchiectomy [9]. Although prostate cancers are usually initially "castration sensitive" and respond to ADT [10], nearly all patients progress to castration resistant prostate cancer (CRPC), a disease state defined by rising PSA during effective ADT.

It is of importance to provide a better understanding of the clinical course and natural history of prostate cancer and the characteristics of patients at high risk of developing clinical

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metastases such as those developing CRPC; currently, there is little evidence available in the literature, particularly for European populations. In addition, the few studies that have examined predictors of metastasis have largely focused on patient and tumor characteristics at cancer diagnosis, and have not examined how time-varying factors, such as PSA levels, may influence a patient's risk of disease progression. PSA characteristics after diagnosis and after ADT may be equally or more important predictors of bone metastases and survival of men with non-metastatic prostate cancer treated with ADT [11].

The objective of this study was to estimate the cumulative incidence (CI) and evaluate PSA-based predictors of (1) bone metastasis, (2) any metastasis, (3) death, and (4) bone metastasis-free survival (BMFS) in the population of non-metastatic prostate cancer patients treated with continuous ADT. The objectives also included estimating the CI of CRPC among ADT-treated patients and the CI of becoming at high risk of developing bone metastases among patients with non-metastatic CRPC using clinical trial-based definitions of high risk CRPC [12–14].

2. Patients and methods

2.1. Study design

This retrospective cohort study was based on electronic medical record (EMR) and national registry data in Sweden. Subjects were followed longitudinally in EMR data in a Swedish outpatient urology clinic setting until December 31, 2010. We focused our study population on outpatient urology clinics since non-metastatic prostate cancer patients in Sweden are commonly seen in this setting, as opposed to in inpatient urology clinics or by oncologists. The unique personal identification number that is assigned to all Swedish citizens enabled individual-level linkage from EMRs to several national mandatory registers. The data extraction from EMRs at urology clinics was performed using the extraction platform Pygargus CXP, which was validated in a recent study [15]. The extraction of individual patient-level data is anonymized, and ensured by use of unique anonymous study identification numbers in place of the personal identification numbers. The study was approved by the Regional Ethics Committee in Uppsala in November 2011 (2011/406).

2.2. Study population

The study population included all men with prostate cancer initiating continuous ADT (defined as GnRH agonist/antagonist therapy for $\geq$6 months, or bilateral orchiectomy) between 2000 and 2010, who had not been diagnosed with bone or distant metastasis (hereafter "non-metastatic"), had at least two PSA values recorded after ADT, and who were monitored at eight outpatient urology clinics across Sweden. Selection criteria employed for the urology clinics ensured that study sites had sufficient history and follow-up of prostate cancer patients, adequate and consistent data contained in EMRs for the time period of the study, and geographical representation in Sweden.

Prostate cancer patients who had a diagnosed metastasis (ICD-9 code 196, 197,198 or ICD-10 code C78-79, C77 at distant sites, or M1 status) on or before the date of continuous ADT were excluded from the study. Consistent with TNM classification, men whose prostate cancer diagnosis included local or regional lymph node involvement (ICD-10 C77) were not excluded from the study on this basis alone. The population thus included men diagnosed with stage I-III prostate cancer, or stage IV where the spread of disease was limited to regional lymph nodes. Subset analyses were performed on patients with evidence of CRPC.

2.3. Data

The Swedish Cancer Registry was used to identify prostate cancer diagnosis, date of diagnosis, and the presence of metastasis and lymph node involvement at diagnosis. The overall completeness of this registry is high and comparable to other high quality registers in Northern Europe [16]. The EMRs were used to collect PSA laboratory data, details on GnRH agonist therapy, and concurrent treatments. Data from in- and outpatient care in hospitals were collected from the Swedish National Patient Register (NPR). The NPR is a mandatory national register and a well validated data source that has been used in a wide range of research projects [17]. The NPR allowed for tracking of subjects that transitioned from the urology clinics to (typically) hospital-based oncology clinics and retrieval of C77-C79 diagnoses (metastases) and the dates of those diagnoses. The NPR was also used to collect information on comorbidities and orchiectomies. Finally, to estimate overall survival and incidence of death, EMR data were linked to the Swedish National Register of Cause of Death.

Because outpatient diagnoses were not available in the NPR for the entire study period, comorbidities were based on recorded inpatient diagnoses from 2 years prior to ADT index date until ADT index date. Comorbidities were used for calculation of a baseline Charlson comorbidity index, where each comorbidity has a specific weight and may be categorized into three levels (index score in parenthesis): low (0), medium (1–2) and high (>2) [18,19].

2.4. Statistical analysis

CRPC was defined as two consecutive rises in PSA: PSA1 $<$ PSA2 $<$ PSA3, where PSA2 and PSA3 $\geq$ 1.0 ng/mL. PSA1 could occur at any time after index date (i.e., the date of fulfillment of the continuous ADT criteria). CRPC and high risk CRPC definitions were consistent with recent clinical trials [12,13]. Among CRPC patients, high risk was defined as PSA doubling time (DT) $\leq$6 months based on the highest PSA-DT risk category described by Smith et al. [13] as well as recent clinical trial data [14]. PSA-DT was defined as the natural log of two divided by the slope of the linear regression line of the natural log of PSA (ng/mL) against time (months) [20]. At each time point of a recorded PSA value, no more than the three most recent PSA values were used in the regression of log PSA against time.

The index date marked the start of exposure time at risk for the primary study objectives. In the analysis of any metastasis and bone metastasis, failure was defined as presence of a diagnosis code indicating any metastasis (ICD-9/ICD-10 codes 196-198/C78-C79) and bone metastasis (ICD-9/ICD-10 codes 198.5/C79.5), respectively. CI over time was estimated using CI functions, taking the competing risk of death into account [21]. In the analysis of death and BMFS, Kaplan–Meier survival analysis was employed. Patients were censored at end of data availability (December 31, 2010).

Differences in patient characteristics were evaluated using t-tests for continuous variables and Pearson's chi-squared test for dichotomous and categorical variables. Competing risks regression [22] (for bone metastases and any metastases) and Cox regression (for overall survival and BMFS) analyses were used to examine PSA characteristics as predictors of the outcomes and generate hazard ratios (HR). Patient characteristics at prostate cancer diagnosis, index date, and during ADT were evaluated as potential covariates. PSA values and PSA-DT were measured during follow-up and were thus time-varying exposures. Thus, the data were time-split at the time point where the predictor changed value [23]. Univariate analysis was performed for each of the predictors individually and then a multivariate model was estimated. Covariates were