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Prostate Cancer

Impact of the Site of Metastases on Survival in Patients with Metastatic Prostate Cancer

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Abstract

Background: Limited data exist on the impact of the site of metastases on survival in patients with stage IV prostate cancer (PCa).
Objective: To investigate the role of metastatic phenotype at presentation on mortality in stage IV PCa.
Design, setting, and participants: Overall, 3857 patients presenting with metastatic PCa between 1991 and 2009, included in the Surveillance Epidemiology and End Results–Medicare database were evaluated.
Outcome measurements and statistic analyses: Overall and cancer-specific survival rates were estimated in the overall population and after stratifying patients according to the metastatic site (lymph node [LN] alone, bone, visceral, or bone plus visceral). Multivariable Cox regression analyses tested the relationship between the site of metastases and survival. All analyses were repeated in a subcohort of patients with a single metastatic site involved.
Results and limitations: Respectively, 2.8%, 80.2%, 6.1%, and 10.9% of patients presented with LN, bone, visceral, and bone plus visceral metastases at diagnosis. Respective median overall survival and cancer-specific survival were 43 mo and 61 mo for LN metastases, 24 mo and 32 mo for bone metastases, 16 mo and 26 mo for visceral metastases, and 14 mo and 19 mo for bone plus visceral metastases ($p < 0.001$). In multivariable analyses, patients with visceral metastases had a significantly higher risk of overall and cancer-specific mortality versus those with exclusively LN metastases ($p < 0.001$). The unfavorable impact of visceral metastases persisted in the oligometastatic subgroup. Our study is limited by its retrospective design.
Conclusions: Visceral involvement represents a negative prognostic factor and should be considered as a proxy of more aggressive disease in patients presenting with metastatic PCa. This parameter might indicate the need for additional systemic therapies in these individuals.
Patient summary: Patients with visceral metastases should be considered as affected by more aggressive disease and might benefit from the inclusion in clinical trials evaluating novel molecules.

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1. Introduction

Prostate cancer (PCa) represents the most common non-cutaneous malignancy occurring in men [1]. Although studies have shown that the proportion of patients with metastatic disease has decreased over the last decades, up to 6.7 per 100 000 individuals still present with distant metastases [2]. Lymph nodes (LNs) and the bone represent the most common locations of metastatic disease [3]. However, numerous patients present with atypical metastases at diagnosis [3,4].

The spread of PCa cells to atypical sites of metastases might be the expression of different biologic characteristics (ie, a more aggressive disease that acquires the ability to localize to sites other than LNs and bone) [5]. In addition, visceral involvement might be associated with more severe clinical manifestations. However, limited data exist on the impact of the metastatic site on survival in patients with stage IV PCa [4,6–11]. Indeed, several drawbacks limit the generalizability of previous findings. For example, these observations were obtained evaluating men enrolled in prospective randomized trials, which might represent highly selected patients. In addition, historical cohorts were evaluated. Thus, results obtained in this context might not be applicable to contemporary patients with metastatic PCa. To address this void, we sought to evaluate the role of the metastatic site on survival in a large contemporary cohort of US patients with PCa. Our hypothesis stated that the occurrence of visceral metastases might represent an adverse prognostic factor in these patients.

2. Materials and methods

2.1. Population source

The current study relied on the Surveillance, Epidemiology, and End Results (SEER)–Medicare insurance program-linked database. This database is 98% complete for case ascertainment. The SEER registries covered approximately 28% of the US population with Medicare administrative data. The Medicare insurance program encompasses approximately 97% of Americans aged ≥65 yr.

2.2. Study population

Patients aged ≥65 yr (International Classification of Disease [ICD] for Oncology site code 61.9, histologic code 8140) diagnosed with metastatic PCa between 1991 and 2009 were identified (n = 14 103). Patients receiving definitive treatment aimed at primary PCa, such as radical prostatectomy (n = 418), radiotherapy (n = 2536), and/or brachytherapy (n = 632) were excluded. Because of the lack of radiotherapy site-specific codes, we were not able to differentiate between patients receiving radiotherapy with curative intent or in a palliative setting [12]. We limited this potential bias by excluding from our analyses patients receiving radiotherapy within 6 mo of diagnosis and thus more likely to undergo prostate-directed radiotherapy. Additional exclusions criteria consisted of unknown biopsy Gleason score (n = 1959), unknown site of metastases (n = 4576), unknown survival status (n = 41), and patients diagnosed at autopsy (n = 84). This resulted in a final population of 3857 assessable patients.

2.3. Sites of metastases

The metastatic sites were identified relying on secondary ICD, 9th revision (ICD-9) diagnostic codes: bone and bone marrow (198.5), LNs (196.x), liver (197.7), thorax (including lung [197.0], pleura [197.2], mediastinum [197.1], and other respiratory organs [197.3]), adrenal gland and kidney (198.7 and 198.0), brain and spinal cord (198.3), retroperitoneum and peritoneum (197.6), and digestive system (including large intestine and rectum [197.5], small intestine and duodenum [197.4], and other digestive organs and spleen [197.8]) [3]. For the purpose of analyses, we categorized patients according to the presence of exclusive LN metastases, bone metastases without visceral metastases, visceral metastases, and concomitant bone and visceral metastases. In addition, patients were stratified according to the number of metastatic sites involved (one vs two or more).

2.4. Outcomes

The end point of the study consisted of overall mortality and cancer-specific mortality (CSM), defined using the SEER code for cause of death. The duration of survival was defined as the time interval from PCa diagnosis to the date of death.

2.5. Covariates

For each patient, age, year of diagnosis, race, population density, marital status, education, income, region, and biopsy Gleason score were assigned. The Charlson Comorbidity Index (CCI) was derived from the Medicare claims 1 yr prior to PCa diagnosis using a previously validated algorithm [13]. Data on prostate-specific antigen (PSA) level at diagnosis were available for men diagnosed after the year 2003 (n = 1242). In addition, the use of androgen deprivation therapy (ADT) and chemotherapy was recorded [14]. Data on the type of ADT (gonadotropin-releasing hormone agonist administration or bilateral orchiectomy) were also abstracted [15].

2.6. Statistical analyses

Means, medians, and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The independent t test and chi-square test were used to compare means and proportions, respectively.

Our statistical analyses consisted of four steps. First, Kaplan-Meier curves were used to examine time to overall survival and CSM-free survival in the entire population, and according to sites of metastases and the number of metastatic sites involved. The log-rank test was used to compare mortality rates by patient categories. Second, multivariable Cox regression models were fitted to test the effect of the site of metastases and the number of metastatic sites on the risk of overall mortality and CSM after accounting for confounders (ie, biopsy Gleason score, the administration of ADT and chemotherapy, age, year of diagnosis, race, and CCI). Third, to get the most unbiased estimate of the effect of site of metastases on survival, we repeated our analyses in a cohort of patients who had only one metastatic site involved. Finally, our analyses were repeated after excluding patients with LN metastases only.

All statistical tests were performed using the R statistical package v.3.0.2 (R Project for Statistical Computing, http://www.r-project.org/). All tests were two-sided with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Overall, 3857 patients with metastatic PCa were identified (Table 1). Average age at diagnosis was 77.3 yr (median: 77 yr). The majority of patients had bone metastases (91.1%)

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