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Original Research

Improved survival for patients with *de novo* metastatic prostate cancer in the last 20 years

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Abstract ***Introduction:*** During recent years, several new life-prolonging therapeutic options have been introduced for patients with metastatic prostate cancer (mPCa). The aim of the present study was to evaluate the changes in the survival of patients diagnosed with mPCa prior to and in the early period of the implementation of these new agents.
Patients and methods: The study population consisted of 207 men diagnosed in 1997 and 316 men diagnosed in the period 2007–2013 with *de novo* mPCa and managed with initial endocrine therapy. Men were followed for overall survival and PCa-specific survival.
Results: At the time of diagnosis, men diagnosed in the period 2007–2013 had less comorbidity, lower prostrate-specific antigen levels and lower clinical tumour categories than men diagnosed in 1997. A significantly higher proportion of men diagnosed in 1997 were managed with surgical castration (57% versus 9%). Only one patient diagnosed in 1997 received second-line therapy compared with 81 men (26%) diagnosed in the period 2007–2013. The median overall survival was significantly longer for men diagnosed between 2007 and 2013 compared with men diagnosed in 1997 (39.4 months versus 24.2 months, $p < 0.0001$). Likewise, the cumulative incidence of PCa-specific death was higher among men diagnosed in 1997 compared with men diagnosed between 2007 and 2013, with 5-year cumulative incidences of 72% and 47%, respectively ($p < 0.0001$).

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Conclusion: Survival in men diagnosed with metastatic PCa has improved significantly over time. The improved survival can in part be explained by lead-time bias, but also by the introduction of new life-prolonging treatments.

1. Introduction

Prostate cancer (PCa) is androgen dependent, and endocrine therapy has been a cornerstone in the management of men with metastatic PCa since Huggins and Hodges described the benefits of androgen ablation nearly seven decades ago [1]. Most of the PCas do respond to endocrine therapies; however, most cancers acquire the capability to proliferate despite having reached castrate levels of serum testosterone, i.e. become castration resistant (CRPC) [2]. Until recently, endocrine therapies—either as castration-based androgen deprivation therapy (ADT), androgen receptor inhibitors, oestrogens or combinations thereof—were the only available treatment options for men with metastatic PCa. However, during the last decade, a number of therapies have demonstrated a survival benefit for CRPC patients in randomised controlled trials [3].

First, two taxan-based chemotherapies, docetaxel [4,5] and cabazitaxel [6], have been approved for men with symptomatic metastatic CRPC. Second, new androgen-targeting therapies, abiraterone acetate [7,8] and enzalutamide [9,10], were approved for men with metastatic CRPC both before and after chemotherapy. Most recently, radium-223 [11] has been approved in the clinical management of men with metastatic CRPC.

While each of these new therapies has demonstrated survival benefits in randomised clinical trials, less is known about their efficacy in unselected populations managed outside clinical trials. Furthermore, an increased awareness of the disease, even in a population where PCa screening is not recommended, may have affected survival in patients with mPCa due to lead-time bias, introducing an apparent survival benefit in patients within the same clinical category. To further elucidate the survival changes for men diagnosed with *de novo* mPCa before and after the implementation of the new life-prolonging treatments, we compared the survival between two cohorts of Danish men diagnosed with mPCa in two different time periods; a historical nation-wide cohort of men diagnosed in 1997 and a contemporary cohort of men diagnosed between 2007 and 2013.

2. Patients and methods

The study populations derive from two cohorts of men diagnosed with *de novo* mPCa who received endocrine therapy as the first-line treatment. The historical cohort consists of men diagnosed with *de novo* mPCa identified among all Danish men diagnosed with PCa in the last 8 months of 1997. As previously described in detail, all men were identified in the Danish Cancer Registry. The date of diagnosis and tumour characteristics, including the results from diagnostic workups, were retrieved from the Danish Cancer Registry and patient records [12]. A total of 35 men with mPCa were excluded from the original study population, as they did not receive immediate endocrine therapy.

The contemporary cohort consists of an unselected, consecutive series of men identified in the local pathology database. These men were diagnosed with *de novo* mPCa at the Department of Urology, Frederiksberg Hospital, Denmark between January 1st 2007 and December 31st 2013 [13]. The following diagnostic information was registered retrospectively from patient records: age, prostate-specific antigen (PSA) level, Charlson comorbidity index (CCI), clinical tumour category (cT), histological grade (World Health Organisation grade or Gleason score), distant metastasis and primary treatment. Subsequent life-prolonging therapies, vital status and cause of death were updated until December 31st 2014 and January 31st 2016 for the historical cohort and the contemporary cohort, respectively. The study was approved by the Danish Data Protection Agency (file no. 2011-41-7017) and by the Capital Region of Denmark (file no. 2012-58-0004).

2.1. Statistics

Differences in baseline characteristics between the cohorts were tested using the chi-squared-test for categorical variables and the Mann–Whitney *U* test for continuous variables. Kaplan–Meier survival analysis was used to estimate the overall survival and log-rank analysis was used to compare survival between the two cohorts. The cumulative incidences of PCa-specific death and other-cause mortality were analysed using the Aalen–Johansen method for competing risks. Non-PCa death was treated as a competing event when analysing the risk of PCa death and vice versa. Gray's test was used to assess differences in the cumulative incidence between the cohorts [14]. Cox regression analyses were used to estimate the risk of death for men with complete baseline information and included age (continuous), PSA (continuous), CCI (0, 1, $\geq$2), cT (cT1, cT2, cT3 and cT4) and primary treatments (GnRH agonists, orchiectomy, total androgen blockade, androgen receptor inhibitors and oestrogens). The results