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Original article

The risk of prostate cancer mortality and cardiovascular mortality of nonmetastatic prostate cancer patients: A population-based retrospective cohort study

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Abstract

Purpose: To assess the risk of prostate cancer (PCa) specific mortality (PCSM) compared to cardiovascular disease mortality (CVDM), or other-cause mortality (OCM) of men with nonmetastatic PCa according to PCa risk groups, primary treatment, and age.

Patients and methods: This retrospective population-based cohort study identified 1,908 nonmetastatic PCa patients in the cancer registry Zurich and Zug, diagnosed between 2000 and 2009 living in the City of Zurich. Multiple imputation methods were applied to handle missing PCa information. Fine and Gray competing risk regression analysis was used to estimate subdistribution hazard ratios for the outcomes PCSM, CVDM, or OCM

Results: Ten years after diagnosis the cumulative probability of PCSM and CVDM was 16.4% and 10.0%, respectively. We observed an increased adjusted risk of PCSM in men treated with androgen deprivation therapy (ADT) compared to surgery, but could not observe an association between ADT and CVDM. The probability of PCSM was significantly higher for patients on active surveillance or watchful waiting, compared to surgery. Age and PCa risk categories were positively associated with risk of PCSM, whereas there was no evidence for an association with CVDM or OCM based on risk groups.

Conclusions: Overall, men with PCa were more likely to die from non-PCa related outcomes. Nevertheless, the analyses showed a high proportion of PCSM among men on ADT, older men and men with a high-risk tumor. However, further research is needed to understand comprehensively the benefits of the respective treatments.

Keywords: Prostate cancer; Cause-Specific Mortality; Survival analysis; Cancer registry; Treatment; ADT

1. Introduction

Prostate cancer (PCa) is the most common male cancer in Switzerland; about 1,000 cases annually are registered in the Canton of Zurich [1]. The number of incident cases increased in the last decade [2], mainly due to the increasing number of men having a PCa screening examination, namely a PSA (prostate-specific antigen) test [3]. Therefore, more men are diagnosed earlier, but usually with a low-risk tumor [4]. In contrast, the number of men dying from PCa decreased over the last decades. Men with a low-risk tumor have a higher risk of dying from other causes than of PCa [5]. Hence, for some men there is overtreatment [6] of PCa with an unneeded effect on quality of life through severe adverse effects like incontinence or impotence [7,8]. Accordingly, the challenge is to identify those men who have a higher risk of dying from PCa and those who are more likely to die of other causes.

In Switzerland, the leading causes of death in men are cancer (30%) and cardiovascular diseases (CVD, 31%) [9]. Studies have shown that PCa patients treated with androgen

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deprivation therapy (ADT) might have an excess risk of dying from CVD [10,11], such that we, in addition to death of other causes, included death from CVD in our analysis. For Switzerland, it is currently unclear in which way treatment affect long-term survival of PCa patients. In contrast to several other countries, Switzerland has a universal health insurance system, which provides equal access and state-of-the-art treatment options for all patients, which might affect treatment outcomes and survival compared with other countries. To our knowledge, this is the first study in Switzerland that assesses the risk of PCa-specific mortality (PCSM) compared to cardiovascular disease (CVDM) or other-cause mortality (OCM) of men with nonmetastatic PCa according to PCa risk groups, primary treatment, and age.

2. Patients and methods

2.1. Study population

The epidemiological Cancer Registry Zurich and Zug is the largest cancer registry in Switzerland covering roughly 1.6 million inhabitants. The Registry was established in 1980 to register every cancer patient living in the canton of Zurich (since 2011, the canton of Zug is also included). The Registry is almost complete. Using the flow method, Lorez et al. [12] have shown that in Zurich 89.6% of all cancer sites are captured within 3 years of diagnosis and 97% after 5 years. In addition, the differences between mortality: incidence ratio and 1-relative survival was 5.6% (values $>10\%$ are considered as under-registered).

We included PCa patients who lived in the City of Zurich at time of diagnosis. PCa was defined as C61 based on the ICD-10 coding (International Statistical Classification of Diseases and Related Health Problems). We restricted our data to patients with nonmetastatic PCa as first primary cancer diagnosis. Of the 2,030 nonmetastatic PCa cases diagnosed between 2000 and 2009, we excluded 18 DCO (death certificate only) cases (0.89%) and 93 autopsy cases (4.58%). In addition, 11 cases (0.54%) were excluded due to missing information on cause of death. Finally, we included 1,908 patients in the analysis. We obtained data of the patient's vital status from the Citizen Services Department of the City of Zurich. Men were followed-up until death or were censored on 31 December 2014, whichever came first.

PCa cases were categorized into 3 risk groups based on T-stage, Gleason score, and initial PSA concentration as described by D′Amico [13]. Low-risk was defined as T-stage = T1–2a, and Gleason score $\leq$6, and PSA $\leq$ 10 ng/ml; intermediate-risk as T-stage = T2b and/or Gleason score = 7 and/or PSA $>$10 to 20 ng/ml; and high-risk as T-stage $\geq$ T2c or Gleason score 8 to 10 or PSA $>$ 20 ng/ml.

Only the primary treatment during the first 6 months was considered. We distinguished between surgical procedures, radiotherapy, ADT, active surveillance (AS), and watchful waiting (WW). Although ADT is not the recommended primary monotherapy for localized PCa [14–17], it is commonly used in practice [18–20]; hence,we included ADT as primary monotherapy in our analysis. As we cannot directly distinguish between AS and WW, we defined AS for men $<$70 years and WW for men $\geq$70 years. Age was divided into 4 groups ($<$ 60, 60–69, 70–79, and $>$79 y).

The Swiss Federal Statistical Office (FSO) provided cause of death information. Causes of death are based on death certificates and are coded using the ICD-10 coding. The outcomes of interests were PCSM, CVDM, or OCM. CVDM was defined by I00-I99 based on ICD-10.

2.2. Statistical methods

In order to handle missing values for Gleason score, T-stage, and PSA, multiple imputation with chained equations (MICE) was applied to impute the incomplete data [21–23]. The imputation model included the incomplete variables Gleason score, T-stage, and PSA level, and the complete variables date of diagnosis, age at diagnosis, survival time, vital status and primary treatment, as well as the main cause of death (outcome) [24]. We categorized the missing variables in the following risk groups before performing multiple imputation. Gleason score was categorized into $\leq$ 6, 7, and 8 to 10, T-stage was categorized into T1–2a, T2b, and $\geq$T2c, and PSA was grouped as $\leq$10 ng/ml, $>$10 to 20 ng/ml, and $>$20 ng/ml. Variables categorized as missing were imputed using a multinomial logit model. Since the fraction of missing information was approximately 3% for Gleason score, 6% for T-stage, and 18% for PSA, we created 25 complete datasets. For each dataset, the analyses were performed separately and merged afterwards using Rubin's rule [25]. We compared the results with a complete-case analysis. The results of the multiple imputation and the complete-cases analysis differ slightly but lead to the same conclusion. For that reason, only the results of the multiple imputation are shown in this publication.

Cox proportional hazards regression was used to estimate all-cause mortality, and Fine and Gray competing risk regression analysis to estimate subdistribution hazard ratios (SHR) for the outcomes PCSM, CVDM, or OCM [26]. Multivariable analyses were adjusted for age, risk, and treatment groups. Since the year of diagnosis did not show an effect on cause of death, it was not included into the model. In addition, 10-year cumulative probabilities of death-smoothed plots were generated for age, risk, and treatment groups. Gray's k-mean P value was used to compare cumulative probability of PCSM or OCM (including CVD) for men who underwent surgery [27]. AS/WW were stratified by age $<$70 years and $\geq$70 years. All statistical analyses were performed using R Version 3.4.0. The R package "MICE" [28] was used to impute the missing data, "survival" [29] to perform the Cox regression models, and "cmprsk" [30] to estimate the subdistribution