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The effect of age at diagnosis on prostate cancer mortality: A grade-for-grade and stage-for-stage analysis

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Abstract

Objective: To evaluate the effect of advancing age on cancer-specific mortality (CSM) after radical prostatectomy (RP).
Materials and methods: Overall, 205,551 patients with PCa diagnosed between 1988 and 2009 within the Surveillance Epidemiology and End Results (SEER) database were included in the study. Patients were stratified according to age at diagnosis: ≤50, 51–60, 61–70, and ≥71 years. The 15-year cumulative incidence CSM rates were computed. Competing-risks regression models were performed to test the effect of age on CSM in the entire cohort, and for each grade (Gleason score 2–4, 5–7, and 8–10) and stage (pT2, pT3a, and pT3b) subcohorts.
Results: Advancing age was associated with higher 15-year CSM rates (2.3 vs. 3.4 vs. 4.6 vs. 6.3% for patients aged ≤50 vs. 51–60 vs. 61–70 vs. ≥71 years, respectively; $P < 0.001$). In multivariable analyses, age at diagnosis was a significant predictor of CSM. This relationship was also observed in sub-analyses focusing on patients with Gleason score 5–7, and/or pT2 disease (all $P \leq 0.05$). Conversely, age failed to reach the independent predictor status in men with Gleason score 2–4, 8–10, pT3a, and/or pT3b disease.
Conclusions: Advancing age increases the risk of CSM. However, when considering patients affected by more aggressive disease, age was not significantly associated with higher risk of dying from PCa. In high-risk patients, tumor characteristics rather than age should be considered when making treatment decisions.

Keywords: Prostate cancer; Radical prostatectomy; Cancer-specific survival; Competing-risks; Age at diagnosis

Introduction

Prostate cancer (PCa) remains the most common non-cutaneous malignancy for men. With the aging population in the United States, it is projected that by the year 2030 incidence of PCa will increase by 55%, where 71% of men with the disease will be 65 years old or older.[1]

In other urological malignancies, younger age portends to more favorable cancer control outcomes.[2] In the context of PCa, however, the effect of age has not been elucidated. Some suggest that the underuse of potentially curative therapy in older individuals may be the reason for differences in survival relative to their younger counterparts.[3,4] On the other hand, others proposed that surgery in older men

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diagnosed with PCa might not result in an overall survival benefit relative to active surveillance.[5] Specifically, given a certain age, a significant proportion of men is at higher risk of dying from other causes than the tumor itself.[6–12]

To date, the impact of age at diagnosis on cancer-specific mortality (CSM) in PCa patients is still debated. Most of the available studies are based on institutional series that relied on historical data,[10–13] and only one report relied on a large cohort of patients treated with surgery.[14] Unfortunately, this study did not account for competing causes of mortality, where given the protracted nature of the disease, when unaccounted for, can result in a significant overestimation of survival differences according to age.

To address this issue, we set out to assess the impact of age on long-term CSM rates in a large cohort of patients with clinically localized PCa treated with radical prostatectomy (RP). Our hypothesis stated that, although other-cause mortality (OCM) represents the leading cause of death in older patients, the risk of dying from PCa is similar between young and elderly patients, even after adjusting for disease characteristics.

Patients and methods

Population source

The Surveillance, Epidemiology, and End Results (SEER) program based on 18 registries was used to extract the study population. The SEER collects patient demographics and publishes cancer incidence and survival data from population-based cancer registries, covering approximately 28% of the United States population. The characteristics of the SEER population are comparable with that of the general population of the United States.

Study cohort

Patients with a primary diagnosis of PCa between years 1988 and 2009 were identified using *International Classification of Disease for Oncology* (ICD-O) code C61.9 ($N = 696{,}697$). Those with histological subtypes other than that of adenocarcinoma (8140) were excluded. We included in our analyses only those aged between 35 and 75 years old who underwent RP ($N = 272{,}392$). Furthermore, patients with metastatic disease ($N = 40{,}250$), anaplastic or unknown tumor grade ($N = 2257$) and stage ($N = 17{,}093$) were excluded. For the purpose of our study, only individuals with pT2/3 N0/x PCa of all grades were considered. This resulted in 205,551 assessable patients.

Variable definition

Covariates include patient age at diagnosis, year of diagnosis, race, marital status, population density, college education, annual median income, region, pelvic lymph node dissection, and SEER registry. For the purpose of our study, age was stratified into 5 groups: ≤50 vs. 51–60 vs. 61–70 vs. ≥71 years. Disease characteristics include tumor grade: well differentiated (Gleason score 2–4), moderately differentiated (Gleason score 5–7), and poorly differentiated (Gleason score 8–10), and pathological tumor stage (pT_2 vs. pT_3a vs. ≥pT_3b).

Outcomes

The cause of death was defined using the SEER cause of death code. Patients who died from PCa (ICD-9185.9 or ICD-10 C619) were classified as cancer-specific mortality (CSM), while patients who succumbed to all other causes were classified as other-cause mortality. The duration of survival was defined as the time interval from PCa diagnosis to the date of death.

Statistical analyses

Means, medians, and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The independent *T* and chi-square tests were used to compare the statistical significance of differences in means and proportions, respectively. The Kruskal–Wallis test was used to compare median age at surgery stratified according to year of diagnosis.

We relied on the competing-risks regression methodology to assess 15-year CSM rates.[15,16] Age-stratified cumulative incidence CSM rates were generated for different groups and compared with the Gray test.[16] Uni- and multivariable competing-risks regression models were used to test the effect of age at diagnosis (≤50, 51–60, 61–70, and ≥71) on CSM rates, after accounting for OCM. Covariates included race, marital status, population density, year of diagnosis, annual median income, college education, region, pathological stage and pathological Gleason score. To assess the magnitude of the effect related to age at diagnosis, we repeated all multivariable competing-risks regression models after stratifying according to pathological Gleason score and pathological tumor stage.

All statistical tests were performed using the *R* statistical package (v2.15.2). All tests were 2-sided with a significance level set at $P < 0.05$.

Sensitivity analyses

In separate analyses, we tested the effect of age at diagnosis (≤50, 51–60, 61–70, and ≥71) on overall mortality (OM). Kaplan–Meier analyses were used to assess the 15-year overall survival rates in the overall population, and after stratifying patients according to age at diagnosis. Finally, Cox multivariable regression analyses tested the effect of age on OM, after accounting for potential confounders.