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Original article

Very long-term survival patterns of young patients treated with radical prostatectomy for high-risk prostate cancer

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Abstract

Objective: In patients with a long life expectancy with high-risk (HR) prostate cancer (PCa), the chance to die from PCa is not negligible and may change significantly according to the time elapsed from surgery. The aim of this study was to evaluate long-term survival patterns in young patients treated with radical prostatectomy (RP) for HRPCa.

Materials and methods: Within a multiinstitutional cohort, 600 young patients ($\leq$59 years) treated with RP between 1987 and 2012 for HRPCa (defined as at least one of the following adverse characteristics: prostate specific antigen $>$20, cT3 or higher, biopsy Gleason sum 8–10) were identified. Smoothed cumulative incidence plot was performed to assess cancer-specific mortality (CSM) and other cause mortality (OCM) rates at 10, 15, and 20 years after RP. The same analyses were performed to assess the 5-year probability of CSM and OCM in patients who survived 5, 10, and 15 years after RP. A multivariable competing risk regression model was fitted to identify predictors of CSM and OCM.

Results: The 10-, 15- and 20-year CSM and OCM rates were 11.6% and 5.5% vs. 15.5% and 13.5% vs. 18.4% and 19.3%, respectively. The 5-year probability of CSM and OCM rates among patients who survived at 5, 10, and 15 years after RP, were 6.4% and 2.7% vs. 4.6% and 9.6% vs. 4.2% and 8.2%, respectively. Year of surgery, pathological stage and Gleason score, surgical margin status and lymph node invasion were the major determinants of CSM (all $P \leq 0.03$). Conversely, none of the covariates was significantly associated with OCM (all $P \geq 0.09$).

Conclusions: Very long-term cancer control in young high-risk patients after RP is highly satisfactory. The probability of dying from PCa in young patients is the leading cause of death during the first 10 years of survivorship after RP. Thereafter, mortality not related to PCa

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became the main cause of death. Consequently, surgery should be consider among young patients with high-risk disease and strict PCa follow-up should enforce during the first 10 years of survivorship after RP.

Keywords: Survival; Competing risk; High-risk; Young patients; Prostate cancer; Radical prostatectomy

1. Introduction

Clinical characteristics of prostate cancer (PCa) patients have changed dramatically with the introduction of prostate specific antigen (PSA) as a screening tool for PCa, with a step forward toward more localized disease [1]. However, from 14% to 24% of individuals with newly diagnosed PCa are still classified as high-risk patients [2]. High-risk PCa represents a heterogeneous group of patients with a wide range of prognoses. Patients at higher risk of death from PCa are those with worse tumor characteristics, longer life expectancy, and lower comorbidity profile. Despite the lack of randomized clinical trials testing the role of radical prostatectomy (RP) in high-risk PCa, European Association of Urology [3], National Comprehensive Cancer Network [4], and American Urological Association guidelines [5], support the discussion of surgery among men with high-risk disease. This is based on several retrospective data reporting favorable long-term cancer-specific mortality (CSM) free survival rates after RP either alone or in combination with postoperative treatments [6–14]. However, none of these studies focused exclusively on young high-risk patients. In addition none, except one [14], relied on methods accounting for competing risks, which accounts for other cause mortality (OCM), to examine the main endpoint, namely CSM in this subgroup of patients. Moreover, only few studies [15,16] in this setting relied on methods accounting for competing risks after stratification according to age. However, in all above mentioned studies [6–16], the estimate of CSM free survival rates was limited to a certain time point after surgery. Nevertheless, the chance to die from PCa may change significantly according to the time elapsed from surgery, especially in young patients who have a long life expectancy. Given these considerations, we evaluated: (1) very long-term cancer control in a large contemporary population of young high-risk PCa treated with RP using a competing risk regression methodology and (2) the effect of the time elapsed from surgery on the subsequent risk of CSM, after accounting for the risk of death for other cause.

2. Materials and methods

2.1. Study population

Overall, 7,650 consecutive patients with high-risk PCa treated with open RP and pelvic lymph node dissection between 1987 and 2012 at 7 European tertiary care referral centers were identified. High-risk PCa was defined as the presence of at least one of the following risk factors: preoperative PSA level $>$ 20 ng/ml, clinical stage T3 or higher, or biopsy Gleason sum 8 to 10. For the aim of our study, we focused exclusively on young patients ($\leq$59 years). These selection criteria yielded 1,831 assessable patients. Additional exclusions criteria consisted of men with unknown Charlson comoridity index (CCI) (n = 1,134), unknown pathological stage (n = 46), unknown pathological Gleason score (GS) (n = 18), unknown lymphnode status (n = 1), unknown surgical margin status (n = 1), and unknown cause of death (n = 31). These resulted in a final population of 600 patients with complete clinical, pathological, and follow-up data.

2.2. Variable definition, follow-up, and outcomes

Patient health status was assessed by the CCI [17], which was set to 0 vs. $\geq$1. Tumor characteristics included preoperative PSA values, clinical stage (T1, T2, and T3), biopsy Gleason sum ($\leq$6, 7, and 8–10), cumulative number of risk factors (PSA level $>$ 20 ng/ml, clinical stage T3 or higher, or biopsy Gleason sum 8–10), pathological stage (organ confined, nonorgan confined) and GS ($\leq$6, 7, and 8–10), surgical margin status and lymphnode status (negative—pN0, positive—pN1). Decision of adjuvant treatments such as androgen deprivation therapy or radiotherapy or both were made according to the individual institutional protocols. Adjuvant treatment was started within 3 months following surgery.

Patients underwent follow-up visits every 3 months during the first year and every 6 months thereafter. The cause of death was defined by the attending urologist or oncologist who followed the patients or death certificate [18]. Patients who died from PCa were classified as CSM, whereas patients who died from other causes were classified as OCM.

2.3. Statistical analyses

Frequencies and proportions were reported for categorical variables. Medians and interquartile ranges (IRs) were reported for continuously coded variables.

Our analyses consisted of 3 steps. First, estimates of 10-, 15-, and 20-year CSM and OCM were plotted using the Poisson smoothed cumulative incidence method, as previously described [15].

Second, using the same methodology, we calculated the 5-year probability of CSM among patients who survived 5, 10, and 15 years after surgery accounting for OCM.

Finally, multivariable competing-risk models were used to identify the predictors of CSM and OCM after accounting for year of surgery, CCI, pathological stage, pathological GS, surgical margin status, and lymphnode invasion (LNI).

All statistical analyses were performed using R statistical package (version 0.98.1091). All tests were 2-sided with a significance level set at $P < 0.05$.