Low Other Cause Mortality Rates Reflect Good Patient Selection in Patients with Prostate Cancer Treated with Radical Prostatectomy

Katharina Boehm, Alessandro Larcher, Zhe Tian, Philipp Mandel, Jonas Schiffmann, Pierre I. Karakiewicz, Markus Graefen, Hartwig Huland* and Derya Tilki*,†

From the Martini-Klinik Prostate Cancer Center (JS, MG, HH, DT) and Department of Urology, University Hospital Hamburg-Eppendorf (KB, PM, DT), Hamburg, Germany, Cancer Prognostics and Health Outcomes Unit (KB, AL, ZT) and Department of Urology, University of Montreal Health Center (PIK) and McGill University, Department of Epidemiology, Biostatistics and Occupational Health (ZT), Montreal, Quebec, Canada, and Unit of Urology, Division of Oncology, Urological Research Institute, National Institute for Research and Treatment Ospedale San Raffaele (AL), Milan, Italy

Abbreviations and Acronyms

CCI = Charlson comorbidity index
CSM = cancer specific mortality
OCM = other cause mortality
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy

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* Equal study contribution.

† Correspondence: Martini-Klinik Prostate Cancer Center, Martinistrasse 52, 20246 Hamburg, Germany (e-mail: d.tilki@uke.de).

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Purpose: Treatment decisions in patients with prostate cancer are affected by patient age regardless of higher life expectancy compared to the baseline population. Our aim was to quantify cancer specific and other cause mortality rates after radical prostatectomy.

Materials and Methods: A total of 8,741 patients with prostate cancer underwent radical prostatectomy between 1992 and 2009 at a European center. Ten-year other cause and cancer specific mortality rates were determined by age and comorbidities, and age and Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) risk groups. Competing risk regression was used for risk factor analyses including clinical and pathological variables.

Results: Ten-year other cause mortality rates increased with patient age, including 4.8%, 9.8%, 13.6% and 16.5% in men younger than 60, 60 to 64, 65 to 69 and 70 years or older, respectively. Cancer specific mortality was the leading cause of death in CAPRA-S high risk cases regardless of age. On multivariate analyses age groups achieved independent predictor status for other cause mortality (ages 60 to 64 years HR 1.81, 95% CI 1.26–2.62, 65 to 69 years HR 2.48, 95% CI 1.73–3.56 and 70 years or greater HR 3.02, 95% CI 1.97–4.62) as well as Charlson comorbidity indexes 1 (HR 1.45, 95% CI 1.00–2.09) and 3 or greater (HR 3.99, 95% CI 1.57–10.1). Gleason score 3 + 4 and 4 + 3 or greater, pT3b stage, lymph node invasion and positive margin status achieved independent predictor status when the end point was cancer specific mortality. The CAPRA-S high risk constellation increased cancer specific mortality risk in multifold fashion (HR 26, 95% CI 16–56).

Conclusions: In patients with the CAPRA-S high risk constellation the rate of cancer specific mortality increased in multifold fashion and contributed to most deaths regardless of patient age. Low other cause mortality rates in all age groups showed reasonable patient selection.

Key Words: prostatic neoplasms, age groups, mortality, prostate cancer, risk

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PROSTATE cancer is more frequently diagnosed and treated in older men. RP is the most commonly used treatment modality for clinically localized PCa in Western countries.[1] Often treatment decisions in older patients are heavily affected by patient chronological age and clinical cancer characteristics are not given as much impact as in younger patients.[2] As a result older patients may be less likely to receive curative treatment.[3,4] It is also notable that patients have higher life expectancy than the baseline population, at least in the United States.[5] Therefore, life expectancy may be underestimated, especially in older patients. In consequence, it is important to test whether unfavorable tumor characteristics carry the same weight for CSM in older patients with PCa as they do in younger patients, especially after many years of followup when comorbidities may interfere and lead to death from causes other than PCa.

On the other hand, there is ongoing discussion about patient selection before radical prostatectomy. We tested whether patients selected for surgery have long life expectancy. Additionally, we assessed risk factors for OCM in our select cohort. In this context our objective was to quantify CSM and OCM rates after RP in patients stratified by age categories and comorbidity status. Moreover, we investigated the impact of CAPRA-S risk groups on CSM stratified according to age groups. Finally, we attempted to identify clinical and pathological risk factors that predispose to particularly elevated CSM or OCM rates.

PATIENTS AND METHODS

Study Population and Intervention

A total of 8,741 patients with PCa treated with RP between 1992 and 2009 at a single high volume European center were included in study. A total of 163 patients with missing clinical or pathological data were excluded.

RP was performed via an open retropubic approach by staff urologists as described previously.[6–8] The pathological specimen was processed using serial step segmentation at 3 mm intervals according to the Stanford protocol.[9] Tumors were graded according to the Gleason system[10] and pathological stage was assigned using the 2002 TNM system.[11] Annual questionnaires and death reports of the national cancer registry were used for followup. All data were prospectively stored in the institutional Martini-Klinik Prostate Cancer Center database using FileMaker® Pro 10.

Covariables

Patients were stratified according to age into 4 classes, including 60 years or younger, 60 to 64, 65 to 69 and 70 years old or older. Comorbidities were assessed with the CCI[12] and stratified according to the absence (CCI 0) or the presence (CCI 1 or greater) of comorbidities. CCI was pseudo continuously coded (CCI 0 vs 1 vs 2 vs 3 or greater) for multivariable models. Pathological Gleason pattern and pT stage were stratified into 3 groups, including 3 + 3 or less, 3 + 4 and 4 + 3 or greater, and pT2, pT3a and pT3b or greater, respectively. PCa risk was stratified by the CAPRA-S scoring system into low, intermediate and high risk PCa as previously described.[13–15] Briefly, the CAPRA-S scoring system is based on PSA levels and 5 pathological variables, namely pathological Gleason score, extracapsular extension, seminal vesicle invasion, lymph node invasion and margin status.

Statistical Analyses

Cumulative incidence smoothed plots were used to illustrate CSM and OCM 10 years following RP, stratified according to age groups and CCI. Stratified plots were then generated to show the effect of age and CAPRA-S risk group on OCM and CSM.

Competing risk regression models were fitted to test the effect of age groups, CCI and pathological characteristics as well as CAPRA-S risk groups on CSM and OCM.[16] Investigating competing causes of mortality is particularly important when prolonged survival is expected. This is the case in patients with surgically treated PCa, in whom treatment decisions are based on long life expectancy. All tests were 2-tailed with $p < 0.05$ considered statistically significant. Statistical analyses were performed with RStudio®, version 0.98.953.

RESULTS

The patient population consisted of 8,741 men treated with radical prostatectomy between 1992 and 2009 at a single high volume European center. Of those men 2,452 (28.1%) were younger than 60 years, 2,538 (29.0%) were between 60 and 64 years old, 2,773 (31.7%) were between 65 and 69 years old, and 978 (11.2%) were older than 70 years. Table 1 lists patient characteristics.

Median followup in all patients was 65.6 months (IQR 48.3–96.7), which did not differ significantly between age groups. Overall 1,409 patients had followup in excess of 10 years or died. During the study period 453 patients (5.2%) died.

Cumulative incidence smoothed survival plots showed 10-year CSM and OCM rates of 3.2% and 5.9%, respectively, in the entire patient cohort. After stratification according to 4 age groups and CCI 0 vs 1 or greater the 10-year CSM rates were comparable in all 8 groups (range 2.1% to 4.3%). Conversely, for the end point OCM 10-year OCM rates were lower in younger patients than in older patients without comorbidities (CCI 0 in 2.2%, 5.4%, 7.8% and 6.5% at ages less than 60, 60 to 64, 65 to 69 and greater than 70 years, respectively). Ten-year OCM rates were also lower in younger patients than in older patients with comorbidities (CCI 1 or greater in 9.2%, 8.8%, 13.0% and 16.2% at ages less than 60, 60 to 64, 65 to 69 and greater than 70 years, respectively) (fig. 1).