



EUO Priority Article– Prostate Cancer

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Heterogeneity in Definitions of High-risk Prostate Cancer and Varying Impact on Mortality Rates after Radical Prostatectomy

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Abstract

Background: Multiple definitions of high-risk prostate cancer (PC) exist in clinical practice. Prior studies have primarily evaluated the variability in prediction of biochemical recurrence.

Objective: To examine the impact of different definitions on mortality after radical prostatectomy (RP).

Design, setting, and participants: Retrospective study of 6477 men with clinically localized disease undergoing RP at Barnes-Jewish Hospital (St. Louis, MO, USA) and Cleveland Clinic (Cleveland, OH, USA) between 1995 and 2007.

Outcome measurements and statistical analysis: Seven pretreatment definitions of high-risk PC (prostate-specific antigen [PSA] ≥ 20 ng/ml, biopsy Gleason score 8–10, clinical stage $\geq T2c$, cT3, D'Amico definition, National Comprehensive Cancer Network definition, Kattan nomogram) were evaluated. The Kaplan-Meier method was used to generate unadjusted survival estimates. Multivariable Cox proportional hazard regression models (controlling for age) were used to estimate the hazard ratio (HR) for PC-specific mortality (PCSM) and overall mortality (OM) in the high-risk group compared to men with lower risk not meeting that definition.

Results and limitations: 6477 men were treated with RP from 1995 to 2007 and were followed for a median of 67 mo. Depending on the definition, patients with high-risk PC comprised between 0.7% (when using cT3 as the criterion) and 8.2% (when using the D'Amico criterion) of the population. The 10-yr PC survival estimates varied from 89.7% (PSA ≥ 20 ng/ml) to 69.7% (cT3) and overall survival ranged from 83.4% to 58.1%. On multivariable analysis, all high-risk definitions were associated with a higher risk of PCSM compared to lower risk (HR ranging from 4.38 for PSA ≥ 20 ng/ml to 19.97 for cT3; all $p < 0.001$). All definitions of high risk except for preoperative PSA ≥ 20 ng/ml were associated with a higher risk of OM (HR 1.72 for D'Amico to 3.31 for cT3; all $p < 0.01$).

Conclusions: Heterogeneity in outcomes existed, depending on the pretreatment definition of high-risk PC. Clinical stage T3 and Gleason score 8–10 were most strongly associated with PCSM and OM.

Patient summary: There is variability in prostate cancer outcomes after surgery, depending on the definition of pretreatment high-risk disease used. Clinical stage T3 and high Gleason score were most strongly associated with prostate cancer-specific mortality and overall mortality.

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1. Introduction

Prostate cancer (PC) is the most common cancer in males and affects 16% of men during their lifetime [1]. The majority of men have low- or intermediate-risk PC that is effectively managed with surgery, radiation, active surveillance, or observation [2]. Unfortunately, a subset of men have locally aggressive and potentially lethal cancer, which is not as easily managed. These men with high-risk disease have a significant mortality risk when compared to men with low-risk PC [3–6]. Therefore, there is potentially resistance to aggressive local treatment with surgery because of concerns about the effectiveness and side effects of treatment.

However, this skepticism is often unfounded because of durable outcomes after radical surgery [7–9]. Although randomized trials of treatment in men exclusively with high-risk disease are lacking, evidence suggests there may be a potential survival advantage for the treatment of PC in a population with more aggressive disease [10,11]. In addition, utilization of neoadjuvant systemic treatment may become more important in the future [12,13]. Identifying men with high-risk disease will become increasingly critical to guiding management. However, there are multiple definitions of high-risk disease. The proportion of men diagnosed with high-risk PC and their respective cancer-specific mortality vary, depending on the definition utilized [9,14]. Exploring the impact of different definitions may be clinically valuable in helping to counsel patients, select treatment options, and predict mortality. In this study, the purpose was to examine the prevalence of clinical high-risk PC in a large multi-institutional group of men treated with radical prostatectomy (RP) and specific pretreatment definitions of high-risk PC to evaluate mortality in men who underwent RP.

2. Patients and methods

A total of 6477 men underwent RP at Barnes-Jewish Hospital (St. Louis, MO, USA) and Cleveland Clinic (Cleveland, OH, USA) between 1995 and 2007. Each patient in the cohort was thought to have localized disease and no patients had clinical T4 disease. The surgical approach was either open or minimally invasive RP. Concomitant pelvic lymph node dissection was at the discretion of the treating surgeon. Subsequent receipt of adjuvant or salvage external beam radiation therapy or androgen deprivation therapy (ADT) was at the discretion of the treating physician.

On the basis of clinical data available before surgery, each patient was classified as whether having high-risk PC or not using seven common definitions: (1) preoperative prostate-specific antigen (PSA) ≥ 20 ng/ml; (2) biopsy Gleason score 8–10; (3) clinical stage $\geq T2c$; (4) clinical stage T3; (5) National Comprehensive Cancer Network (NCCN) definition (PSA ≥ 20 ng/ml or clinical stage T3 or biopsy Gleason score 8–10); (6) D'Amico definition (PSA ≥ 20 ng/ml or clinical stage $\geq T2c$ or biopsy Gleason score 8–10) [16]; and (7) Kattan nomogram [17] 5-yr biochemical recurrence-free probability of $\leq 50\%$. Mortality was assessed based on clinical follow-up, correspondence, and query of the National Death Index. Cause of death was classified as from PC or another cause, and patients were censored at the date of death or last known follow-up.

To compare the relative outcomes for different definitions of high-risk PC, unadjusted survival estimates for PC-specific and overall survival were calculated using the Kaplan-Meier method. For each of the seven definitions of high-risk PC, a multivariable Cox proportional hazards regression model including age as a covariate was used to estimate hazard ratios for PC-specific mortality (PCSM) and overall mortality (OM) for men meeting that specific high-risk definition compared to men who did not meet that specific definition (the remaining men in the cohort of 6477 who did not meet the specific definition of high-risk PC). Age was included a priori in the multivariate model as it is known to be associated with overall mortality. Analysis was performed using SPSS v.17 (SPSS, Chicago, IL, USA) and SAS v. 9.2 (SAS Institute, Cary, NC, USA). We considered $p < 0.05$ as statistically significant. Institutional review board approval was obtained for the study.

3. Results

The overall study cohort of 6477 men who underwent RP had a median age of 62 yr and median PSA of 5.6 ng/ml. The proportion of the study population with high-risk disease varied from 0.7% (44/6477) for cT3 disease to 8.2% (529/6477) for the D'Amico definition (Table 1). The proportion was 2.2% for clinical stage $\geq T2c$, 3% for the Kattan nomogram of 5-yr recurrence-free survival $\leq 50\%$, 3.2% for PSA ≥ 20 ng/ml, 4.2% for Gleason score 8–10, and 7% for the NCCN criterion for high-risk PC. The median follow-up for the entire cohort was 67 mo, with death occurring in 464 men. Death was from PC in 76 men and other causes in 388 men.

Survival curves for PC are shown in Figure 1. The 10-yr Kaplan Meier PC survival estimates varied from 89.7% for PSA ≥ 20 ng/ml to 69.7% for cT3 as the high-risk criterion. The overall survival by different definitions of high-risk PC showed a similar trend (Fig. 2) as the 10-yr Kaplan Meier overall survival, for which estimates varied from 83.4% for PSA ≥ 20 ng/ml to 58.1% for cT3 as the high-risk criterion.

On multivariable analysis, all high-risk definitions were associated with a higher risk of PCSM in comparison to patients who did not meet the specific definition of high-risk PC (Table 2). Hazard ratios for PCSM ranged from 4.38 for PSA ≥ 20 ng/ml to 19.97 for cT3 as the criterion (all $p < 0.0001$). For OM (Table 3), all the definitions of high-risk PC except preoperative PSA ≥ 20 ng/ml (HR 0.98; $p = 0.99$) were associated with a higher risk of OM in the high-risk group compared to patients who did not meet the definition (HR 1.72 for D'Amico, 1.73 for stage $\geq T2c$, 1.75 for Kattan, 1.88 for NCCN, 2.63 for Gleason 8–10, 3.31 for cT3; all $p < 0.01$).

Table 1 – Number of men meeting seven different criteria defining high-risk prostate cancer among the cohort of 6477 patients who underwent radical prostatectomy

Definition of high-risk prostate cancer	Men, n (%)
Clinical stage T3	44 (0.7)
Clinical stage $\geq T2c$	141 (2.2)
Kattan nomogram 5-yr recurrence-free survival $\leq 50\%$	193 (3.0)
Prostate-specific antigen ≥ 20 ng/ml	208 (3.2)
Biopsy Gleason score 8–10	275 (4.2)
National Comprehensive Cancer Network high risk	454 (7.0)
D'Amico high risk	529 (8.2)

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