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Original article

Stage at presentation and survival outcomes of patients with Gleason 8–10 prostate cancer and low prostate-specific antigen

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Abstract

Objective: To evaluate outcomes for men with high Gleason score and low prostate-specific antigen (PSA) prostate cancer. Low PSA levels among men with Gleason 8–10 prostate cancer may be owing to cellular dedifferentiation rather than low disease burden. We hypothesized that men with Gleason 8–10 prostate cancer and low PSA levels have increased risk for advanced disease and worse survival.

Materials and methods: Men diagnosed from 2004 to 2007 with Gleason 8–10 prostate adenocarcinoma in the National Cancer Data Base were included. Patients were stratified by PSA levels at diagnosis: 0.1 to 3.9, 4.0 to 9.9, 10.0 to 19.9, and ≥20.0 ng/ml. Outcomes were clinical TNM category, pathologic stage (for prostatectomy patients), and overall survival (OS). Kaplan-Meier analysis and Cox proportional hazards models were used.

Results: A total of 37,283 patients were included. Men with PSA levels of <4.0 ng/ml were more likely than those with PSA levels of 4 to 9.9 ng/ml to present with clinical T3–4 disease (15% vs. 10%, $P < 0.001$), nodal (4% vs. 2%, $P < 0.001$) and distant (5% vs. 3%, $P < 0.001$) metastasis. However, among patients treated with prostatectomy, lower PSA levels were not associated with increased likelihood of pathologic T3–4 disease or nodal metastasis. Six-year OS was 89.1% (PSA: 0.1–3.9 ng/ml) vs. 91.0% (PSA: 4.0–9.9 ng/ml) for prostatectomy (log-rank $P < 0.001$), and 75.8% vs. 81.0% for radiotherapy ($P < 0.001$). Multivariable analyses showed OS of patients with PSA levels of 0.1 to 3.9 ng/ml to be similar to those with PSA levels of 10 to 19.9 ng/ml.

Conclusions: Patients with Gleason 8–10 cancer and PSA levels of <4.0 ng/ml have more aggressive disease than those with PSA levels of 4 to 9.9 ng/ml; these low PSA cancers behave more like those with PSA levels of 10 to 19.9 ng/ml. Further study is needed to evaluate potential biological differences in these patients with low PSA-producing cancers.

Keywords: High-risk prostate cancer; PSA; Survival; NCDB

1. Introduction

High pretreatment serum levels of prostate-specific antigen (PSA) are associated with worse prostate cancer outcomes [1,2], likely due to PSA levels reflecting tumor burden. However, some high-grade cancers (Gleason score 8–10) can involve tumor cell dedifferentiation, which may be associated with low PSA production. It is possible that patients with Gleason 8–10 cancers but a low PSA level may have the most aggressive form of prostate cancer and worse survival outcomes after treatment.

Few studies have specifically examined the outcomes of patients with high-Gleason low-PSA prostate cancers. In a series of 354 patients who underwent a radical prostatectomy

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by a single surgeon, McGuire et al. [3] reported inferior progression-free survival and increased seminal vesicle invasion among men with Gleason 8–10 prostate cancer and PSA < 2.5 ng/ml compared with patients with PSA levels between 2.6 and 10 ng/ml. Another study using the Swedish National Prostate Cancer Register of patients from 1996 to 2005 found that PSA < 4.0 ng/ml was associated with a worse relative survival for all Gleason scores; the difference was most pronounced among men with Gleason 8–10 prostate cancer [4].

The present study is the first large-scale US study to address this question by examining men treated in recent years with contemporary techniques. In this study, we used data from the National Cancer Data Base (NCDB) to evaluate the relationship between pretreatment PSA level and survival outcomes among men with biopsy Gleason 8–10 prostate cancer. Results from this study are clinically relevant because pretreatment disease characteristics inform decisions regarding optimal treatment selection, which may be especially important for high-risk disease where cure rates from current standard therapies are suboptimal [5]. Our hypothesis is that men with Gleason 8–10 prostate cancer and low PSA (3.9 ng/ml or less) have a higher risk for advanced disease and worse survival compared to patients with higher PSA levels.

2. Materials and methods

2.1. Data source

The NCDB is the largest oncology database in the United States, containing approximately 70% of cancer patients nationwide, and is jointly maintained by the American College of Surgeons and the American Cancer Society [6]. NCDB contains patient-level demographic information such as race, age, and insurance status. Regional-level education and household income information is available and is reported by U.S. postal zip code. The NCDB also contains details regarding disease characteristics (year of diagnosis, clinical stage, PSA at diagnosis, and biopsy Gleason score), first course of treatment (e.g., radiotherapy and prostatectomy), and pathologic stage for patients who received surgery.

2.2. Patient cohort

Men diagnosed with prostate cancer between 2004 and 2007 were included. These years of diagnosis were chosen to allow for sufficient follow-up time to evaluate survival. In addition, patients from before 2004 were not included because PSA and Gleason score were not routinely collected. Included patients all had biopsy Gleason score of 8–10 adenocarcinoma, known PSA, and known clinical T category at diagnosis. Men with prior cancers were excluded as prior cancers can impact a patient's treatments and survival. A patient exclusion schema is shown in the Supplemental Table. The final analytic cohort consisted of 37,283 patients.

2.3. Statistical analysis

Patients were analyzed in 4 different groups based on PSA level at diagnosis: 0.1 to 3.9, 4.0 to 9.9, 10.0 to 19.9, and ≥20.0 ng/ml. For each group, descriptive statistics were used to summarize the clinical presentation (clinical T, N, and M category, biopsy Gleason score). Differences among patient groups were compared using the chi-square test, first across all 4 groups, then between the lowest PSA group (0.1–3.9 ng/ml) and the next higher group (4.0–9.9 ng/ml).

In addition, for patients who received radical prostatectomy, pathologic T and N categories were compared among groups.

Survival analyses were performed for patients who were not known to have nodal or distant metastatic disease and received definitive treatment. Patients treated with radical prostatectomy were analyzed separately from those who received external beam radiotherapy. Overall survival (OS) was evaluated using the Kaplan-Meier method, and log-rank P values were calculated to determine the statistical significance of observed differences among groups. Cox proportional hazards models were used to calculate hazard ratios (HR) for OS. Reported HR were adjusted for potentially relevant factors including year of diagnosis, race, age, U.S. region, regional income and education, insurance status, comorbidity (Charlson/Deyo score), biopsy Gleason score, and clinical T category at diagnosis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided P values were calculated with a level <0.05 considered statistically significant.

3. Results

Patient characteristics are summarized in Table 1. Overall, 69% of patients were white, and 92% had private insurance or Medicare coverage. Radiotherapy was the initial treatment for 46% of patients and 25% of men received radical prostatectomy.

The distribution of clinical T, N and M categories at diagnosis for each of the PSA groups is summarized in Table 2. Men with the lowest PSA level (0.1–3.9 ng/ml) were more likely than those with PSA levels of 4.0–9.9 ng/ml to present with clinical T3–4 disease (15.0% and 9.7% respectively; $P < 0.001$), nodal metastasis (3.8% vs. 2.1%, $P < 0.001$), and distant metastasis (5.4% vs. 2.6%, $P < 0.001$). Men with PSA ≥ 20.0 ng/ml were significantly more likely to present with metastatic disease compared to all other groups (27% vs. 3%–8%, $P < 0.001$).