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Clinical and Genomic Characterization of Low–Prostate-specific Antigen, High-grade Prostate Cancer

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Abstract

Background: The consequences of low prostate-specific antigen (PSA) in high-grade (Gleason 8–10) prostate cancer are unknown.
Objective: To evaluate the clinical implications and genomic features of low-PSA, high-grade disease.
Design, setting, and participants: This was a retrospective study of clinical data for 494 793 patients from the National Cancer Data Base and 136 113 patients from the Surveillance, Epidemiology, and End Results program with cT1–4N0M0 prostate cancer (median follow-up 48.9 and 25.0 mo, respectively), and genomic data for 4960 patients from the Decipher Genomic Resource Information Database. Data were collected for 2004–2017.
Outcome measurements and statistical analysis: Multivariable Fine-Gray and Cox regressions were used to analyze prostate cancer–specific mortality (PCSM) and all-cause mortality, respectively.
Results and limitations: For Gleason 8–10 disease, using PSA 4.1–10.0 ng/ml (n = 38 719) as referent, the distribution of PCSM by PSA was U-shaped, with an adjusted hazard ratio (AHR) of 2.70 for PSA ≤2.5 ng/ml (n = 3862, $p < 0.001$) versus 1.97, 1.36, and 2.56 for PSA of 2.6–4.0 (n = 4199), 10.1–20.0 (n = 17 372), and >20.0 ng/ml (n = 16 114), respectively. By contrast, the distribution of PCSM by PSA was linear for Gleason ≤7 (using PSA 4.1–10.0 ng/ml as the referent, n = 359 898), with an AHR of 0.41 (p = 0.13) for PSA ≤2.5 ng/ml (n = 37 812) versus 1.38, 2.28, and 4.61 for PSA of 2.6–4.0 (n = 54 152), 10.1–20.0 (n = 63 319), and >20.0 ng/ml (n = 35 459), respectively ($p_{interaction} < 0.001$). Gleason 8–10, PSA ≤2.5 ng/ml disease had a significantly higher PCSM than standard high-risk/very high-risk disease with PSA >2.5 ng/ml (AHR 2.15, p = 0.002; 47-mo PCSM 14% vs 4.9%). Among

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Gleason 8–10 patients treated with radiotherapy, androgen deprivation therapy was associated with a survival benefit for PSA >2.5 ng/ml (AHR 0.87; $p < 0.001$) but not ≤2.5 ng/ml (AHR 1.36; $p = 0.084$; $p_{interaction} = 0.021$). For Gleason 8–10 tumors, PSA ≤2.5 ng/ml was associated with higher expression of neuroendocrine/small-cell markers compared to >2.5 ng/ml ($p = 0.046$), with no such relationship for Gleason ≤7 disease.
Conclusions: Low-PSA, high-grade prostate cancer has very high risk for PCSM, potentially responds poorly to androgen deprivation therapy, and is associated with neuroendocrine genomic features.
Patient summary: In this study, we found that low–prostate-specific antigen, high-grade prostate cancer has a very high risk for prostate cancer death, may not respond well to androgen deprivation therapy, and is associated with neuroendocrine genomic features. These findings suggest that current nomograms and treatment paradigms may need modification.

1. Introduction

Most prostate cancers are adenocarcinomas, and a high tumor grade (Gleason 8–10) is an established high-risk feature. Treatment options include radical prostatectomy (RP) or radiotherapy with long-course androgen deprivation therapy (ADT) [1].

Prostate cancer is typically highly androgen-dependent and exquisitely sensitive to ADT [2]. In addition, PSA production is positively regulated by androgens [3]. Although PSA is typically elevated in high-grade disease, some patients present with the discordant scenario of high-grade disease and low PSA. The clinical and biological implications of low PSA in high-grade prostate cancer are unclear [4]. Low-PSA, high-grade disease may represent a unique entity with underlying dedifferentiated biology, and as such may respond poorly to current standard treatments, particularly ADT. However, there are few clinical and biological data to support this hypothesis [5–8].

The canonical low–PSA-producing prostate cancer is neuroendocrine prostate cancer, including the small-cell variant, which represents an aggressive and hormone-resistant entity [9–12]. There is low sensitivity for the detection of neuroendocrine features on biopsy or RP specimens [9]. Emerging genomic characterization of neuroendocrine prostate cancer has identified common mutations that represent a "molecular signature" that may aid in detection and targeted therapy [12–15]. Whether low-PSA, high-grade disease shares genomic features with neuroendocrine prostate cancer has not been explored.

Understanding the biology and behavior of low-PSA, high-grade prostate cancer is highly relevant; there is an active effort to improve the understanding and outcomes of aggressive localized prostate cancers through the utilization of genomics and application of targeted agents [16–19]. Therefore, we characterized the prognostic and predictive values of low PSA in high-grade prostate cancer, as well as the genomic features of this entity among men diagnosed with prostate cancer.

2. Patients and methods

2.1. Study cohorts

2.1.1. NCDB and SEER

The National Cancer Data Base (NCDB) captures 70% of incident cancers in the USA [20] and identified 494 793 patients diagnosed with cT1–4N0M0 prostate cancer from 2004 to 2011. The Surveillance, Epidemiology and End Results (SEER) program encompasses 28% of the US population [21] and identified 136 113 men diagnosed with cT1–4N0M0 prostate cancer from 2010 to 2013. Patients with neuroendocrine or small-cell histology were excluded. PSA values in SEER from 2010 onwards have been audited for accuracy [22].

Therapy received included RP, radiotherapy (external beam radiotherapy [EBRT] or brachytherapy), and ADT (only available in the NCDB). Gleason scores reflect pathologic grade when available or biopsy otherwise. Race was classified as Black or non-Black. The Charlson-Deyo comorbidity score was reported by the NCDB and was also used.

2.1.2. GRID

The Decipher Genomic Resource Information Database (GRID), a global expression database for urologic oncology (NCT02609269) that includes basic demographic and baseline clinical information, was queried for patients with available grade group and PSA. This cohort comprises of anonymized data from clinical use of the Decipher test between February 2014 and February 2017. Genome-wide expression profiles of formalin-fixed, paraffin-embedded RP samples for 4960 patients from the Decipher GRID with histologically confirmed prostate adenocarcinoma (by central pathology) were analyzed.

2.2. Statistical analysis

2.2.1. Baseline characteristics

The Wilcoxon rank-sum and Mantel-Haenszel χ^2 tests were used to compare distributions of continuous and categorical covariates, respectively, stratified by predetermined PSA levels [8].

2.2.2. Prognostic analysis: estimates of PCSM and ACM by PSA level, stratified by Gleason score

The primary independent variable of interest was PSA level at diagnosis (stratified by Gleason ≤7 vs 8–10), and endpoints were prostate cancer-specific mortality (PCSM for SEER, which provides cause of death) and all-cause mortality (ACM for NCDB, which only provides vital status).

We used multivariable Fine-Gray competing-risks and Cox regressions to define hazard ratios by PSA level stratified by Gleason score for PCSM (SEER) and ACM (NCDB), respectively. Variables included in the models were PSA level (≤2.5, 2.6–4.0, 4.1–10.0 [referent], 10.1–20.0, >20.0 ng/ml), clinical tumor stage (T1 [referent], T2, T3, T4), age (continuous), race (non-Black [referent], Black), initial treatment (none [referent], RP, radiotherapy; adjusted for ADT in the NCDB), and Charlson-Deyo comorbidity score in the NCDB (0 [referent], 1, ≥2). To ascertain the risk of PCSM and ACM in low-PSA, high-grade disease, our models included PSA level (≤2.5 vs >2.5 ng/ml) × Gleason (≤7 vs 8–10) as an interaction term.

A second set of Fine-Gray competing-risks and Cox regressions were used to define hazard ratios for PCSM and ACM by National Comprehensive Cancer Network (NCCN) risk groups [1] compared to

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