Original Study

Prostate Cancer in Patients With High Prostate-Specific Antigen Levels but Otherwise Very-Low-Risk Disease Behaves Like Prostate Cancer in High-Risk Patients

Matthew M. Gestaut,[1] Jessica E. Pruszynski,[2] Gregory P. Swanson[1]

Abstract

A review was conducted of divergent-risk prostate cancer patients treated with radiation. These patients exhibited a low-volume, low-risk Gleason score but high-risk prostate-specific antigen level. The clinical outcomes were compared with those of classically high-risk and ultra-low risk patients. The disease prognosis of the divergent-risk group was equally poor as their classically high-risk counterparts. These patients should be treated similarly to classically high-risk patients.

Introduction: Rarely, patients with prostate cancer present with prostate-specific antigen (PSA) scores > 20 ng/mL but with otherwise very-low-risk disease. Oncologists have debated whether the malignancies in these patients behave more comparably to low-risk or high-risk disease. Our objective was to elucidate the behavior of these malignancies. **Materials and Methods:** A retrospective review was conducted of prostate cancer patients treated with radiation from 2000 to 2013. The inclusion criteria for very-low-risk disease included stage T1a-T1c, Gleason score ≤ 6, ≤ 3 positive cores, ≤ 50% involvement of any core, and PSA level < 10 ng/mL. The divergent-risk group met all the same criteria but had a PSA score of 20 to 80 ng/mL. The high-grade, low-volume group consisted of patients with stage T1c-T2a, PSA level < 20 ng/mL, Gleason score of 4+4, and < 4 positive cores. Treatment failure was defined as a PSA nadir plus 2 ng/mL. **Results:** A total of 18, 60, and 19 patients were in the divergent, low-risk, and high-grade groups, respectively. Biochemical progression-free survival at 5 years was 71.3% for the divergent group, 68.8% for the high-grade group, and 98.3% for the low-risk group. The biochemical failure rate for the divergent group differed significantly from the low-risk group ($P = .021$), and that for the low-risk group was significantly different from that of the high-grade group ($P = .025$). However, the divergent group did not appear different from the high-grade group ($P = .53$). **Conclusion:** The results of our study have shown that the disease prognosis for the divergent-risk group is worse than that for the very-low-risk disease group and does not appear to be different from that for the low-volume, high-grade disease group. Oncologists should be aware that the outcomes for divergent patients are similarly poor to their low-volume, classically high-risk counterparts.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Divergent risk, High PSA, High-risk disease, Low-volume disease, Very-low-risk prostate cancer

Introduction

The National Comprehensive Cancer Network risk stratification system offers a well-validated method of determining the appropriate treatment options for patients with prostate cancer.[1] Retrospective analyses have revealed 3 prognostic factors that correlate with biochemical progression-free survival.[2-4] Low-risk disease includes patients with stage T1a to T2a, prostate-specific antigen (PSA) level < 10 ng/mL, or Gleason score (GS) < 7. Intermediate-risk disease includes patients with stage T2b, PSA level of 10 to 20 ng/mL, or GS of 7. High-risk disease includes patients with stage T2c or greater, PSA level > 20 ng/mL, or GS of ≥ 8.[1] Meeting 1 risk factor criterion for stage, PSA, or GS stratifies a patient into a risk group with the associated available treatments.

[1]Department of Radiation Oncology, Scott and White Memorial Hospital, Texas A&M University Health Science Center School of Medicine, Temple, TX
[2]Department of Biostatistics, Scott and White Memorial Hospital, Temple, TX

Submitted: Jul 20, 2016; Revised: Sep 21, 2016; Accepted: Oct 10, 2016

Address for correspondence: Matthew M. Gestaut, MD, Department of Radiation Oncology, Scott and White Memorial Hospital, Texas A&M University Health Science Center School of Medicine, 2401 South 31st Street, Temple, TX 76508
E-mail contact: Matthew.Gestaut@BSWHealth.org

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2016.10.003

In recent years, a fourth risk group, known as very low risk, was developed.[1,5] Patients in the very-low-risk group have stage T1c, GS of ≤ 6, PSA level < 10 ng/mL, < 3 positive prostate biopsy cores in $< 50\%$ of any core, and PSA density of < 0.15 ng/mL/g. This very-low-risk group differs from the low-, intermediate-, and high-risk groups in that active surveillance might be selected in lieu of definitive treatment. The earliest series of active surveillance data also included patients with low-volume disease and a GS of 3+4.[6] With strict monitoring adherence, the cancer-specific mortality for these patients was $< 2\%$.[5,6] The optimal inclusion criteria are still evolving for patient selection for active surveillance.

Currently, the specific stratification factors offering the most weighting for appropriate prognostication within each risk group are unknown. Ongoing investigations aim to elucidate further subclassifications within risk groups.[7-9] As a stand-alone factor, the PSA level contributes significantly to early prostate cancer detection.[10] The PSA level is also a proxy for predicting higher risk pathologic disease findings such as seminal vesicle invasion and extracapsular invasion.[11] However, PSA's specificity in determining prognostication as an independent variable tends to be one of the weakest when considering other risk factors.[12-16]

A rare subset of patients with prostate cancer presents with a biochemically divergent risk stratification. They have a high PSA level but otherwise very-low-risk findings for GS, stage, and the number and/or percentage of cores affected by cancer. Given the weak correlates of PSA as an independent risk factor, uncertainty exists regarding whether the prostate cancer of these patients behaves more similarly to low-risk or high-risk disease. For these cases, evidence for appropriate risk stratification is lacking.

Surgical series have offered some insight into the course of patients with an elevated PSA level but otherwise low-risk disease found in biopsy specimens. These studies have confirmed the PSA level as a predictor of high-risk pathologic features found on resection. In a radical prostatectomy series at Johns Hopkins University, an approximately 60% upstaging to pT3a or greater was found. The disease of nearly 50% of these patients was also upgraded to a GS of 7, with 18% exhibiting GS $\geq$ 4+3. The high-risk factors for biochemical recurrence include both stage T3a disease and GS of 4+3. Currently, no evidence exists regarding the efficacy of radiation therapy for patients with very-low-risk disease but divergent, high-risk PSA levels. This patient population is often treated as having high-risk disease based solely on the PSA values. Owing to the poor prognostication value of an elevated PSA level alone, it remains unclear how aggressively the disease behaves among patients receiving definitive radiation therapy. The objective of the present analysis was to compare these divergent-risk patients undergoing radiation therapy with their very-low-risk and low-volume, high-grade counterparts.

Materials and Methods

Our goal was to compare the outcomes of 3 different low-volume (as measured by the number of positive cores) prostate cancer cohorts. These included very low risk, divergent risk (low volume, low grade but high PSA), and high grade with low volume. By definition, the latter 2 are considered high-risk disease. The institutional review board the retrospective review of patients with low-volume and low-grade versus low-volume and high-grade prostate cancer. The tumor registry was queried for patients meeting the predefined inclusion criteria from 2000 to 2012. Very-low-risk disease was defined by the presence of all the following conditions: stage T1a-T2a, GS of ≤ 6, ≤ 3 positive cores, $\leq 50\%$ involvement of any core, and PSA level < 10 ng/mL. The divergent-risk group were low-risk patients (stage T1a-T1c, GS ≤ 6, ≤ 3 positive cores, and $\leq 50\%$ involvement of any core) but with a PSA value of 20 to 80 ng/mL. The low-volume plus high-grade group consisted of patients with all the following characteristics present: stage T1c-T2a, PSA level < 20 ng/mL, GS of 4+4 only, and < 4 positive cores. A higher absolute number of total positive biopsy cores was used owing to the paucity of patients presenting with GS 4+4 disease and ≤ 3 positive cores. The patients were required to have received definitive radiation therapy consisting of external beam radiation therapy or low-dose rate brachytherapy, or both. For inclusion in the present study, all patients in the divergent-risk and high-grade groups were required to have undergone metastatic imaging studies with negative findings, including a bone scan and/or whole body computed tomography scan. Androgen deprivation therapy (ADT) was permitted either neoadjuvantly or adjuvantly. Patients were excluded if they met any of following conditions: previous radical prostatectomy, a history of pelvic radiation treatment, incomplete risk stratification before treatment, or not meeting all the inclusion criteria.

Additional pretreatment features for risk stratification were collected, including prostate size (for calculation of the PSA density). The treatment specifics obtained were the duration and type of ADT, radiation dose, and inclusion or exclusion of lymph nodes in the treatment field. The PSA values were trended to nadir and recorded as recurrence using the definition of the nadir plus 2 ng/mL.

Statistical Analysis

The characteristics of the sample were assessed using descriptive statistics. The frequencies and percentages were recorded for categorical variables. The mean $\pm$ standard deviation was calculated for the symmetric continuous variables, and the median and interquartile range were recorded for nonsymmetric continuous variables. The distributions of the variables of interest were compared among the low-risk, high-grade, and divergent-risk groups using both 1-way analysis of variance and the Kruskal-Wallis test, as appropriate. The biochemical recurrence rate was described using a Kaplan-Meier plot. A log-rank test was used to measure the rates among the risk groups. Statistical significance was indicated by $P < .05$.

Results

Patient Characteristics

The data from 97 patients were evaluated. Of the 97 patients, 18, 60, and 19 were in the divergent-, low-risk, and high-grade groups, respectively. The mean PSA follow-up duration was 56 months for the divergent-risk, 74 months for the low-risk, and 64 months for the high-grade group ($P = .404$). Of the study population, 85% had unilateral disease found on biopsy. No meaningful difference was found among the groups in terms of bilateral versus unilateral distribution ($P = .336$). The mean number of positive biopsy cores for all subjects was 1.9 (median, 2; range, 1-4; $P = .0004$). A comparison among the groups for the number of positive biopsy cores showed no difference between the low- and divergent-risk