PSA Failure Following Definitive Treatment of Prostate Cancer Having Biopsy Gleason Score 7 With Tertiary Grade 5

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The widely used Gleason scoring system for the pathological grading of adenocarcinoma of the prostate is based on the architectural patterns of prostatic glands seen at low-power magnification. The system was developed and refined by Donald Gleason based on analysis of more than 4000 prostatectomy specimens from the Veterans Administration Cooperative Urological Research Group series between 1960 and 1975.1,2 Since then, many studies3-5 have confirmed the prognostic significance of the Gleason score with respect to time to recurrence and death following definitive local therapy.

The Gleason scoring system assigns a grade of 1 to 5 (higher grade being less differentiated) to the predominant pattern and to the second most prevalent pattern in the specimen. The 2 grades are summed to arrive at a final score between 2 and 10 inclusive.6 Although the Gleason scoring formalism does not incorporate a third pattern, the presence of more than 2 Gleason patterns in an individual tumor is widely recognized to occur and many pathologists comment on a tertiary pattern.6,7 In fact, significant heterogeneity has been shown to exist in the patterns of reporting tertiary Gleason grade among pathologists.8 However, the prognostic significance of such a tertiary pattern was not known.

For the situation of biopsy, Gleason score 7 (3 + 4 or 4 + 3) with a tertiary pattern of 5 warrants further investigation as to its prognostic signifi-

Context In 2005, the International Society of Urologic Pathology consensus conference recommended that men with biopsy Gleason score 3 + 4 or 4 + 3 prostate cancer and tertiary pattern 5 should have their cancer classified as Gleason score 8 or 9, respectively. Yet, the management of men with Gleason score 7 vs 8 or 9 prostate cancer differs.

Objective To compare the prognostic significance of Gleason score 7 with tertiary grade 5 vs other Gleason scores with respect to time to prostate-specific antigen (PSA) failure in men with prostate cancer.

Design, Setting, and Patients From 1989 to 2005, 2370 men with clinical tumor category 1c to 3b, node-negative, and nonmetastatic prostate cancer underwent definitive therapy with surgery or radiation therapy with or without hormonal therapy. A pathologist with expertise in genitourinary cancers assigned Gleason scores to the prostate needle biopsy specimens. Cox regression was used to assess whether a significant association existed between the presence of tertiary grade 5 in men with Gleason score 7 disease and time to recurrence compared with men with Gleason score 7 without tertiary grade 5, Gleason score 5 to 6, or 8 to 10 disease, adjusting for known prognostic factors and treatment.

Main Outcome Measure Time to PSA failure.

Results Men with Gleason score 7 and tertiary grade 5 disease had a significantly shorter time to PSA failure than men with 7 without tertiary grade 5 (median time, 5.0 vs 6.7 years, respectively; adjusted hazard ratio (HR), 0.56; 95% confidence interval [CI], 0.32-0.97; P = .04) or score of 6 or less (median time, 15.4 years; adjusted HR, 0.24; 95% CI, 0.13-0.43; P < .001). However, a significant difference was not observed when these men were compared with men with Gleason score 8 to 10 disease (median time, 5.1 years; adjusted HR, 0.96; 95% CI, 0.54-1.71; P = .90).

Conclusion In this study population, men with prostate cancer having biopsy Gleason score 7 and tertiary grade 5 had a higher risk of PSA-failure when compared with men with Gleason score 7 without tertiary grade 5 and had a comparable risk with men with Gleason score 8 to 10.

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cance. Specifically, there are published studies evaluating the implications of tertiary grade 5 within radical prostatectomy specimens, but only 1 study with 172 patients examining this situation within biopsy specimens. The existing literature uniformly demonstrates that patients with a prostatectomy Gleason score of 7 and a tertiary pattern of 5 have a significantly shorter time to prostate-specific antigen (PSA) progression than patients with Gleason score 7 tumors without tertiary grade 5 at radical prostatectomy. Also, these men with clinically organ-confined prostate cancer and tertiary pattern 5 are more likely to be found to have extraprostatic disease at prostatectomy.

In 2005, the International Society of Urologic Pathology held a consensus conference to address controversial issues surrounding the Gleason grading system. Their recommendations regarding tertiary Gleason grade 5 differed depending on the source of the specimen. For radical prostatectomy specimens, they recommended reporting the primary and secondary Gleason patterns, with a comment as to the tertiary pattern. For needle biopsy specimens, they recommended deriving the final Gleason score from the sum of the most prevalent pattern and the highest grade pattern so that tumors with tertiary grade 5 that would have traditionally been reported as Gleason score 3 + 4 or 4 + 3 would be assigned a total score of 8 (3 + 5) and 9 (4 + 5), respectively.

Evidence supporting this recommendation based on time to recurrence following definitive therapy for men with localized or locally advanced prostate cancer is lacking. Therefore, in this study, such men are evaluated to determine whether a significant association exists between the presence of tertiary grade 5 in men with Gleason score 7 prostate cancer and time to recurrence compared with men with Gleason score 7 without tertiary grade 5 and men with Gleason score 5 to 6 or 8 to 10 disease adjusting for known prognostic factors.

### METHODS

#### Patient Characteristics and Treatment

The study cohort comprised 2370 men with clinically tumor (T) category T1c to T3b, node-negative and nonmetastatic adenocarcinoma of the prostate treated between 1989 and 2005 at Harvard-affiliated hospitals (St Anne’s Hospital, Brigham and Women’s Hospital, and Dana Farber Cancer Institute). Patients were treated with radical prostatectomy (n = 1242), radiation therapy (n = 806), or radiation therapy with 2 months each of neoadjuvant, concurrent, and adjuvant androgen suppression therapy (AST) (n = 322). Patients were excluded if they had undergone radical prostatectomy and received preoperative or postoperative AST, or adjuvant radiation therapy. The study was performed with the approval of the institutional review board of the participating institutions, and each patient signed an informed consent form. All Gleason scores were assigned by a single pathologist (A.A.R.) who has expertise in grading cancers of the genitourinary tract.

In all cases, radical prostatectomy consisted of a radical retropubic prostatectomy with bilateral lymph-node sampling. Radiation therapy was delivered using shaped blocks based on computed tomography–defined volumes transferred onto pelvic plain films prior to 1994, and thereafter, computed tomography-based 3-dimensional conformal treatment planning was used. A total dose of 70.2 Gy was administered consistently. Adjuvant androgen suppression therapy was achieved by combined blockade with a luteinizing hormone-releasing hormone agonist (leuprolide or goserelin) and a nonsteroidal antiandrogen (bicalutamide or flutamide). Injections of leuprolide (7.5 mg/mo) or goserelin (3.6 mg/mo) were given in either 1-month or 3-month formulations. Bicalutamide (50 mg/d) or flutamide (250 mg every 8 hours) were taken orally starting at 1 to 3 days prior to luteinizing hormone-releasing hormone agonist initiation to block the transient testosterone surge.

#### Follow-up

The median follow-up was 4.2 (interquartile range [IQR], 1.8-6.7) years with censoring occurring at the time of PSA failure, beginning on the date of radical prostatectomy or initiation of other therapy and concluding on March 8, 2005, or the date of death, whichever was earlier. Routine follow-up included a serum PSA measurement followed by a digital rectal examination generally every 3 months for 2 years, then every 6 months for an additional 3 years, and annually thereafter. Prostate-specific antigen recurrence following radiation therapy (with or without AST) was defined as the date at which the PSA level became 2 ng/mL higher than the nadir, according to the 2006 consensus definition of the American Society for Treatment of Prostate Cancer. The American Federation of Clinical Research and the American Society for Clinical Oncology have listed this study as a Type 1 clinical trial.
for Therapeutic Radiology and Oncology. Prostate-specific antigen recurrence for surgical patients was defined on the date at which the PSA level became higher than 0.2 ng/mL with a second confirmatory value higher than 0.2 ng/mL.

**Statistical Methods**

**Time to PSA Failure Analyses.** Descriptive statistics were used to define the patient population at baseline. Cox regression univariate and multivariate analyses were performed with the primary end point being time to PSA failure following treatment. Gleason score, tumor category, and treatment modality were analyzed as categorical variables, whereas age and PSA level were considered as continuous variables. For categorical variables, the cut points were defined prior to analyzing the data, according to established strata. These categories included Gleason score 6 or less without tertiary grade 4 or 5; 7 without tertiary grade 5; 7 with tertiary grade 5; and 8 to 10; Clinical T1c category 1c, 2, and 3; treatment with radical prostatectomy, radiation therapy plus AST, or radiation therapy. Baseline groups were Gleason score 7 with tertiary grade 5, clinical T1c category, and treatment group radiation therapy and AST. For all Cox regression analyses, the assumptions of the proportional hazards model were tested and met, and all statistical tests were 2-sided. Adjusted and unadjusted hazard ratios (HRs) for PSA recurrence with the associated 95% confidence intervals (CIs) were calculated for all covariates.

**Propensity Analysis.** A propensity analysis was performed to account for biases in treatment effect arising from nonrandom allocation of patients to different treatment groups. Propensity analysis required calculation of conditional probabilities for the 3 treatment groups using a multivariate logistic regression model. Two of the propensity scores (for radical prostatectomy and radiation therapy) were then used in the Cox regression model.

Estimates of PSA failure stratified by Gleason Score. For the purpose of illustration, estimates of time to PSA recurrence following treatment and stratified by the categorical covariates of Gleason score were displayed and these estimates were made using the method of Kaplan and Meier. These estimates were compared using a log-rank test, and an adjustment for multiple comparisons was made with the use of a Bonferroni correction. The median time to PSA recurrence was calculated using the Kaplan-Meier estimator and described. A 2-sided P value of .05 or less was considered statistically significant. Analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

**RESULTS**

**Clinical Characteristics of the Study Cohort**

As shown in Table 1, the median age of the 2370 men who comprised the study cohort at the time of initial therapy was 66 (IQR, 59-72) years. The median PSA level was 7.4 (IQR, 5.1-12) ng/mL. The distribution of the men by Gleason score was 1059 (45%) with Gleason score 6 or less, 999 (42%) with Gleason score 7 without tertiary grade 5, 36 (1.5%) with Gleason score 7 with tertiary grade 5, and 276 (12%) with Gleason score 8 to 10.

**Time to PSA Failure**

The median time to PSA failure was 5.0 years for men with Gleason score 7 and tertiary grade 5 disease, 5.1 years for men with Gleason score 8 to 10, 6.7 years for men with Gleason score 7 without tertiary grade 5, and 15.4 years for men with Gleason score 6 or less. As shown in Table 2, after adjusting for known prognostic factors including the PSA level, age, tumor category, and therapy received and including a propensity score in the multivariate model to further

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**Table 2. Unadjusted and Adjusted Hazard Ratios of Clinical Factors Describing the Risk of Prostate-Specific Antigen Recurrence Following Definitive Therapy**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Gleason Score at biopsy ≤6</td>
<td>0.29 (0.17-0.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>7 Without tertiary grade 5</td>
<td>0.53 (0.31-0.88)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>7 With tertiary grade 5</td>
<td>1 [Reference]</td>
<td>.2</td>
</tr>
<tr>
<td>8 to 10</td>
<td>0.86 (0.50-1.46)</td>
<td>.57</td>
</tr>
<tr>
<td>Age in years at time of treatment per 1-y increase</td>
<td>1.04 (1.02-1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PSA level at diagnosis, per 1 ng/mL increase</td>
<td>1.02 (1.02-1.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor stage at diagnosis</td>
<td>1 [Reference]</td>
<td>.2</td>
</tr>
<tr>
<td>T1c</td>
<td>1.78 (1.49-2.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T2</td>
<td>3.69 (2.69-5.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type of treatment</td>
<td>0.87 (0.67-1.13)</td>
<td>.30</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>2.34 (1.82-3.03)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>External beam radiation therapy</td>
<td>1 [Reference]</td>
<td>.2</td>
</tr>
<tr>
<td>External beam radiation therapy + AST</td>
<td>3.57 (0.83-15.41)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: AST, androgen suppression therapy; CI, confidence interval; PSA, prostate-specific antigen. *Reference group for the Cox regression analysis.
Table 3. Adjusted Hazard Ratios of Clinical Factors Describing the Risk of PSA Recurrence Stratified by Treatment Modality

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Radical Prostatectomy (n = 1242)</th>
<th>Radiation Therapy (n = 806)</th>
<th>Radiation Therapy + Hormonal Therapy (n = 322)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Adjusted Hazard Ratio (95% CI) P Value</td>
</tr>
<tr>
<td>Gleason score at biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>0.10 (0.03-0.28)</td>
<td>&lt;.001</td>
<td>0.46 (0.22-0.94)</td>
</tr>
<tr>
<td>7 Without tertiary grade 5</td>
<td>0.38 (0.14-1.04)</td>
<td>.06</td>
<td>0.71 (0.35-1.46)</td>
</tr>
<tr>
<td>7 With tertiary grade 5</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>8 to 10</td>
<td>0.53 (0.19-1.49)</td>
<td>.23</td>
<td>1.10 (0.52-2.33)</td>
</tr>
<tr>
<td>PSA level at diagnosis, per 1 ng/mL increase</td>
<td>1.00 (0.98-1.01)</td>
<td>.60</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>Tumor stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>T2</td>
<td>1.13 (0.86-1.50)</td>
<td>.38</td>
<td>1.52 (1.15-1.99)</td>
</tr>
<tr>
<td>T3</td>
<td>0.93 (0.13-6.80)</td>
<td>.95</td>
<td>2.25 (1.54-3.60)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PSA, prostate-specific antigen.

Figure. Estimates of Prostate-Specific Antigen (PSA) Recurrence Following Radical Prostatectomy or External Beam Radiation Therapy With or Without Androgen Suppression Therapy

<table>
<thead>
<tr>
<th>No. at Risk, Gleason Score at Biopsy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 to 10</td>
<td>0.46 (0.22-0.94)</td>
</tr>
<tr>
<td>7 With tertiary grade 5</td>
<td>0.71 (0.35-1.46)</td>
</tr>
<tr>
<td>7 Without tertiary grade 5</td>
<td>1.10 (0.52-2.33)</td>
</tr>
<tr>
<td>≤6</td>
<td>1.00 (0.99-1.03)</td>
</tr>
</tbody>
</table>

Gleason scores 6 or less vs 7 with tertiary grade 5, P < .001; 6 or less vs 7 without tertiary grade 5, P < .001; 7 without tertiary grade 5 vs 7 with tertiary grade 5, P = .011; and 7 with tertiary grade 5 vs 8 to 10, P = .57. After applying the Bonferroni correction, P values < .0125 are significant.

Adjust for any potential bias associated with treatment selection, Cox regression multivariate analysis revealed that men with biopsy Gleason score 7 and a tertiary grade 5 component had a significantly shorter time to PSA failure than men with biopsy Gleason score 7 without tertiary grade 5 (adjusted HR, 0.56; 95% CI, 0.32-0.97; P = .04) and men with biopsy Gleason score 6 or less (adjusted HR, 0.24; 95% CI, 0.13-0.43; P < .001). However, the time to PSA failure was not significantly different between men with biopsy Gleason score 7 and tertiary grade 5 and Gleason score 8 to 10 (adjusted HR, 0.96; 95% CI, 0.54-1.71; P = .90) disease. Other clinical factors that were significantly associated with time to PSA failure on multivariate analysis included the PSA level at diagnosis (adjusted HR, 1.02; 95% CI, 1.01-1.03; P < .001), treatment with radiation therapy (adjusted HR, 3.02; 95% CI, 2.32-3.93; P < .001), and tumor category T3 (adjusted HR, 2.42; 95% CI, 1.57-3.73; P < .001). Age (P = .83), treatment with radical prostatectomy (P = .26), and tumor category T2 (P = .06) were not significantly associated with time to PSA failure. Detailed in Table 3 are the results of the Cox regression analysis of these covariates separated by treatment group (radical prostatectomy, radiation therapy, or radiation therapy plus AST).

Estimates of PSA Failure Stratified by Gleason Score

After a median follow-up of 4.2 (IQR, 1.8-6.7) years, there were 613 PSA recurrences. As shown in the figure, estimates of PSA-recurrence were significantly higher among men with biopsy Gleason score 7 with tertiary grade 5 than among men with Gleason score 7 without tertiary grade 5 (P = .01) and men with Gleason score 6 (P < .001) but were not significantly different from...
men with Gleason score 8 to 10 ($P=.57$). Specifically, estimates at 5 years following treatment were 21% (95% CI, 18% to 25%) for men with Gleason score 6 or less, 33% (95% CI, 29% to 37%) for men with Gleason score 7 without tertiary grade 5, 56% (95% CI, 37% to 77%) for men with Gleason score 7 without tertiary grade 5, and 50% (95% CI, 43% to 57%) for men with Gleason score 8 to 10 disease.

**COMMENT**

In the present study, we evaluated the time to recurrence in 2370 men treated with radical prostatectomy, or radiation therapy with or without AST. We found that men with biopsy Gleason score 7 prostate cancer and tertiary grade 5 had a time to PSA recurrence that was significantly shorter than men with Gleason score 7 cancer without tertiary grade of 5 and men with Gleason score 6 or less but not significantly different from men with Gleason score 8 to 10 disease after adjusting for known prognostic factors. If these findings are validated by additional studies in other populations, they may affect the management of care for men with Gleason score 7 prostate cancer for which the currently practiced management standards include dose-escalated radiation therapy including prostate brachytherapy with or without supplemental radiation therapy,22-24 short course AST,25,26 or radical prostatectomy. Specifically, given the time to recurrence (Figure), management options for men with Gleason score 7 who also have tertiary grade 5 disease could include treatments that are the current standards of care for men with Gleason 8 to 10 prostate cancer. These standards of care based on the results of randomized trials25-28 include radiation therapy and short25-26 or extended-course AST.27,28 or radical prostatectomy with the expectation that further therapy may be needed postoperatively depending on the final pathology findings of the radical prostatectomy and postoperative PSA level. Moreover, men with Gleason score 7 and tertiary grade 5 might be considered for enrollment in randomized trials for which men with Gleason score 8 to 10 disease are eligible.

A potential limitation of our study is the median follow-up time of 4.2 years not permitting an assessment of the time to prostate cancer specific and all-cause mortality end points. The sample size of our study, while large, was not large enough to provide the statistical power to distinguish the effect of tertiary grade 5 with Gleason 7 disease among various treatment modalities. Although a trend toward significance is seen in the subsets, true statistical significance only emerges when the data are pooled. The power of the study is limited by the sample size of men with Gleason score 7 and tertiary grade 5 disease. Specifically, this limited power is reflected in the wide 95% CI of the HR comparing the risk of PSA failure in men with Gleason score 7 with or without tertiary grade 5. A much larger data set would be required to demonstrate significant differences among the treatment subgroups because of the low prevalence of tertiary grade 5 in biopsy specimens. However, the study had consistent Gleason scoring performed by a single pathologist who has expertise in cancers of the genitourinary tract, a large sample size and significant number of PSA failures and included all treatment modalities that are currently considered standard for men with localized or locally advanced prostate cancer with the exception of prostate brachytherapy.

In conclusion, men with biopsy Gleason score 7 prostate cancer and tertiary grade 5 disease may have a risk of PSA failure following definitive therapy comparable with men with biopsy Gleason score 8 to 10 disease. These findings warrant further investigation in additional studies and different populations.

**Author Contributions:** Dr D’Amico had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Patel, Renshaw, D’Amico.

**Acquisition of data:** Renshaw.

**Analysis and interpretation of data:** Patel, Chen, Renshaw, D’Amico.

**Drafting of the manuscript:** Patel, D’Amico.

**Critical revision of the manuscript for important intellectual content:** Patel, Chen, Renshaw, D’Amico.

**Statistical analysis:** Chen, D’Amico.

**Study supervision:** D’Amico.

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Let what you observe penetrate your inmost soul, let it be so warm and replenish you with your thoughts constantly referring to it, and then you will find true pleasure and delight in your intellectual labors.
—Theodore Billroth (1829-1894)