Tertiary Gleason Pattern 5 is a Powerful Predictor of Biochemical Relapse in Patients With Gleason Score 7 Prostatic Adenocarcinoma

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Purpose: In radical prostatectomy specimens Gleason score 7 is among the most commonly assigned scores for prostate carcinoma accounting for 30% to 50% of cases. Gleason score 7 is different from other more differentiated prostate carcinomas (tumors of Gleason scores 5 and 6) with a significantly worse outcome and higher rate of recurrence. Nonetheless, Gleason score 7 tumors are heterogeneous. In this study we examined the differences in clinical outcome between primary Gleason grade 3 and 4 tumors in patients who underwent radical prostatectomy, and determined the influence of tertiary Gleason pattern 5 on patient outcome.

Materials and Methods: A total of 504 patients underwent radical prostatectomy for prostate cancer and 228 of the patients (45%) had a Gleason score of 7. Cases were analyzed for a variety of clinical and pathological parameters. The influence of primary Gleason pattern and tertiary Gleason pattern 5 on patient outcome was assessed in the Cox regression model.

Results: Among 228 patients with Gleason score 7 prostatic adenocarcinoma, 91 (40%) had a primary Gleason pattern 4 and 137 (60%) had primary Gleason pattern 3. Patients of the former group were more likely to have a higher pathological stage ($p = 0.003$), more likely to have PSA recurrence ($p = 0.02$) and more likely to have a tertiary Gleason pattern 5 ($p < 0.0001$). A total of 37 (41%) patients with primary Gleason 4 had a tertiary Gleason pattern 5, whereas only 13 (9%) patients with primary Gleason 3 had a tertiary Gleason pattern 5. In the Cox regression model controlling for tumor stage and surgical margin status, the primary Gleason pattern was not an independent predictor of PSA recurrence ($p = 0.80$), whereas the presence of tertiary Gleason pattern 5 was a significant predictor of PSA recurrence (hazard ratio 2.10, 95% CI 1.24-3.55, $p = 0.006$). Five-year PSA recurrence-free survival was 70% for patients without a tertiary Gleason pattern 5 compared to 19% for those patients with a tertiary Gleason pattern 5.

Conclusions: Among patients with Gleason score 7, primary Gleason grade 4 indicates a likelihood of higher tumor stage and higher probability of PSA recurrence than does primary pattern 3. However, it does not independently predict a worse outcome after controlling for other known prognostic parameters associated with disease progression. Regardless of whether the primary Gleason pattern is 3 or 4, a tertiary Gleason pattern 5 is the strongest predictor of a worse outcome in patients with Gleason grade 7 prostatic adenocarcinoma. Therefore, tertiary pattern 5 should be reported in radical prostatectomy specimens.

Key Words: prostate, adenocarcinoma, prostatectomy, neoplasm staging, prognosis

Since its formulation in 1974, the Gleason grading system has proven to be a reliable and fairly reproducible parameter in predicting the outcome in patients undergoing radical prostatectomy for prostatic adenocarcinoma.[1–4] In radical prostatectomy specimens, Gleason score 7 is the most commonly assigned grade, ranging in frequency from 30% to 50%.[5–7] Gleason score 7 adenocarcinomas have been shown to behave significantly worse than adenocarcinomas with Gleason scores of 6 or less, and to have a better prognosis than those with Gleason 8 or more.[5,7,8] However, Gleason score 7 tumors are heterogeneous.[9–12] One of the weaknesses of the current grading system is that a Gleason score of 7 does not differentiate between tumors with primary (most prevalent) Gleason grade 3 and those with primary Gleason grade 4. This may explain the heterogeneity in the clinical outcome inherent to Gleason score 7 prostatic adenocarcinomas. We examined the differences in clinical outcome between primary Gleason grade 3 and 4 tumors in patients who underwent radical prostatectomy, and determined the influence of tertiary Gleason pattern 5 on patient outcome.

METHODS

A total of 504 men with clinically localized prostate cancer underwent radical retropubic prostatectomy between 1990

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Study received Indiana University Institutional Review Board approval.

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and 1998 at Indiana University Hospital. None of the patients had preoperative radiation or androgen deprivation therapy. Clinical records were reviewed to determine patient age, preoperative serum PSA and evidence of biochemical recurrence (defined by consecutively increased postoperative serum PSA levels (at least 0.1 ng/ml after surgery). Average patient age was 62 years. PSA followup information was available for 459 patients (91%). This research was approved by the Indiana University Institutional Review Board.

The microscopic examination of the radical prostatectomy specimens and Gleason grading were performed retrospectively by a single genitourinary pathologist (LC), without the knowledge of clinical outcome. The prostatectomy specimens were weighed, measured, inked, and fixed in 10% neutral formalin. Following fixation, the apex and bladder base were amputated and serially sectioned at 3 to 5 mm intervals in the vertical, parasagittal plane. The seminal vesicles were amputated and sectioned with representative sections submitted for examination. The remaining prostate was serially sectioned at 4 mm intervals perpendicular to the long axis from the apex of the prostate to the bladder base with representative sections from each quadrant submitted for examination.

Sections (5 micron) were then prepared and stained with hematoxylin and eosin. Tumors were graded according to the Gleason grading system[13] and staged according to the 1997 American Joint Committee on Cancer tumor, lymph node, metastasis (TNM) staging system. To calculate the Gleason score of each tumor, glass slides with histological sections from each block were examined by light microscopy and the prevalent and second most prevalent Gleason grades were recorded after examination of all tumor foci. Among the 504 cases examined, 228 (45%) had a Gleason score of 7. The presence or absence of tertiary Gleason pattern 5 was also recorded. The tumor was assigned with Gleason score 6 if the tertiary Gleason pattern 4 or 5 is less than 5% of the entire tumor, and is not the subject of the current study.

Association of categorized clinical and pathological variables with Gleason score 3 + 4 vs Gleason score 4 + 3 was assessed with the F-test using 1-way ANOVA. The effect of Gleason score 3 + 4 vs Gleason score 4 + 3 on biochemical recurrence of prostate cancer was assessed in the Cox regression model additionally controlling for pathological stage, Gleason pattern 5, and surgical margin status. Gleason score was analyzed as a continuous variable. Results were considered significant if the p value was less than 0.05.

RESULTS

Among the 228 patients with Gleason score 7, 137 (60%) had primary Gleason pattern 3 and 91 showed primary Gleason pattern 4. Patients ranged in age from 34 to 80 years (median 63, mean 62). The mean followup was 44 months (median 36, range 1.5 to 144). Clinical and pathological parameters are listed in table 1.

Univariate analysis showed a significant association between primary Gleason pattern 3 vs primary Gleason pattern 4 and PSA recurrence ($p = 0.02$), tumor stage ($p = 0.003$), and the presence of a tertiary Gleason pattern 5 ($p < 0.0001$). A total of 37 (41%) patients with primary Gleason 4 group had a tertiary Gleason pattern 5, in contrast, only 13 (9%) patients with primary Gleason 3 group had a tertiary Gleason pattern 5. There was no significant association with patient age ($p = 0.24$), preoperative PSA ($p = 0.51$), surgical margin status ($p = 0.76$), seminal vesicle invasion ($p = 0.12$), perineural invasion ($p = 0.71$), prostate weight ($p = 0.16$), high grade prostatic intraepithelial neoplasia ($p = 0.08$) and lymph node metastasis ($p = 0.55$) (table 1). A tertiary component of Gleason pattern 5 was present in 50 patients and was more frequent in patients with primary Gleason pattern 4 (41%) than in patients with primary Gleason pattern 3 (9%) ($p < 0.001$).

In a multiple Cox regression model controlling for pathological stage, surgical margin status and the presence of a tertiary Gleason pattern 5, the primary Gleason pattern was no longer a significant predictor of PSA recurrence ($p = 0.80$) (table 2). A tertiary Gleason pattern 5, on the other hand, was found to independently predict the rate of PSA recurrence regardless of the primary Gleason pattern (hazard ratio 2.10, 95% CI 1.24-3.55, $p = 0.006$, see figure). Five-year PSA recurrence-free survival was 70% for patients without tertiary Gleason pattern 5 compared to 19% for those patients with tertiary Gleason pattern 5.

DISCUSSION

The Gleason grading system was originally devised based on clinical evidence which suggested that the behavior of a tumor consisting of 2 patterns was not dictated solely by the worst grade, but rather by the predominant and second most prevalent pattern.[13] Since the Veterans Administration Cooperative Urological Research Group studies were largely based on information derived from nonradical prostatectomy specimens, a tertiary pattern was rarely reported and the need for a grading system to account for more than 2 patterns of adenocarcinoma was simply not present.[13,14] While reporting of 3 or more Gleason patterns may be subject to sampling bias in needle biopsy or transurethral resection specimens and is statistically less likely, radical prostatectomy specimens allow for a more detailed and accurate account of the various proportions of the Gleason patterns present. In the last 3 decades radical prostatectomy has emerged as the preferred method of treatment for prostatic carcinoma.[2] There have been many clinicopathological studies which have focused on radical prostatectomy specimens, but only a small number of these have investigated the significance of a tertiary component. Pan et al proposed that the Gleason system for radical prostatectomy specimens be modified to consider small volumes (less than 5%) of patterns 4 and 5.[15] This proposal followed the finding of a significantly higher tumor stage in patients with a tertiary component of pattern 4 or 5 in Gleason score 5, 6 and 7 tumors compared to their counterparts lacking a high grade tertiary component.[15]

Since prostate carcinoma is a multifocal disease it comes as no surprise that more than 2 Gleason patterns may be found in a single radical prostatectomy specimen.[16] In a detailed study of 115 whole mount radical prostatectomy specimens, Arora et al found that 87% of all specimens contained 2 or more foci of adenocarcinoma and that the Gleason scores of individual foci often did not correlate with the overall Gleason score.[17] Furthermore, in evaluating a series of 364 consecutive radical prostatectomies processed by whole mount technique, our group demonstrated that