Prognostic Value of Percent Gleason Grade 4 at Prostate Biopsy in Predicting Prostatectomy Pathology and Recurrence

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Purpose: The importance of primary Gleason grade among men with Gleason score 7 disease has been well-defined. However, this dichotomization may oversimplify the continuous spectrum of absolute percent Gleason grade 4 disease (G4%). In this study we report the prognostic value of G4% in cancer related outcomes of men undergoing radical prostatectomy.

Materials and Methods: Patients who underwent radical prostatectomy for clinically localized Gleason 6-8 prostate cancer from 2005 to 2013 were included in the study. G4% was determined as biopsy tumor length containing Gleason pattern 4/total tumor length, which performed better than alternative quantifications of pattern 4 involvement. G4% was correlated with time to biochemical recurrence and presence of adverse radical prostatectomy pathology, defined as primary Gleason 4 or pT3 or greater, by multivariable Cox and logistic regressions.

Results: Of 1,691 patients 517 (30.6%) had adverse pathological features and 86 (5.6%) experienced biochemical recurrence. On multivariable analyses G4% was a significant predictor of adverse pathology (OR 1.04, 95% CI 1.03−1.05) and time to biochemical recurrence (HR 1.02, CI 1.01−1.03). G4% was also a significant independent predictor of adverse pathology in subsets of patients with

Abbreviations and Acronyms

ADT = androgen deprivation therapy

BCR = biochemical recurrence

G4% = percent Gleason pattern 4 involvement

PSA = prostate specific antigen

RP = radical prostatectomy

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Gleason score 7 (OR 1.05, 95% CI 1.03−1.06), 3+4 (OR 1.06, 95% CI 1.04−1.08) and 4+3 cancer (OR 1.05, 95% CI 1.03−1.06). We found a significantly increased risk of adverse pathology at potentially meaningful G4% thresholds (1% to 10% vs 20% to 30%).

Conclusions: The incremental percentage of Gleason grade 4 disease in biopsy specimens is an important predictor of adverse pathology and biochemical recurrence across the entire range of G4% disease. Accounting for G4% can improve risk assessment even among those patients with Gleason 3+4 or 4+3 cancer and may help inform patient counseling.

Key Words: biopsy, prostatic neoplasms, prostatectomy, recurrence, neoplasm grading

NUMEROUS studies during the last 40 years have demonstrated that prostate biopsy Gleason score is strongly associated with adverse pathological outcomes at radical prostatectomy, subsequent prostate specific antigen recurrence and disease specific mortality.[1−3] One of the most important modifications of the Gleason scoring system occurred in 2005, when recommendations confirmed that limited secondary patterns of a lower grade tumor (less than 5%) should be ignored in the setting of a high grade cancer. Conversely, a low volume of higher grade tumor (less than 5%) in the setting of an otherwise low grade cancer should be reported in light of its potential clinical relevance and impact on long-term outcomes.[4]

These scoring guidelines reflect the concept that increasing amounts of high grade disease appear to drive clinical outcomes. Multiple studies have demonstrated heterogeneity within Gleason 7 tumors with Gleason score 4+3 tumors portending significantly worse outcomes than Gleason 3+4 tumors.[5−7] As a result, a new grade grouping system was proposed in 2013 and was recently endorsed by the International Society of Urological Pathology (ISUP).[8,9] In the new 5-grade grouping system, Gleason score 3+4 and 4+3 tumors are assigned grade groups 2 and 3, conveying their distinct prognostic differences.[10]

The continued focus on improving the Gleason grading system speaks to the importance of optimizing risk stratification at the time of diagnosis. An increasing number of tools are available for risk stratification, including clinical nomograms,[11] molecular biomarkers[12,13] and multiparametric magnetic resonance imaging.[14] While these appear to add potentially relevant data, the majority of treatment decisions are still made without these additional markers. In the current study we determined the relevance of G4% as an existing but potentially underused predictor of key cancer related outcomes in men with prostate cancer. We hypothesized that an increase in the proportion of Gleason pattern 4 in prostate needle biopsy specimens would be closely associated with adverse pathology at RP and biochemical recurrence after RP.

MATERIALS AND METHODS

Under an institutional review board approved protocol we performed a retrospective review of the medical records of 2,203 consecutive patients who underwent RP as the primary treatment for clinically localized prostatic adenocarcinoma between September 2005 (corresponding to the modification of the Gleason scoring guidelines) and 2013. All patients were assigned a biopsy Gleason score and corresponding percent of each Gleason pattern in each biopsy core during routine pathological evaluation performed by board certified anatomical pathologists. The majority of cases were signed out by pathologists with subspecialty training in genitourinary pathology.

Given our aim to focus on biopsy characteristics that would be clinically meaningful for patients who may be candidates for active surveillance, patients with a preoperative PSA greater than 20 ng/ml and clinical stage T3-T4 disease were excluded from analysis. Patients with Gleason scores 6-8 were included in our data set to provide the extremes of G4% for comparative purposes. Patients with biopsy Gleason scores 3+5=8, 5+3=8, 9-10 and those who had received any treatments before prostatectomy (hormonal therapy or radiation) were also excluded from the study. Patients who underwent RP more than 1 year from the last biopsy were excluded to avoid undetected disease progression,[15] leaving 1,990 patients.

For patients with multiple biopsies the data from the last biopsy before RP were used. Complete clinical and pathological data were available from 1,691 patients and this constituted the final study cohort. Preoperative PSAs were obtained for all patients and postoperative followup included routine PSA monitoring approximately every 3 to 6 months. Clinical, pathological and outcome data were collected prospectively, and were supplemented by medical record review. Prostatectomy specimens were submitted per institutional protocol as described previously.[16]

Gleason pattern 4 involvement was quantified using the 2 distinct approaches of overall Gleason pattern 4% and maximum Gleason pattern 4% (see supplementary figure, http://jurology.com/). Overall Gleason pattern 4% proved to have better performance characteristics for the prediction of the primary outcome (supplementary table 1, http://jurology.com/) and, thus, was used for all subsequent analyses (see supplementary Materials and Methods, http://jurology.com/). Overall G4% was calculated as Gleason pattern 4 tissue summed across all cores (mm)/total positive tumor tissue summed across all cores