Whom to Treat

Postdiagnostic Risk Assessment with Gleason Score, Risk Models, and Genomic Classifier

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KEYWORDS

• Prostate cancer • Risk assessment • Treatment • Gleason score • Risk models • Nomograms • Genomic assays

KEY POINTS

- Accurate risk stratification at time of diagnosis is crucial to providing the best treatment recommendation for each patient diagnosed with prostate cancer.
- Traditional risk grouping by the D'Amico classification or its extensions (eg, NCCN or American Urological Association risk groups) is still widely used; however, this approach has multiple, major limitations and is not adequate for contemporary practice.
- Multivariable nomograms and risk scores using clinical characteristics at time of diagnosis have been developed to predict outcomes and to stratify patients more accurately.
- Genomic assays, novel imaging, and other biomarkers may complement current risk assessment tools in men with newly diagnosed prostate cancer, but must be shown to improve on a multivariable clinical risk assessment.

INTRODUCTION

With the implementation of prostate-specific antigen (PSA) screening in current clinical practice, the incidence of prostate cancer (PCa) increased substantially.[1,2] However, the lack of specificity of PSA for PCa may lead to unnecessary biopsies and overdiagnosis of indolent disease. Once diagnosed, management of patients with PCa must be individualized based on the variable and usually prolonged natural history of this disease. Accurate risk stratification at the time of diagnosis is therefore the cornerstone for clinical decision-making and optimal management for each patient.

Clinicians use various clinical parameters, such as PSA level, biopsy Gleason grade, and clinical T stage, to estimate PCa aggressiveness. In more recent years, prognostic scores and nomograms based on these variables have been validated to risk-stratify patients with good accuracy. With the advent of genomic analysis, genome data may now be incorporated into these prediction tools to improve accuracy. In this review

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of the literature, we discuss established and novel concepts in risk stratification for men with confirmed PCa. The aim is to evaluate how these tools may guide treatment decisions and enable more accurate postdiagnosis risk stratification in men with PCa.

HISTOPATHOLOGIC GRADING OF PROSTATE CANCER

Gleason Grading

Since the introduction of the Gleason grading system 50 years ago, the two most prevalent patterns of glandular architecture, each scored from 1 to 5 during histologic review, are reported as the Gleason score (GS).[3,4] The GS at biopsy consists of the Gleason grade of the most extensive pattern plus the highest pattern, regardless of its extent.[5] At the consensus conference in 2005, the International Society of Urological Pathology (ISUP) updated the Gleason grading system. The ISUP changes were mainly aimed at limiting the scope of glandular architecture pattern 3 while widening the scope of pattern 4.[4,6,7] As a result, some cancers previously considered Gleason pattern 3 were subsequently reclassified as Gleason pattern 4. All cribriform cancers are also now considered pattern 4.[3,6] In radical prostatectomy specimens, a Gleason pattern comprising less than or equal to 5% of PCa volume is not incorporated in the GS but reported separately if tertiary grade 4 or 5 is noted.[5] Billis and colleagues[8] showed that the revised Gleason system better predicts biochemical-free progression after radical prostatectomy compared with the current system.

Recently, there has been increasing interest in histologic subtypes of Gleason pattern 4. Among the subtypes, a finding of cribriform architecture has been a new focus of interest. The finding of PCa glands with cribriform architecture has been associated with more aggressive disease, compared with poorly formed or fused glands. Recent literature has also shown it to be associated with extraprostatic extension, positive surgical margins, distant metastases, and cancer-specific mortality.[9–12]

Limitations of Gleason grading may include intraobserver and interobserver variability. In the study of McKenney and coworkers,[13] interobserver reproducibility among genitourinary subspecialist pathologists for classic Gleason patterns was substantial (κ 0.76). However, interobserver reproducibility for histopathologic distinction of tangentially sectioned Gleason pattern 3 from Gleason pattern 4 was only fair (κ 0.27).[13] Mean intraobserver reproducibility was 81.5% (range, 65%–100%).[13]

Grade Group System

To better predict clinical outcomes, Pierorazio and colleagues[14] recommended collapsing Gleason grades into prognostic grade groups (GG) that more accurately reflect prognosis while offering a simplified, intuitive classification system for physicians and patients. The authors proposed a modified PCa grading system using GG based on the likelihood of biochemical recurrence (BCR)[14]: GS less than or equal to 6 (GG 1), GS 3 + 4 = 7 (GG 2), GS 4 + 3 = 7 (GG 3), GS 4 + 4 = 8 (GG 4), and GS 9 to 10 (GG 5). The GG system was presented and accepted for use at the 2014 grading consensus of ISUP, initially to be used in conjunction with the Gleason system.[7,15]

This new GG system was validated in 2016 by Epstein and colleagues[16] with a multi-institutional study of BCR in more than 20,000 men treated by radical prostatectomy and more than 5000 men who underwent radiotherapy. In the surgical cohort, Gleason 3 + 4 versus 4 + 3 and Gleason 8 versus 9 differed significantly in rates of BCR. Relative to GS 6, each increasing score was associated with higher risk of BCR (hazard ratio [HR], 1.9 [95% confidence interval (CI), 1.7–2.2] for Gleason 3 + 4; HR, 5.1 [95% CI, 4.4–6.0] for Gleason 4 + 3; HR, 8.0 [95% CI, 6.7–9.5] for Gleason 8; and HR, 11.7 [95% CI, 9.9–13.8] for Gleason 9 to 10).[16] These differences were also observed in the radiotherapy arm.[16] In a national population-based cohort, the new five-tier GG system demonstrated a predictive accuracy similar to that of the current three- and four-tier classifications.[17] The new GG system did not improve prediction of clinical recurrence in radical prostatectomy patients.[18] However, other studies have demonstrated that the GGs correlated well with metastasis and PCa-specific death.[19,20]

To be clear, the new GGs represent a renaming of the primary + secondary grading convention, not a new grading system. The advantages include clear distinction between GS 3 + 4 (GG 2) and GS 4 + 3 (GG 3), and better clinical interpretation for patients (ie, the lowest GG is 1 rather than the lowest GS being 3 + 3 = 6). The new groups, however, have not been shown to be more accurate than the old naming convention, and still do not constitute a linear scale, requiring modeling as an ordinal variable in prediction studies.

Quantitative Gleason Score

Gleason 3 + 4 implies a relative proportion of high-grade disease ranging from 5% to 49%, and risk heterogeneity certainly exists along