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Brief Correspondence

Validation of a Contemporary Five-tiered Gleason Grade Grouping Using Population-based Data

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Abstract

This population-based study assesses whether a proposed five-tiered Gleason grade grouping (GGG) system predicts prostate cancer–specific mortality (PCSM). Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 331 320 prostate cancer patients who had primary and secondary Gleason patterns diagnosed between January 2006 and December 2012. We used the Fine and Gray proportional hazards model for subdistributions and the corresponding cumulative incidence to quantify the risk of PCSM. We found that the risk of PCSM approximately doubled with each GGG increase. Among men who underwent radical prostatectomy and using GGG1 (Gleason score $\leq$6) as the reference group, the adjusted hazard ratio for PCSM was 1.13 (95% confidence interval [CI] 0.83–1.54) for GGG2, 1.87 (95% CI 1.33–2.65) for GGG3, 5.03 (95% CI 3.59–7.06) for GGG4, and 10.92 (CI 8.03-14.84) for GGG5. Similar patterns were observed regardless of the type of primary cancer treatment received or clinical stage. In summary, our study, with large, racially diverse populations that reflect real world experiences, demonstrates that the new five-tiered GGG system predicts PCSM well regardless of treatment received or clinical stage at diagnosis.

Patient summary: In this report we examined prostate cancer mortality using the new five-tiered cancer grading system using data for a large US population. We found that the new five-tiered cancer grading system can predict prostate cancer–specific mortality well, regardless of the type of primary cancer treatment and clinical stage. We conclude that this new five-tiered cancer grading system is useful in guiding treatment decisions.

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Clinicians have relied on the Gleason grading system since it was introduced in 1974 [1]. Gleason originally described nine patterns of glandular growth that were consolidated into five grades in a classic teaching diagram. The Gleason score is the sum of the primary and secondary grades. The system was validated by Veterans Administration Cooperative Urological Research Group studies on prostate cancer [1].

Over the past four decades the Gleason grading system has consistently proven to be the most powerful predictor

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of prostate cancer–specific mortality (PCSM). Since its introduction, however, the original grading system has undergone multiple revisions. Gleason patterns 1 and 2 are rarely assigned, and glands containing cribriform growth patterns are now classified as Gleason pattern 4. Pierorazio et al [2] proposed a new five-tiered Gleason grade grouping (GGG) in which Gleason scores ≤6 comprise GGG1; Gleason score 3 + 4, GGG2; Gleason score 4 + 3, GGG3; Gleason score 8, GGG4; and Gleason scores 9 and 10, GGG5. Validation studies have shown that the new system predicts the risk of biochemical recurrence–free survival and recurrence-free progression [2–4]. To date, however, no studies have assessed whether the new system predicts PCSM. This population-based study was undertaken to assess whether the five-tiered GGG system predicts PCSM using Surveillance, Epidemiology, and End Results (SEER) data.

We identified men diagnosed with prostate cancer between January 1, 2006 and December 31, 2012 (n = 408 396) from the SEER database, as major Gleason scoring revisions were adopted at the 2005 International Society of Urological Pathology Consensus Conference [5]. Patients who did not have both primary and secondary patterns recorded (n = 45 101), patients diagnosed with prostate cancer at the time of death (n = 31 852) and patients with missing survival data (n = 55) or of pediatric age (n = 68) were excluded. The final study cohort totaled 331 320 patients. PCSM data were available up to December 2012.

For patients undergoing radical prostatectomy (RP), the Gleason pattern was based on a surgical specimen. Otherwise, the biopsy-based Gleason pattern was used. We analyzed survival data by cancer treatment received within 1 yr of cancer diagnosis and by clinical stage (T1,T2, and T3/4). If a patient received more than one treatment, the treatment group was assigned using the following hierarchy: RP, radiotherapy, other treatments. Patients may have received subsequent therapy, such as salvage radiation or prostatectomy, and probably received hormonal therapy before they died from prostate cancer.

Multivariate competing-risks hazard ratios (HRs) and confidence intervals (CIs), as well as cumulative incidence estimates, were computed using the Fine and Gray proportional hazards (PH) model for subdistributions [6]. GGG1 (Gleason score ≤6) was chosen as the reference group. The multivariate competing-risks PH model accounted for age, race, marital status, geographic region, diagnosis period (2006–2009 or 2010–2012), regional lymph node involvement, and metastasis status. Data for prostate specific antigen (PSA) values at diagnosis were unavailable [7].

All analyses except for competing risks were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Fine and Gray competing risks models were fitted using the *stcreg* procedure in STATA version 14 (StataCorp LP, College Station, TX, USA).

Reclassification of the study cohort according to the proposed five-tiered GGG system resulted in the following distribution: 43.3% for GGG1, 29.5% for GGG2, 11.7% for GGG3, 8.1% for GGG4, and 7.5% for GGG5. Most patients received either RP (36.4%) or radiation therapy (32.6%) as primary therapy. During the follow-up period, 9198 of patients died from prostate cancer and 19 482 died from other causes. The median follow-up was 38 mo (interquartile range 18–60). The number of patients followed for at least 5 yr was 40 238 for GGG1, 23 331 for GGG2, 8423 for GGG3, 5784 for GGG4, and 3803 for GGG5. Characteristics for the 331 320 men are summarized in Supplementary Table 1.

Using GGG1 as the reference group, the PCSM hazard ratio increased with each GGG increment, regardless of the primary treatment provided. For example, men who underwent RP the adjusted hazard ratio was 1.13 (95% CI 0.83–1.54) for GGG2, 1.87 (95% CI 1.33–2.65) for GGG3, 5.03 (95% CI 3.59–7.06) for GGG4, and 10.92 (95% CI 8.03–14.84) for GGG5. The HR approximately doubled for each GGG increment and differed significantly from each of the others. Similar patterns were observed for the radiotherapy and other treatment groups, and for models by clinical stage (Table 1). As variability in Gleason pattern assessment may

Table 1 – Results of competing-risks regression for prostate cancer–specific survival by Gleason grade grouping (GGG)[d]

GGG	By treatment[a]			By clinical stage[b]		
	Other treatments[c] HR (95% CI)	Radical prostatectomy HR (95% CI)	Radiotherapy HR (95% CI)	Stage T1 HR (95% CI)	Stage T2 HR (95% CI)	Stage T3/4 HR (95% CI)
GGG1	Reference	Reference	Reference	Reference	Reference	Reference
GGG2	2.48 (2.18–2.83)*	1.13 (0.83–1.54)	1.78 (1.51–2.09)*	1.92 (1.67–2.21)*	1.90 (1.64–2.21)*	1.27 (0.82–1.96)
GGG3	4.74 (4.16–5.40)*	1.87 (1.33–2.65)*	2.88 (2.42–3.43)*	3.46 (2.99–4.02)*	3.24 (2.78–3.78)*	2.36 (1.55–3.62)*
GGG4	7.94 (7.03–8.97)*	5.03 (3.59–7.06)*	4.98 (4.24–5.84)*	5.78 (5.04–6.63)*	6.19 (5.37–7.13)*	3.78 (2.49–5.73)*
GGG5	14.22 (12.61–16.04)*	10.92 (8.03–14.84)*	9.88 (8.38–11.63)*	12.61 (10.99–14.47)*	10.61 (9.22–12.22)*	6.96 (4.64–10.46)*

HR = hazard ratio; CI = confidence interval.
* $p < 0.05$.
[a] Treatment models were adjusted by age, race, marital status, region, clinical stage (T1 vs T2 vs T3/T4), diagnosis period (2006–2009 vs 2010–2012), regional lymph node metastasis (N0 vs others), and distant metastasis status (M0 vs others).
[b] Clinical stage models were adjusted by age, race, marital status, region, treatment (RP, radiotherapy, or other treatments), diagnosis period (2006–2009 vs 2010–2012), regional lymph node metastasis (N0 vs others), and distant metastasis status (M0 vs others).
[c] Other treatments included watchful waiting, active surveillance, or androgen deprivation therapy.
[d] For patients with RP the Gleason pattern was based on a surgical specimen. Otherwise, biopsy-based Gleason pattern was used.

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