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Independent surgical validation of the new prostate cancer grade-grouping system

Daniel E. Spratt*, Adam I. Cole†, Ganesh S. Palapattu†, Alon Z. Weizer†, William C. Jackson*, Jeffrey S. Montgomery†, Robert T. Dess*, Shuang G. Zhao*, Jae Y. Lee*, Angela Wu†, Lakshmi P. Kunju‡, Emily Talmich*, David C. Miller†, Brent K. Hollenbeck†, Scott A. Tomlins‡, Felix Y. Feng*, Rohit Mehra‡ and Todd M. Morgan†

*Departments of Radiation Oncology, †Urology, and ‡Pathology, University of Michigan, Ann Arbor, MI, USA

D.E.S. and A.I.C. contributed equally to first authorship. R.M. and T.M.M. contributed equally to senior authorship.

Objective

To report the independent prognostic impact of the new prostate cancer grade-grouping system in a large external validation cohort of patients treated with radical prostatectomy (RP).

Patients and methods

Between 1994 and 2013, 3 694 consecutive men were treated with RP at a single institution. To investigate the performance of and validate the grade-grouping system, biochemical recurrence-free survival (bRFS) rates were assessed using Kaplan–Meier tests, Cox-regression modelling, and discriminatory comparison analyses. Separate analyses were performed based on biopsy and RP grade.

Results

The median follow-up was 52.7 months. The 5-year actuarial bRFS for biopsy grade groups 1–5 were 94.2%, 89.2%, 73.1%, 63.1%, and 54.7%, respectively ($P < 0.001$). Similarly, the 5-year actuarial bRFS based on RP grade groups was 96.1%, 93.0%, 74.0%, 64.4%, and 49.9% for grade groups 1–5, respectively ($P < 0.001$). The adjusted hazard ratios for bRFS relative to biopsy grade group 1 were 1.98, 4.20, 5.57, and 9.32 for groups 2, 3, 4, and 5, respectively ($P < 0.001$), and for RP grade groups were 2.09, 5.27, 5.86, and 10.42 ($P < 0.001$). The five-grade-group system had a higher prognostic discrimination compared with the commonly used three-tier system (Gleason score 6 vs 7 vs 8–10).

Conclusions

In an independent surgical cohort, we have validated the prognostic benefit of the new prostate cancer grade-grouping system for bRFS, and shown that the benefit is maintained after adjusting for important clinicopathological variables. The greater predictive accuracy of the new system will improve risk stratification in the clinical setting and aid in patient counselling.

Keywords

prostate cancer, prostate cancer grading, radical prostatectomy

Introduction

Since its introduction in the 1960s, the Gleason score has been one of the most important predictors of adverse outcomes in prostate cancer [1]. The Gleason grading system has undergone significant modifications since its inception; however, issues still exist with the current system. The reporting of Gleason scores 2–5 has become virtually extinct [2], and men with Gleason score 6 cancer may misinterpret their disease as intermediate-risk cancer on a 2–10 scale. Several risk-stratification schemas, including the D'Amico and National Comprehensive Cancer Network (NCCN) classifications, place patients into risk-groups based in part on a three-tier Gleason grouping (Gleason score 6 vs 7 vs 8–10), yet heterogeneity exists within these risk-groups. Patients with Gleason score 7 cancer are deemed intermediate-risk; however, this is a heterogeneous group with Gleason score 4+3=7 tumours portending a worse prognosis than Gleason 3+4=7 tumours [3–6]. Similarly, patients with Gleason score 8–10 cancer are deemed high-risk, but multiple studies have shown that the presence of Gleason pattern 5 disease is associated with worse clinical outcomes [7–9]. The granularity of what was initially a system consisting of 25 possible combinations of primary and secondary patterns has been largely reduced to three risk groups.

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To address these concerns, a new grading system was proposed by the group from Johns Hopkins Hospital in 2013 that placed patients into five distinct grade groups: Grade group 1 (Gleason score ≤6), group 2 (Gleason score 3+4=7), group 3 (Gleason score 4+3=7), group 4 (Gleason score 8), and group 5 (Gleason score 9–10) [10]. This system was validated by Epstein et al. [11] in a large, multi-institutional analysis that demonstrated significant prognostic differences between the new grade groups for predicting biochemical recurrence (BCR), and this classification showed slightly higher prognostic discrimination when compared against alternative Gleason grade categorisations. As a result, this grading system was recently endorsed by the International Society of Urological Pathology (ISUP) [11].

Despite overwhelming endorsement, this proposal was validated primarily from institutions that had previously reported significant differences in some of these groups, e.g. between groups 2 and 3 (Gleason score 3+4 vs 4+3) [5,6,12–14]. Thus, independent validation from a distinct cohort may provide further corroboration of this new system. Furthermore, the follow-up of the primary study was short (~2 years). In the present study, we sought to assess the validity of the new grading system in an external cohort of surgical patients treated at a single institution.

Patients and Methods

Under an Institutional Review Board-approved protocol, we performed a retrospective review of the medical records of 3 715 consecutive men treated with radical prostatectomy (RP) for clinically localised prostate cancer, from 1994 to 2013, at a single institution. Patients were excluded if they did not have both a biopsy and RP grade, yielding 3 694 patients that formed the study cohort. All biopsy and RP specimens were assigned a traditional biopsy Gleason score during routine pathological evaluation performed by board-certified anatomical pathologists. The highest Gleason score sampled in biopsy samples was used to assign the biopsy grade. Tertiary Gleason score was not routinely collected and was not included in any analyses. The majority of cases were assessed by pathologists with subspecialty training in genitourinary pathology.

Preoperative PSA levels were obtained for all patients, and postoperative follow-up included routine PSA monitoring approximately every 3–6 months. Clinical, pathological, and long-term oncological data were collected prospectively and were supplemented by medical record review.

To assess the new grade-grouping system, patients were categorised according to Gleason grade as previously described (≤6, 3+4=7, 4+3=7, 4+4=8, and 9–10) and assigned to groups 1–5, respectively [10]. Separate analyses were performed using biopsy grade and RP grade for group assignment.

Statistical Analysis

The primary outcome was biochemical recurrence-free survival (bRFS) defined from the time of RP to BCR or last follow-up. BCR was defined as two consecutive postoperative serum PSA levels of >0.2 ng/mL. For the primary analyses, univariable and multivariable Cox regression were performed to evaluate the association between the grade groupings and bRFS. All significant variables in the univariable analysis were included in the multivariable analysis. The covariates in the biopsy multivariable model included: grade groupings (1–5), clinical T-stage (T1c/T2a, T2b/c, T3–T4), preoperative PSA level (<10, 10–20, >20 ng/mL), and year of treatment (before and after 2005). The covariates in the RP multivariable model were the same as in the biopsy model with the exception of pathological T-stage (T2a, T2b/T2c, T3–T4), which was used in place of clinical staging.

Kaplan–Meier analysis with the log-rank test was also used to determine the bRFS among the grade groupings. Unadjusted and adjusted Kaplan–Meier curves were constructed to show the differences in bRFS between groups. The adjusted Kaplan–Meier curves were adjusted using the same covariates as in the respective multivariable Cox regression analysis. Using both biopsy and RP specimens, the estimated area under the receiver operating characteristic curves (AUC) was determined for the new grade groupings (1–5), and the conventional three-grouped stratification schema (Gleason score 6 vs 7 vs 8–10). This was performed for the entire cohort, with subsequent stratification by date of treatment (pre-2005 vs post-2005) due to the change in Gleason grading at that time (ISUP) [15]. For all statistical analyses, two-tailed *P* values of ≤0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Across 3 715 consecutive men treated with RP from 1994 to 2013, the median follow-up of the cohort was 52.7 months. The median (range) age of our cohort was 60 (34–83) years (Table 1). Half of the cohort (49.8%) was treated before 2005, and the remaining patients were treated from 2005 until 2013. Almost all patients were either NCCN low risk (41.2%) or intermediate risk (50.2%), while only 8.6% were high risk. Similarly, most patients were clinical stage T1c/T2a (88.9%) and had pre-treatment PSA levels of <10 ng/mL (84.1%). Distribution of biopsy and RP grade groupings are shown in Table 1.

Biopsy Grade Groupings

The 5-year actuarial bRFS for biopsy grade groups 1–5 were 94.2%, 89.2%, 73.1%, 63.1%, and 54.7%, respectively ($P < 0.001$; Fig. 1a). All comparisons between groups were significant with

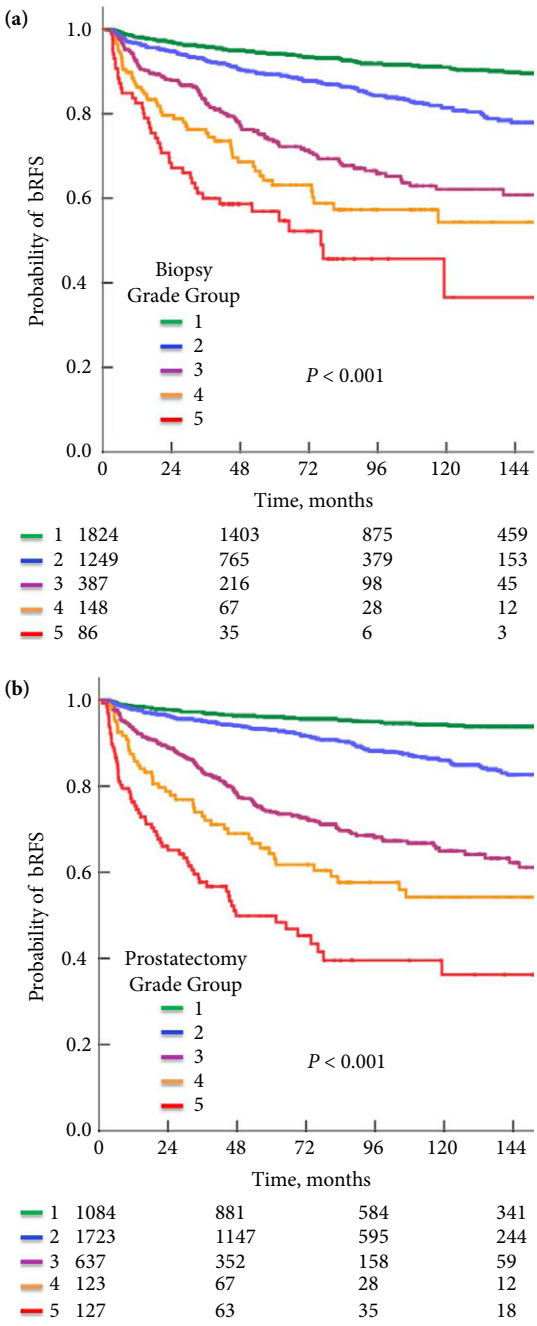
Table 1 Baseline characteristics.

Variable	Value
Median (range) age, years	60 (34–83)
N (%)	
Year of treatment	
<2005	1838 (49.8)
>2005	1856 (50.2)
NCCN risk group	
Low	1521 (41.2)
Intermediate	1854 (50.2)
High	319 (8.6)
Biopsy grade group	
1 (3+3=6)	1824 (49.4)
2 (3+4=7)	1249 (33.8)
3 (4+3=7)	387 (10.5)
4 (8)	148 (4.0)
5 (9–10)	86 (2.3)
Clinical T-stage	
T1c/T2a	3283 (88.9)
T2b/T2c	399 (10.8)
T3a	8 (0.2)
T3b	4 (0.1)
Baseline PSA level, ng/mL	
<10	3108 (84.1)
10–20	486 (13.2)
>20	100 (2.7)
RP grade group	
1 (3+3=6)	1084 (29.3)
2 (3+4=7)	1723 (46.6)
3 (4+3=7)	637 (17.2)
4 (8)	123 (3.3)
5 (9–10)	127 (3.4)
Pathological T-stage	
T2a	741 (20.1)
T2b/T2c	2306 (62.4)
T3a	470 (12. 7)
T3b	165 (4.5)
T4	12 (0.3)

the exception of groups 4 with group 5 ($P = 0.067$; Table 2). On univariable analysis, biopsy grade group, clinical T-stage, preoperative PSA level, and year of treatment were significant predictors of bRFS, while age was not. Biopsy grade grouping had an incremental increase in the hazard for BCR; relative to biopsy grade group 1, the hazard ratios (HRs) were 2.1, 4.8, 6.9, and 10.6 for groups 2, 3, 4, and 5, respectively (all $P < 0.001$).

On multivariable analysis after adjusting for clinical T-stage, preoperative PSA level, and year of treatment, there was a statistically significant increase in the adjusted HR (aHR) for BCR across all grade groupings. The aHRs relative to biopsy grade group 1 were 1.98, 4.20, 5.57, and 9.32 for groups 2, 3, 4, and 5, respectively (all $P < 0.001$; Table 3). Additionally, an increase in clinical T-stage (T1c/T2a as the reference) was significantly associated with an increased aHR for BCR; T2b/T2c (aHR 1.52, 95% CI 1.27–1.82; $P < 0.001$), and T3–4 (aHR 2.27, 95% CI 1.00–5.17; $P = 0.050$). Preoperative PSA level was also significantly associated with an increase in aHR for BCR, as was year of treatment. Adjusted Kaplan–Meier curves of the five biopsy grade groupings after adjustment for clinical T-stage, preoperative PSA level and year of treatment are shown in Figure S1a.

Fig. 1 Unadjusted Kaplan–Meier analyses of bRFS for (**a**) biopsy grade and (**b**) RP grade.



RP Grade Groupings

The 5-year actuarial bRFS for RP grade groups 1–5 were 96.1%, 93.0%, 74.0%, 64.4%, and 49.9%, respectively ($P < 0.001$; Fig. 1b). All comparisons between groups were

Table 2 Pairwise log-rank comparisons of biopsy and RP grade groupings for bRFS.

Grade groupings	1	2	3	4	5
Biopsy					
1	–	<0.001	<0.001	<0.001	<0.001
2	<0.001	–	<0.001	<0.001	<0.001
3	<0.001	<0.001	–	0.024	<0.001
4	<0.001	<0.001	0.024	–	0.067
5	<0.001	<0.001	<0.001	0.067	–
RP					
1	–	<0.001	<0.001	<0.001	<0.001
2	<0.001	–	<0.001	<0.001	<0.001
3	<0.001	<0.001	–	0.028	<0.001
4	<0.001	<0.001	0.028	–	0.006
5	<0.001	<0.001	<0.001	0.006	–

Table 3 Multivariate analysis for bRFS based on preoperative features (biopsy grade grouping and clinical T-stage).

Variable	bRFS	
	HR (95% CI)	*P*
Biopsy grade group		
Group 1	Reference	
Group 2	1.98 (1.58–2.48)	<0.001
Group 3	4.20 (3.26–5.40)	<0.001
Group 4	5.57 (4.02–7.72)	<0.001
Group 5	9.32 (6.41–13.54)	<0.001
Clinical T-stage		
T1c/T2a	Reference	
T2b/c	1.52 (1.27–1.82)	<0.001
T3–T4	2.27 (1.00–5.17)	0.050
Preoperative PSA level, ng/mL		
<10	Reference	
10–20	2.31 (1.89–2.83)	<0.001
>20	3.17 (2.32–4.34)	<0.001
Year of treatment (<2005 vs >2005)	0.48 (0.39–0.59)	<0.001

Table 4 Multivariate analysis for bRFS based on postoperative features (RP grade grouping and pathological T-stage).

Variable	bRFS	
	HR (95% CI)	*P*
RP grade group		
Group 1	Reference	
Group 2	2.09 (1.54–2.82)	<0.001
Group 3	5.27 (3.86–7.19)	<0.001
Group 4	5.86 (3.91–8.78)	<0.001
Group 5	10.42 (7.09–15.32)	<0.001
Pathological T-stage		
T2a	Reference	
T2b/c	1.44 (1.06–1.96)	0.02
T3–T4	3.38 (2.47–4.64)	<0.001
Preoperative PSA level, ng/mL		
<10	Reference	
10–20	1.80 (1.46–2.21)	<0.001
>20	2.17 (1.58–2.99)	<0.001
Year of treatment (<2005 vs >2005)	0.48 (0.39–0.59)	<0.001

Table 5 Results of receiver-operating curve discriminatory analysis (AUC) for the entire cohort, those treated before 2005 and after 2005 for the classical three-tier Gleason grouping (6, 7, and 8–10) and the new five-tier grade-grouping system.

	Discrimination (AUC)	
	Biopsy bRFS	RP bRFS
Entire cohort (n = 3 694)		
Three-tier Gleason grouping (6 vs 7 vs 8–10)	0.65	0.66
New five-tier grade grouping (6 vs 3+4 vs 4+3 vs 8 vs 9–10)	0.67	0.72
Before 2005 (n = 1 838)		
Three-tier Gleason grouping (6 vs 7 vs 8–10)	0.67	0.68
New five-tier grade grouping (6 vs 3+4 vs 4+3 vs 8 vs 9–10)	0.68	0.73
After 2005 (n = 1 856)		
Three-tier Gleason grouping (6 vs 7 vs 8–10)	0.72	0.70
New five-tier grade grouping (6 vs 3+4 vs 4+3 vs 8 vs 9–10)	0.76	0.80

significant (Table 2). On univariable analysis, RP grade group, pathological T-stage, preoperative PSA level, and year of treatment were significant predictors of bRFS, while age was not. Grade group was associated with an incremental increase in the hazard for BCR; relative to biopsy grade-group 1, the HRs were 2.3, 7.3, 10.4, and 18.9 for groups 2, 3, 4, and 5, respectively (all $P < 0.001$).

On multivariable analysis after adjusting for clinical T-stage, preoperative PSA level, and year of treatment, there was a statistically significant increase in the aHR for BCR across all grade groupings ($P < 0.001$). The aHRs relative to RP grade group 1 were 2.09, 5.27, 5.86, and 10.42 for groups 2, 3, 4, and 5, respectively (Table 4). Additionally, an increase in pathological T-stage (T2a as the reference) was significantly associated with an increased aHR for BCR; T2b/T2c (aHR 1.44, 95% CI 1.06–1.96; $P = 0.02$), and T3–4 (aHR 3.38, 95% CI 2.47–4.64; $P < 0.001$). Preoperative PSA level was also significantly associated with an increase in aHR for BCR, as was year of treatment. Adjusted Kaplan–Meier curves of the five RP grade groupings after adjustment for pathological T-stage, preoperative PSA level and year of treatment are shown in Figure S1b.

Discrimination Analyses

To compare the discriminatory power of the new grade-grouping system to the commonly used three-tier Gleason groupings (Gleason score 6 vs 7 vs 8–10), AUC analyses were performed (Table 5). There was an improvement in the AUC for bRFS for both the biopsy (0.65 vs 0.67) and the RP (0.66 vs 0.72) samples. These findings held true when analysing pre-2005 patients before the ISUP update occurred (biopsy

0.67 vs 0.68, and RP 0.68 vs 0.73). However, this was most prominent after 2005 (biopsy 0.72 vs 0.76, RP 0.70 vs 0.80). The RP grade consistently had more discriminatory power than biopsy grade using the new grade-grouping system.

Discussion

In 1966, Donald Gleason [16] first proposed criteria for grading prostate cancer based on architectural patterns and subsequently demonstrated that the sum of the primary and secondary histological patterns (Gleason score) was strongly correlated with mortality [17]. Since then, Gleason score has remained one of the strongest predictors of long-term outcomes in prostate cancer, including PSA recurrence and disease-specific mortality [18–20].

While the essence of this original system is still largely used today, the clinical practice and presentation of prostate cancer has changed dramatically over the past 50 years. In the late 1960s, there was no PSA screening, DRE screening was not routinely performed, and biopsy techniques were more limited [21]. Consequently, men presented with more advanced disease [17]. In 2005, the ISUP convened a consensus conference to address controversial issues relating to the Gleason system, which had been largely unchanged for 40 years. This conference resulted in many modifications, but perhaps the largest change was the refinement of different histological categories that limited the definition of pattern 3, while widening the scope of pattern 4 disease [15]. These modifications improved prognostication: in a study by Dong et al. [22], patients with original (before 2005) Gleason score 6 disease that were upgraded to modified Gleason score 7 or 8 disease had worse bRFS and metastasis-free survival compared with patients with original and modified Gleason score 6 disease.

Despite the improved prognostication, significant stage migration occurred as a result of the modified system. Gleason score 6 cancers are now a more homogeneous group with an artificially improved prognosis due to the reclassification of higher-risk patients out of this group, consistent with the 'Will Rogers phenomenon' [23]. The diagnosis of Gleason score ≤6 has become less common, as shown by a large Surveillance, Epidemiology and End Results (SEER) and National Cancer Data Base (NCDB) analysis from 2004 to 2011 [24]. The 2005 modifications also limited the clinical use of low-grade patterns, recommending against the diagnosis of Gleason score 1+1=2, and declaring that the diagnosis of Gleason scores 3–4 should be made 'rarely, if ever' on needle biopsy. The first recommendation for Gleason scores 2–4 not to be made on biopsy was from an editorial by Epstein [25] in 2000, which was adopted in the consensus conference in 2005. Helpap and Egevad [2] reported that the percentage of RP specimens with Gleason scores 2–5 decreased from 6.3% to 0% when comparing original and modified grading criteria. Thus, the reporting of Gleason scores 2–5 has become virtually extinct in modern practice. The current Gleason scoring system may lead patients to incorrectly perceive 'grade 6' as intermediate-risk on a 10-point scale, which may potentially contribute to disease overtreatment [26]. This is in stark contrast to the low probability of BCR at 5 years for patients with Gleason score 6 disease (94.2% and 96.1% 5-year actuarial bRFS for biopsy and RP grade, respectively). A label of 'grade-group 1' may more accurately reflect the relatively low-risk nature of this group.

There have been multiple studies showing the prognostic differences between Gleason score 3+4 and 4+3 disease, the former associated with increased bRFS [3,6,12], lower rates of distant metastases [3,12], and higher disease-specific survival [3,12]. However, current clinical practice guidelines, including the NCCN guidelines, incorporate the overall Gleason score into their risk-stratification schemas with no formal role for the primary Gleason pattern. As such, patients with Gleason scores 3+4 and 4+3 are both labelled 'intermediate-risk' despite their prognostic differences. We show significant differences in bRFS for patients 3+4 vs 4+3 disease (89.2% vs 73.1% biopsy 5-year actuarial BCR and 93.0% vs 74% RP 5 year-actuarial BCR; both $P < 0.001$).

In addition, most risk-stratification schemas classify patients with Gleason scores 8–10 as high-risk, without discrimination between Gleason score 8 vs 9–10. However, multiple studies have reported significantly worse outcomes in patients with Gleason pattern 5 [8,9,27]. Sabolch et al. [8] assessed the impact of Gleason pattern 5 in patients treated with dose-escalated radiation therapy and showed that patients with Gleason pattern 5 had significantly lower freedom from metastasis ($P < 0.002$), cause-specific survival ($P < 0.001$), and overall survival ($P < 0.001$). Nanda et al. [27] also reported significant differences in PSA recurrence for men with Gleason score 8 disease vs those with Gleason scores of 9–10. Our present analysis confirms bRFS differences for patients with Gleason score 8 vs 9–10 disease (63.1% vs 54.7% biopsy 5-year actuarial bRFS; 64.4% vs 49.8% RP 5-year actuarial bRFS).

This new grading system was recently endorsed by the ISUP and has been accepted by the WHO [11]. Our present study provides an independent external validation of this new grading schema from a distinct surgical cohort. To our knowledge, this is the first to show a difference in adjusted bRFS based on these grade groupings.

As a retrospective study, our present analysis has important limitations. Although multiple clinical variables were included in our models, it is possible that there are additional unmeasured cofounders that may have affected the results. We attempt to control for stage migration by including the year of treatment in our analysis. One-half of the patients in the

present study preceded 2005 when grading was different than what is currently recommended. It should also be emphasised that although the new grade-group system was accurate in the pre-2005 cohort, it was more accurate after 2005 in support that the post-2005 grading better correlates with prognosis. Additionally, BCR, rather than metastases or cancer-specific survival, was used as the primary end-point of our present study because (i) to validate the similar endpoint of prior studies, and (ii) due to the rarity of these other outcomes in a localised surgical cohort. Lastly, submission of the entire prostate for histopathological evaluation at RP is not routinely performed at our institution; however, this would be expected to impact cases equally across grade groups.

In conclusion, we provide independent validation of the new grading system. We show a step-wise, increased risk of BCR in these groupings based on both biopsy and RP grade. Additionally, the grade groupings demonstrated higher prognostic discrimination when compared against the more traditional Gleason grade categorisation. This new system may allow for improved prognostication, and these results support their clinical implementation. Future work is needed to understand the clinical impact the new grade-grouping system has on patient decision making.

Conflict of Interest

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Correspondence: Daniel E. Spratt, Department of Radiation Oncology, University of Michigan Medical Center, 1500 East Medical Center Dr, Ann Arbor, MI 48109-0010, USA.

e-mail: sprattda@med.umich.edu

Abbreviations: AUC, area under the receiver operating characteristic curve; BCR, biochemical recurrence; bRFS, biochemical recurrence-free survival; (a) HR, (adjusted) hazard ratio; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Adjusted Kaplan–Meier Analyses of bRFS for (a) biopsy grade and (b) RP grade.

