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Original contribution

New prostate cancer grade grouping system predicts survival after radical prostatectomy ☆

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Summary Histological Gleason grading of prostate cancer has been through modifications and conjoined into a Grade Grouping system recently. The aim of this study was to determine whether the new Grade Grouping system predicts disease-specific and all-cause mortality after radical prostatectomy. We constructed a clinical database consisting of all consecutively radical prostatectomy–treated men between 1983 and 1998 and between 2000 and 2005 at the Helsinki University Hospital and at the Turku University Hospital, respectively. Patients' all-cause and prostate cancer–specific mortality information was updated in November 2015 from the Finnish Cancer Registry. Secondary therapy information was also available from the patients' records at Helsinki. Univariate and multivariate statistical analyses were performed to assess predictive significance of the Grade Grouping system. Grade Grouping associated independently with increased risk of prostate cancer–specific mortality within 15 years of follow-up in a multivariable model containing age at operation, diagnostic prostate-specific antigen, pathological stage and lymph node status at operation. Additionally, the all-cause mortality-free survival time and time to secondary therapies were different between the Grade Groups, emphasized in the subanalysis of Grade Groups 1-2 versus Grade Groups 3-5. We can conclude that the new Grade Grouping system is feasible in predicting prostate cancer–specific survival after radical surgical treatment. Grade Grouping offers a simpler way to interpret the predicted course of the disease to individual patients and thus may help in justifying more conservative follow-up approaches, especially in the lower Grade Group patients.

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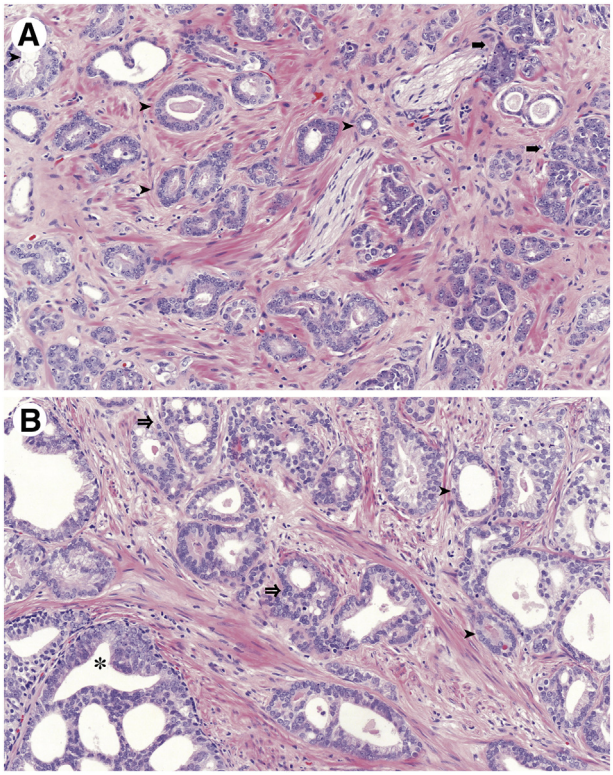


Fig. 1 Histological examples of the growth patterns that had been adopted to variable extent after the ISUP 2005 consensus meeting but unanimously incorporated into distinct Gleason grades and Grade Groups at the 2014 ISUP consensus meeting. A, Separate glands should be assigned a Gleason grade pattern 3, regardless of the size or, for example mucinous excretion (arrowheads). Fusing glands of Gleason grade pattern 4 shown on the right, partially perineurally (arrows). B, Cribriform and glomeruloid glands are assigned as Gleason grade pattern 4 (open arrows), regardless of the size (Gleason grade pattern 3 glands shown in comparison, arrowheads). Intraductal carcinoma (asterisk) should not be given a Gleason grade.

1. Introduction

Gleason grading holds the position as the strongest predictor of survival after initial treatment of prostate cancer. Since the introduction of the Gleason grade patterns and score in 1966, the modifications done to the overall Gleason score (GS) over the years have led to clustering of new prostate cancer diagnoses mainly into GS 6 and 7 [1-3]. The current consensus is that no GS 2-4 should be assigned in biopsies and even GS 5 is very rare [4]. There is strong evidence that GS 3 + 4 = 7 and 4 + 3 = 7 differ in terms of survival [5,6]. As a whole, the aforementioned "grade inflation" and sources of confusion for the patients have led to a consensus work-up for a new Grade Group (GG) system recently introduced in the World Health Organization classification for prostate cancer [4,7-9]. Histologically, the variable adaptation of the modifications to Gleason grading after the International Society of Urological Pathology (ISUP) 2005 consensus meeting have now been incorporated into a consensus statement with uniform acceptance, and grading is performed with more unified criteria (Fig. 1). The new grading system allows for easier counseling of patients and has potentially increased predictive value over GS. GGs are formed from the contemporary GS criteria (Table 1). Tertiary patterns, now suggested to be referred to as minor high-grade patterns (MHGP), have also been considered in the context of GGs as recent studies have shown that MHGP can potentially add prognostic value to GG. MHGP, however, are not currently considered as an integral part of the GG and are only assessed in radical prostatectomy (RP) specimens [10]. The validation studies for GG thus far have shown the relation of GG to biochemical recurrence-free survival (BRFS) and prostate cancer–specific mortality (PCSM) in RP cohorts, using biopsy and/or RP grades [11-13]. Registry-based re-analyses have shown the strength of GG in predicting PCSM and metastasis-free survival [14]. Also recently, a radiation-treated cohort was analyzed for biopsy GG as predictor of BRFS and PCSM [15]. However, none of the studies have shown that the new GG system has increased predictive power with respect to GS, and most of the studies are hampered by short follow-up times and BRFS as the end-point for the analysis.

Table 1 Gleason Score versus Grade Group

Gleason Score	Grade Group
≤6	1
3 + 4	2
4 + 3	3
4 + 4	
5 + 3	4
3 + 5	
4 + 5	
5 + 4	5
5 + 5	

The weakness for BRFS as end-point is its surrogate nature [16-18]. Altogether, 30%–40% of RP-treated patients experience BRFS during post-operative follow-up [19-21]. However, presumably by the survival-prolonging effect of secondary treatments, only approximately 10% of the patients experience disease-specific mortality in 10 to 15 years after RP [22,23]. Cohorts with an adequate number of patients and sufficient follow-up time for PCSM are rarely available. In addition, pre–magnetic resonance imaging (MRI)–era transrectal ultrasound–guided (TRUS) biopsies are prone to significant sampling error, thus higher grade prostate cancer foci are missed in up to 30% of GS 3 + 3 biopsies [24,25]. Validation of the GG system in predicting the all-cause mortality (ACM) and PCSM compared to conventional Gleason grade pattern scores is essential in order to facilitate its use in patient communication. Here, we have validated the predictive significance of the new GG system after RP in a large patient set with substantially long follow-up time. In addition to the most important outcome, ie, survival, secondary treatment information was incorporated into the analysis.

Table 2 Characteristics of the 2 study cohorts and combined study population

Characteristics	Helsinki cohort (1982-1998)	Turku cohort (2000-2005)	Total
Age at RP, years (n = 831) (median, range)	64 (45-76)	62 (40-73)	63 (40-76)
Diagnostic PSA, ng/mL (n = 715) (n, %)			
≤10.0	145 (50.0)	294 (69.2)	439 (61.4)
10.1-20.0	92 (31.7)	96 (22.6)	188 (26.3)
>20.0	53 (18.3)	35 (8.2)	88 (12.3)
Gleason score at RP (n = 831) (n, %)			
≤6	97 (25.9)	168 (36.8)	265 (31.9)
7	217 (58.0)	197 (43.1)	414 (49.8)
8-10	60 (16.0)	92 (20.1)	152 (18.3)
Grade Group at RP (n = 831) (n, %)			
1	97 (25.9)	168 (36.8)	265 (31.9)
2	95 (25.4)	134 (29.3)	229 (27.6)
3	122 (32.6)	63 (13.8)	185 (22.3)
4	47 (12.6)	70 (15.3)	117 (14.1)
5	13 (3.5)	22 (4.8)	35 (4.2)
pT (n = 784) (n, %)			
2	208 (60.5)	233 (53.0)	441 (56.2)
3	136 (39.5)	207 (47.0)	343 (43.8)
Lymph node status (n = 822) (n, %)			
N0	358 (97.3)	434 (95.6)	792 (96.4)
N1	10 (2.7)	20 (4.4)	30 (3.6)
Follow-up time after RP, years (n = 831) (median, range)	15.7 (0.1-28.6)	9.5 (0.2-14.0)	11.1 (0.1-28.6)
Death from any cause (n = 831) (n, %)	183 (48.9)	73 (16.0)	256 (30.8)
Death from prostate cancer (n = 831) (n, %)	36 (9.6)	19 (4.2)	55 (6.6)
Patients receiving secondary therapy (n = 812) (n, %)	128 (34.2)	136 (31.1)	264 (31.8)

Abbreviations: RP, radical prostatectomy; PSA, prostate-specific antigen; pT, pathological stage.

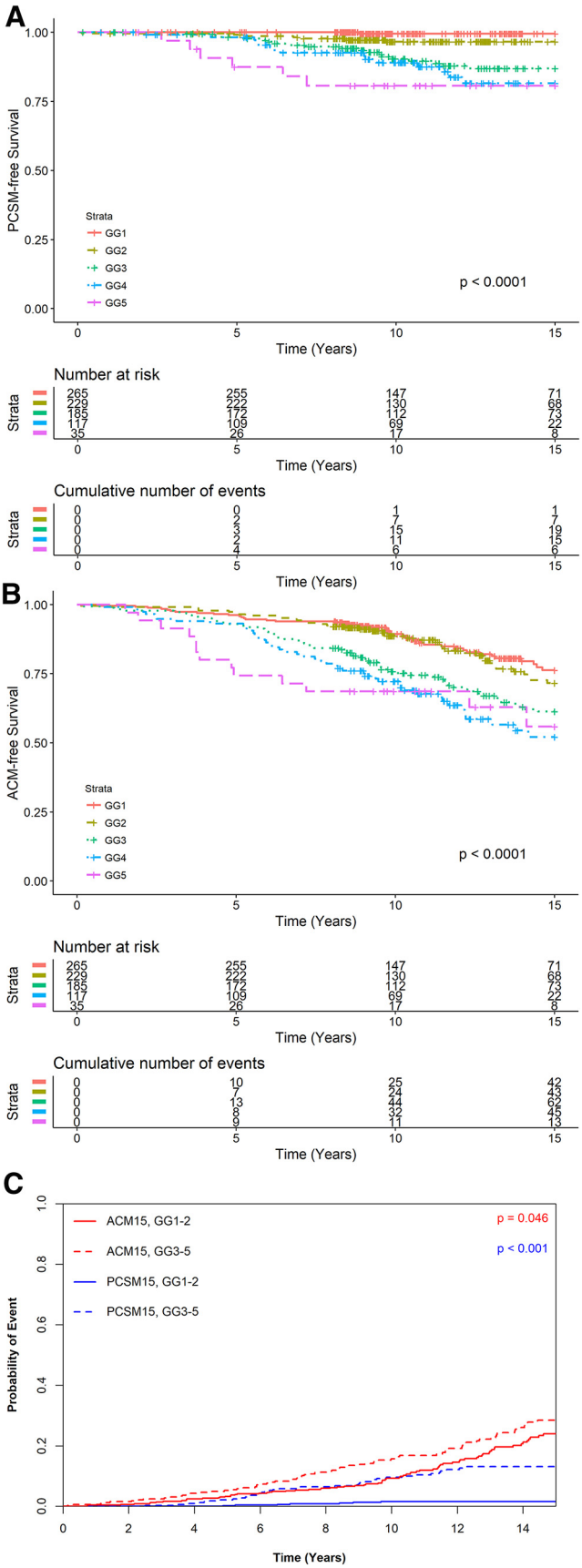
2. Materials and methods

2.1. Patient cohort

The study cohort consisted of patients with comprehensive clinical data and accompanying RP specimens operated on between 1983 and 1998 at Helsinki University Hospital and between 2000 and 2005 at Turku University Hospital. Limited pelvic lymph node dissection accompanied most of the RPs in both cohorts. The clinical databases were combined and updated in November 2015 with the Finnish Cancer Registry's data on patients' all-cause and disease-specific mortality, resulting in a median follow-up time of 15.7 years for the Helsinki cohort (range 0.7-28.6) and 9.5 years (range 0.2-14.0) for the Turku cohort. The median post-RP follow-up time for the entire cohort for PCSM and ACM was 11.9 years, and the median age at RP was 62.4 years. For more detailed demographics of the separate Helsinki and Turku cohorts and the whole cohort, see Table 2.

The Helsinki and Turku cohorts originally included 478 and 532 patients, respectively. For both cohorts, the original clinical RP specimen slides were re-evaluated between years 2005 and 2010 by experienced uropathologists according to the GS criteria of the ISUP 2005 consensus meeting and taking into account the commonly applied recommendations thereafter, to form the classes currently recognized as GGs (the criteria that were approved in the consensus of 2014) (Table 1) [1,2,26]. To avoid possible interference of accompanied treatments on tissue interpretation [1], patients who had received neoadjuvant therapies prior to RP were excluded, leading to 401 and 503 patients in the Helsinki and Turku cohorts, respectively. Complete follow-up data were available for a total of 374 and 457 patients, who were included in the final analysis. Post-operative follow-up was conducted by clinical examinations and prostate-specific antigen (PSA) measurements at least three times during the first year after surgery and at least once a year during the following years. For the Helsinki cohort, also the complete information of the commencement dates for secondary therapies was available (Supplementary Table 1).

The ethical committees of the corresponding hospital districts approved the use of clinicopathological data (Hospital District of Helsinki and Uusimaa, 445/E6/02, and Hospital District of Southwest Finland). Approval for the use of clinical and registry data was obtained from the National Authority for Welfare and Health (Valvira 394/05.01.00.06/2009) and the use of the Finnish Cancer Registry's data was approved by the National Institute for Health and Welfare (THL/1549/5.05.00/2013). Patients' personal information was de-identified prior to analyses.



2.2. Statistical analysis

The primary outcomes in this study were PCSM and ACM within the first 15 years of follow-up. If outcome events occurred after 15 years, the patient's follow-up was encoded as 15 years, and censored. The secondary outcome, analyzed only in the Helsinki cohort, was initiation of secondary therapy. Kaplan-Meier survival analysis with Mantel-Haenzel log-rank test for time to PCSM, time to ACM or time to secondary therapies was performed. Additionally, univariable and multivariable Cox regression analyses were performed to assess risk for outcome events, and included age at operation, PSA at diagnosis, GG, pathological T-stage (pT), and lymph node status in the models. Competing risk analysis was performed comparing the risk of mortality by any causes and by prostate cancer, as stratified by GG. Receiver operating characteristic (ROC) area under the curve (AUC) analyses were performed for the new 5-tiered GG and 3-tiered GS (<7, 7, >7) to compare the predictive accuracy of the two grading systems. Decision curve analyses comparing net benefit of Grade Grouping versus Gleason scoring in the decisionmaking was also performed. All statistical analyses were performed using R Statistical Software v.3.3.3 (Foundation for Statistical Computing, Vienna, Austria) using the packages *survival*, *survminer*, *pROC*, *cmprsk*, and *rms*.

3. Results

3.1. Univariable survival analysis

Amongst the study population, half of the patients were originally graded as GS7 and almost one third as GS ≤ 6. After stratifying patients into GGs, GG2 and GG3 formed almost equally sized groups (Table 2). In Kaplan-Meier survival analyses for ACM and PCSM outcomes, remarkably, GG2 stratified patients similarly to GG1, while the survival profile of patients with GG3 was similar to those patients with GG4 or GG5 (P .0001, Fig. 2A and B). Each unit increase in GG was significantly associated with shorter median secondary therapy treatment-free survival (P < .0001, Supplementary Fig. 1).

In univariable Cox proportional hazard analysis for probability of death after surgical treatment, the hazard ratio for PCSM ranged from 8.015 (P = .052, 95% CI = 0.986-65.14) to 55.799 (P < .001, 95% CI 6.717-463.52) when

Fig. 2 Survival analysis of new Grade Group system and outcomes. Kaplan-Meier analyses for probability of survival during follow-up for prostate cancer–specific mortality (PCSM)–free survival (A), any cause mortality (ACM)–free survival (B). To evaluate the new Grade Grouping system with regards to significance in predicting competing outcomes, Gray's competing risk analysis (C) was performed for low (1-2) versus high (3-5) and cumulative incidence of any-cause mortality within 15 years of follow-up (ACM15) and prostate cancer–specific mortality within 15 years of follow-up (PCSM15).

Table 3 Uni- and multivariate Cox regression analysis of clinicopathological variables and outcome

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
A. Prostate cancer–specific mortality within 15 years of follow-up						
Age at RP ≤60 y	–	–	Ref	–	–	Ref
Age at RP 60.1–70 y	1.137	(0.599-2.156)	.695	1.908	(0.799-4.553)	.146
Age at RP >70 y	1.660	(0.603-4.568)	.327	0.616	(0.075-5.054)	.652
PSA at diagnosis 0-10.0	–	–	Ref	–	–	Ref
PSA at diagnosis 10.1-20.0	1.902	(0.806-4.486)	.142	1.514	(0.623-3.678)	.360
PSA at diagnosis >20	2.913	(1.127-7.528)	.027*	1.145	(0.411-3.188)	.795
Grade Group 1[a]	–	–	Ref	–	–	Ref
Grade Group 2	8.015	(0.986-65.14)	.052	2.699	(0.861-8.464)	.089
Grade Group 3	27.315	(3.656-204.06)	.001*	6.692	(2.215-20.218)	.001*
Grade Group 4	37.136	(4.905-281.16)	<.001*	7.797	(2.037-29.843)	.003*
Grade Group 5	55.799	(6.717-463.52)	<.001*	–	–	Ref
pT stage 2	–	–	Ref	6.224	(1.823-21.247)	.004*
pT stage 3 and 4	16.544	(5.088-53.8)	<.001*	–	–	Ref
LN negative	–	–	Ref	17.481	(4.883-62.582)	<.001*
LN positive in first 6 years	16.068	(6.018–42.90)	<.001*	1.917	(0.24-15.289)	.539
LN positive after first 6 years	4.624	(1.399-15.28)	.012*			
B. Any-cause mortality within 15 years of follow-up						
Age at RP ≤60 y	–	–	Ref	–	–	Ref
Age at RP 60.1–70 y	1.217	(0.882-1.681)	.232	1.281	(0.887-1.85)	.186
Age at RP >70 y	2.933	(1.918-4.486)	<.001*	2.807	(1.664-4.737)	<.001*
PSA at diagnosis 0-10.0	–	–	Ref	–	–	Ref
PSA at diagnosis 10.1-20.0	0.967	(0.667-1.402)	.858	0.879	(0.599-1.29)	.510
PSA at diagnosis >20	1.515	(0.997-2.302)	.052	0.886	(0.553-1.421)	.616
Grade Group 1	–	–	Ref	–	–	Ref
Grade Group 2	1.181	(0.772-1.807)	.444	0.928	(0.569-1.513)	.763
Grade Group 3	2.025	(1.368-2.997)	<.001*	1.291	(0.784-2.126)	.315
Grade Group 4	2.749	(1.805-4.188)	<.001*	1.784	(1.044-3.047)	.034*
Grade Group 5	2.861	(1.536-5.331)	<.001*	1.823	(0.864-3.845)	.115
pT stage 2	–	–	Ref	–	–	Ref
pT stage 3 and 4	1.940	(1.447-2.601)	<.001*	1.520	(1.056-2.188)	.024*
LN negative	–	–	Ref	–	–	Ref
LN positive	3.649	(2.247-5.925)	<.001*	3.492	(1.899-6.419)	<.001*
C. Initiation of secondary therapy						
Age at RP ≤60 y	–	–	Ref	–	–	Ref
Age at RP 60.1–70 y	0.832	(0.481-1.439)	.510	1.226	(0.786-1.911)	.369
Age at RP >70 y	0.876	(0.376-2.043)	.760	1.556	(0.830-2.917)	.168
PSA at diagnosis 0-10.0	–	–	Ref	–	–	Ref
PSA at diagnosis 10.1–20.0	2.152	(1.162-3.983)	.015*	1.896	(1.041-3.454)	.037*
PSA at diagnosis >20	4.047	(2.235-7.327)	<.001*	6.942	(3.957-12.177)	<.001*
Grade Group 1	–	–	Ref	–	–	Ref
Grade Group 2	1.676	(0.626-4.487)	.304	3.376	(1.442-7.903)	.005
Grade Group 3	2.920	(1.139-7.487)	.026*	7.566	(3.421-16.735)	<.001*
Grade Group 4	6.799	(2.455-18.828)	<.001*	12.546	(5.396-29.172)	<.001*
Grade Group 5	26.208	(7.785-88.23)	<.001*	25.591	(9.478-69.097)	<.001*
pT stage 2	–	–	Ref	–	–	Ref
pT stage 3 and 4	2.959	(1.747-5.012)	<.001*	4.586	(3.039-6.919)	<.001*
LN negative	–	–	Ref	–	–	Ref
LN positive	1.406	(0.404-4.895)	.593	4.87	(2.128-11.14)	<.001*

Abbreviations: RP, radical prostatectomy; PSA, prostate-specific antigen; pT, pathological stage; LN, lymph node.

[a] Grade Groups 1 and 2 pooled for multivariate analysis.

* Statistically significant *P*-value, 2-tailed.

GG2 to GG5 were compared to reference of GG1. Similarly, increased GG was associated with increased risk of ACM and initiation of secondary therapy (Table 3).

3.2. Multivariable survival analysis

In testing Cox proportional hazards assumption for a multivariable model with PCSM as the outcome, the lymph node status at RP was found to violate the assumption, and was assessed in a time-dependent manner of less than or equal to 6 years follow-up, or greater than 6 years follow-up. Additionally, due to the low number of PCSM events in GG1 (n = 1), our multivariable model did not converge, and thus we conducted pooled analysis of GG1 and 2 together as the reference group.

In the multivariable Cox regression analysis, pT stage and lymph node positivity predicted significant differences in PCSM. Interestingly, the increased risk of outcome events due to lymph node positivity was observed to be time dependent, with it no longer being associated with PCSM after the first 6 years of follow-up (Table 3A).

3.3. Competing risk analysis of cause of mortality

Gray's competing risk analysis was conducted to analyze the predicted risk of patients with GG 1 and 2, versus GG 3-5 PC progressing to PCSM in comparison to patients who experienced ACM or survival. There was a significant difference of cumulative incidence by GG in patients who experienced PCSM *(P* < .0001) and ACM (*P* = .046) (Fig. 2C).

3.4. Benefits of Grade Grouping in outcome prediction

In order to study the additive effect of GG in survival prediction, ROC-AUC analyses were performed to address the discriminatory power of three-tier GS (<7, 7, >7) and the five-tier GG with outcomes. The receiver-operating curve discriminatory analysis showed increased area under the curve (AUC) values for GG in all of the study outcomes when compared with the three-tier GS (Supplementary Fig. 2A-C).

Lastly, decision curve analyses were performed to compare the net benefit of GG and GS in predicting outcome. Decision curve analysis plots the net benefit of predictors against all probabilities of an event occurring. This allows for comparison of different predictors in assessing the harm-to-benefit ratio for clinical decision of an intervention. For all measured outcomes (PCSM, ACM and secondary therapy–free survival), across all threshold probabilities of outcome events occurring, GG performed better than, or as well as, GS (Supplementary Fig. 3).

4. Discussion

A new predictive prostate cancer grading system has recently been proposed by authors at Johns Hopkins Hospital led by the pathologist Jonathan Epstein using a fairly simple division of Gleason grade pattern sums into GG (Table 1) [4]. The predictive value has been validated in studies of prostate cancer patients treated with different modalities as well as in separate cohorts of RP and radiation-treated patients [12,14,27]. Despite studies assessing the predictive value of GG to predict hard outcomes such as PCSM [13], few studies have comprehensively conducted rigorous discriminatory analysis of GS and GG in the same patient cohort.

Previous studies have compared GG and GS in prediction of BRFS [15,27,28] and have found GG to be a better predictor of outcome than GS. The strengths of these studies include large sample sizes, multi-center analyses, and diverse study populations. The studies, however, suffer from short median follow-up times, and the use of BRFS, which is considered as a surrogate endpoint. Additionally, as commented by Dell'Oglio et al, these studies did not address the most crucial unmet clinical need: assessing the possible superiority of GG over GS with regard to harder outcomes, namely PCSM [29]. In order to address these problems, two other recently published studies, have analyzed harder endpoints [30,31]. In the study by Dell'Oglio et al, no additive benefit for GG over GS could be shown. The authors assessed performance with respect to clinical recurrence (CR), defined as detection of metastasis after BRFS, as an endpoint and a median follow-up of 5.8 years [30]. The authors speculated that a lack of plateau in their Kaplan-Meier curves might suggest increased differences between GGs with longer follow-up. The study by Grogan et al compared the predictive power of GG and GS for BRFS, CR, and PCSM in a single-center cohort. The study cohort featured a rigorous re-evaluation of GS to the ISUP 2005 standard, and a long median follow-up time of 15 years. While their study found GG to be superior to GS in predicting BRFS, CR and PCSM, the authors did not report whether GG remained an independent predictor of PCSM in multivariable analysis for PCSM, despite reporting such data for other study outcomes [31].

To our knowledge, our study is the first multicenter study, with long-term follow-up, to demonstrate increased predictive value of GG over GS in predicting PCSM and ACM. Our study, with a median of 11.1 years follow-up, affirms the power of GG to predict long-term survival in a RP-treated cohort. Our patients had not received neoadjuvant treatments, but had been treated with adjuvant or secondary therapies at any given era according to treating urologist's discretion. Given the fact that GG remarkably associated with probability of receiving secondary therapies and stratified each group to separate survival curves, only patients in GGs 3 to 5 progressed to prostate cancer–specific death in significant numbers. It is also obvious that the greater adjuvant therapy with each successive GG likely lessened the separation of the curves in the cancer-specific mortality Kaplan-Meier curves (Fig. 2A) since adjuvant therapy is associated with delaying the time to death.

One of the strengths of our study compared to other contemporary cohorts is the long median follow-up time needed to study survival endpoints [14]. Only by long follow-up can the significant variables independently associated with

PCSM be assessed, those being age, diagnostic, pT stage, lymph node status and GG in our multivariable analysis. Regardless of the local extent of the disease, GG predicted PCSM after RP. Especially the clear depression in survival probability seen between GG2 and GG3 emphasizes the importance of volume of Gleason grade pattern 4 predominance long term for contributing to disease progression and mortality, despite secondary therapies. All of our patients have been diagnosed before 2005, and thus the treatment decisions were based on the Gleason criteria at that time. Importantly, as we aimed for long follow-up to allow survival endpoints to be studied, we chose a historical cohort, but re-evaluation of the slides was conducted according to 2005 ISUP consensus meeting, supplemented by the modifications later approved in 2014. Our study with re-evaluated RP specimens further states the use of GG in differentiation of Gleason score 7 tumors into groups with significantly different prognosis.

In addition to being a retrospective analysis, other weaknesses of our study include lack of thorough PSA data for BRFS analysis and the lack of information on the tertiary Gleason pattern in RP specimens. A recent study has evaluated how the existence of tertiary higher-grade pattern along with the new GG affects the prognosis after RP [32]. Also, as the biopsies are now more often taken under MRI-TRUS fusion guidance, the issues of undersampling can be better avoided [24]. Based on our results on RP-treated cohorts, we can postulate that GG2 patients react to adjuvant treatments better and can possibly be treated more conservatively post-operatively, or followed-up less frequently as GG $\geq$3 patients. Addition of tissue biomarkers, such as PTEN, to the analysis might further help stratify patients into proper follow-up or adjuvant therapies [33,34].

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.01.027.

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References

[1] Epstein JI. An update of the Gleason grading system. J Urol 2010;183:433-40. https://doi.org/10.1016/j.juro.2009.10.046.
[2] Epstein JI, Allsbrook WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228-42.
[3] Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep 1966;50:125-8.
[4] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-52.
[5] Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol 2009;27:3459-64. https://doi.org/10.1200/JCO.2008.20.4669.
[6] Wright JL, Salinas CA, Lin DW, et al. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4 + 3 and Gleason 3 + 4 tumors in a population based cohort. J Urol 2009;182:2702-7. https://doi.org/10.1016/j.juro.2009.08.026.
[7] Amin MB, Lin DW, Gore JL, et al. The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer: consensus statement with recommendations supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation. Arch Pathol Lab Med 2014;138:1387-405. https://doi.org/10.5858/arpa.2014-0219-SA.
[8] Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. Lyon: IARC; 2016.
[9] Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int 2013;111:753-60. https://doi.org/10.1111/j.1464-410X.2012.11611.x.
[10] Epstein JI, Amin MB, Reuter VE, Humphrey PA. Contemporary Gleason grading of prostatic carcinoma: an update with discussion on practical issues to implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2017;41:e1-. https://doi.org/10.1097/PAS.0000000000000820.
[11] Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016;69:428-35. https://doi.org/10.1016/j.eururo.2015.06.046.
[12] Spratt DE, Cole AI, Palapattu GS, et al. Independent surgical validation of the new prostate cancer grade-grouping system. BJU Int 2016;118:763-9. https://doi.org/10.1111/bju.13488.
[13] Berney DM, Beltran L, Fisher G, et al. Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. Br J Cancer 2016;114:1078-83. https://doi.org/10.1038/bjc.2016.86.
[14] He J, Albertsen PC, Moore D, Rotter D, Demissie K, Lu-Yao G. Validation of a contemporary five-tiered Gleason Grade Grouping using Population-based Data. Eur Urol 2017;71:760-3. https://doi.org/10.1016/j.eururo.2016.11.031.
[15] Spratt DE, Jackson WC, Abugharib A, et al. Independent validation of the prognostic capacity of the ISUP prostate cancer grade grouping system for radiation treated patients with long-term follow-up. Prostate Cancer Prostatic Dis 2016;19:292-7. https://doi.org/10.1038/pcan.2016.18.
[16] Lange PH, Brawer MK. Serum prostate-specific antigen: its use in diagnosis and management of prostate cancer. Urology 1989;33:13-7. https://doi.org/10.1016/S0090-4295 (89)80003-2.
[17] Kuriyama M, Wang MC, Lee CI, et al. Use of human prostate-specific antigen in monitoring prostate cancer. Cancer Res 1981;41:3874-6.
[18] Oesterling JE, Chan DW, Epstein JI, et al. Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. J Urol 1988;139:766-72.
[19] Bjartell A, Bottai M, Persson J, et al. Prediction of clinical progression after radical prostatectomy in a nationwide population-based cohort. Scand J Urol 2016;50:255-9. https://doi.org/10.1080/21681805.2016.1183226.

[20] Beauval J-B, Roumiguié M, Filleron T, et al. Biochemical recurrence-free survival and pathological outcomes after radical prostatectomy for high-risk prostate cancer. BMC Urol 2016;16:26. https://doi.org/10.1186/s12894-016-0146-6.

[21] Abdollah F, Sood A, Sammon JD, et al. Long-term cancer control outcomes in patients with clinically high-risk prostate cancer treated with robot-assisted radical prostatectomy: results from a multi-institutional study of 1100 patients. Eur Urol 2015;68:497-505. https://doi.org/10.1016/j.eururo.2015.06.020.

[22] Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035-41. https://doi.org/10.1200/JCO.2006.08.9607.

[23] Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate Cancer Specific Mortality After Radical Prostatectomy. J Urol 2011;185:869-75. https://doi.org/10.1016/j.juro.2010.10.057.

[24] Gordetsky JB, Nix JW, Rais-Bahrami S. Perineural Invasion in prostate cancer is more frequently detected by multiparametric MRI targeted biopsy compared with standard biopsy. Am J Surg Pathol 2016;40:490-4. https://doi.org/10.1097/PAS.0000000000000546.

[25] Lahdensuo K, Mirtti T, Petas A, Rannikko A. Performance of transrectal prostate biopsies in detecting tumours and implications for focal therapy. Scand J Urol 2015;49:90-6. https://doi.org/10.3109/21681805.2014.936494.

[26] Brimo F, Montironi R, Egevad L, et al. Contemporary grading for prostate cancer: implications for patient care. Eur Urol 2013;63:892-901. https://doi.org/10.1016/j.eururo.2012.10.015.

[27] Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, Stattin P. Evaluation of the 2015 Gleason Grade Groups in a nationwide population-based cohort. Eur Urol 2016;69:1135-41. https://doi.org/10.1016/j.eururo.2015.11.036.

[28] Mathieu R, Moschini M, Beyer B, et al. Prognostic value of the new Grade Groups in prostate cancer: a multi-institutional European validation study. Prostate Cancer Prostatic Dis 2017;20:197-202. https://doi.org/10.1038/pcan.2016.66.

[29] Dell'Oglio P, Stabile A, Gandaglia G, Briganti A. Comment on "Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome." Br J Cancer 2017;116:e3. https://doi.org/10.1038/bjc.2016.346.

[30] Dell'Oglio P, Karnes RJ, Gandaglia G, et al. The new prostate cancer grading system does not improve prediction of clinical recurrence after radical prostatectomy: results of a large, two-center validation study. Prostate 2017;77:263-73. https://doi.org/10.1002/pros.23265.

[31] Grogan J, Gupta R, Mahon KL, et al. Predictive value of the 2014 International Society of Urological Pathology grading system for prostate cancer in patients undergoing radical prostatectomy with long-term follow-up. BJU Int 2017;120:651-8. https://doi.org/10.1111/bju.13857.

[32] Baras AS, Nelson JB, Han M, Parwani AV, Epstein JI. The effect of limited (tertiary) Gleason pattern 5 on the new prostate cancer grade groups. Hum Pathol 2017;63:27-32. https://doi.org/10.1016/j.humpath.2016.12.008.

[33] Lokman U, Erickson AM, Vasarainen H, Rannikko AS, Mirtti T. PTEN loss but not ERG expression in diagnostic biopsies is associated with increased risk of progression and adverse surgical findings in men with prostate cancer on active surveillance. Eur Urol Focus 2017. https://doi.org/10.1016/j.euf.2017.03.004.

[34] Lahdensuo K, Erickson A, Saarinen I, et al. Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy. Mod Pathol 2016;29:1565-74. https://doi.org/10.1038/modpathol.2016.154.