Open Access

Prostate Cancer

ORIGINAL ARTICLE

Predictive efficacy of the 2014 International Society of Urological Pathology Gleason grading system in initially diagnosed metastatic prostate cancer

Guang-Xi Sun[1,*], Peng-Fei Shen[1,*], Xing-Ming Zhang[1], Jing Gong[2], Hao-Jun Gui[1], Kun-Peng Shu[1], Jiang-Dong Liu[1], Jinge Zhao[1], Yao-Jing Yang[1], Xue-Qin Chen[2], Ni Chen[2], Hao Zeng[1]

We compared the predictive ability of the 2014 and 2005 Gleason grading systems in 568 patients initially diagnosed with metastatic prostate cancer (PCa). Outcomes included the duration of castration-resistant prostate cancer-free survival (CFS) and overall survival (OS). Univariate analyses and log-rank tests were used to identify prognosis indicators and assess univariable differences in CFS and OS in Gleason score (GS) groups. Cox proportional hazards and area under the curves of receiver operator characteristics methods were used to evaluate the predictive efficacy of the 2005 and 2014 ISUP grading systems. Univariate analyses showed that the 2005 and 2014 grading systems were prognosticators for CFS and OS; both systems could distinguish the clinical outcome of patients with GS 6, GS 7, and GS 8–10. Using the 2014 criteria, no statistical differences in patient survival were observed between GS 3 + 4 and GS 4 + 3 or GS 8 and GS 9–10. The predictive ability of the 2014 and 2005 grading systems was comparable for CFS and OS ($P = 0.321$). However, the 2014 grading system did not exhibit superior predictive efficacy in patients initially diagnosed with PCa and bone metastasis; trials using larger cohorts are required to confirm its predictive value. To the best of our knowledge, ours is the first study to compare the 2005 and 2014 grading systems in initially diagnosed PCa with bone metastasis. At present, we recommend that both systems should be used to predict the prognosis of patients with metastatic PCa.

INTRODUCTION

The Gleason score (GS) system, first described by Gleason in 1966,[1] is based on tumor cell architecture patterns. Since its inception, the 5-tier scale has proven to be one of the most important risk assessment methods for predicting prostate cancer (PCa) prognosis.

In 2005, over seventy experts at the International Society of Urological Pathology (ISUP) Consensus Conference unanimously agreed to modify the original Gleason grading system to address the challenges of modern practice.[2] The advent of prostate-specific antigen (PSA) screening had enabled increasing numbers of suspected, localized, low-risk PCas to be diagnosed early, and for many of these patients, radical prostatectomy (RP) was the best therapeutic strategy.

In the past 5 years, a number of population-based studies have shown that RP continues to produce better survival outcomes than radical radiotherapy, even in patients with locally advanced, high-risk PCas.[3,4] As such, the predictive value of the modified 2005 Gleason grading system was challenged.

To meet the needs of modern medicine, it was thought necessary to further update the 2005 Gleason grading system; in 2014, over eighty experts, including pathologists, urologists, radiation oncologists, and medical oncologists, attended the Grading System Consensus Conference hosted by the ISUP. Using data from the latest, large-scale databases, the Gleason grading system was reclassified into five groups according to their correlation with biochemical/clinical recurrence, disease-specific survival, and overall survival (OS).[5] Subsequent studies have tentatively validated and confirmed the accuracy of the new 2014 grading system in predicting PCa patient prognosis.[6–8] However, the proposal and validation of the new ISUP 2014 Gleason grading system has principally been based on RP specimens. The prognostic value of the 2014 system in patients treated with endocrine therapy and other therapeutic regimens, especially those that were initially diagnosed metastatic PCa, remains unclear.

The aim of the present study was to determine whether the 2014 ISUP grading system provides superior predictive efficacy to the 2005 grading system in patients with metastatic PCa. The proportion of patients diagnosed with metastatic PCa remains high in Western China because PSA screening is not routinely conducted. We retrospectively analyzed clinical and pathological data from patients who were initially diagnosed with PCa with bone metastasis and analyzed the efficacy of the 2014 and 2005 ISUP grading criteria in predicting castration-resistant PCa (CRPC) occurrence and mortality.

[1]Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [2]Department of Pathology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China.
*These authors contributed equally to this work.
Correspondence: Dr. H Zeng (cdhx510@foxmail.com/kucaizeng@163.com) or Dr. N Chen (chenni1@163.com)
Received: 17 February 2016; Revised: 17 May 2016; Accepted: 06 July 2016

MATERIALS AND METHODS

Patients and methods

A total of 568 patients diagnosed with bone metastatic PCa at Sichuan University, West China Hospital in China, between 2008 and 2014, were included in the study. All patients were diagnosed following ultrasound-guided transperineal prostate biopsy with a needle. The cancer grading was independently reviewed and recorded by two urological pathologists (Ni Chen and Jing Gong) according to the 2005 and 2014 ISUP grading criteria.[2,5] Other clinicopathological parameters, such as the patients' age, baseline PSA level, clinical tumor (T) stage, and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, were also recorded.

All patients were initially treated with standard, long-term, maximal androgen blockade (MAB) until disease progression or death. MAB included orchiectomy (172/568, 30.3%) or medical castration (luteinizing hormone-releasing hormone agonists: goserelin or triptorelin; 396/568, 69.7%) plus nonsteroidal antiandrogens (including bicalutamide [489/568, 86.1%] and flutamide [79/568, 13.9%]). After disease progression, the majority of patients were treated with alternating regimens of nonsteroidal or sequential second-line antiandrogens and palliative care; this was not only for economic and convention reasons of the patients, but also the China Food and Drug Administration disapproved of novel antiandrogen drugs (abiraterone and enzalutamide) at that time. Few patients (75/568, 13.2%) were treated with docetaxel-based chemotherapy.

The primary clinical outcome for this study was CRPC-free survival (CFS) time, defined as the time from initial diagnosis to confirmed CRPC. The secondary outcome was OS, defined as the time from disease diagnosis to death from any causes. The cutoff time for CFS and OS analysis was August 20, 2015. The median follow-up period was 44 months (range 5–85 months).

Statistical analysis

CFS and OS were assessed using the Kaplan–Meier method, and their association with age, ECOG score, baseline PSA, clinical T stage, and the 2005 and 2014 Gleason pattern was assessed. The Chi-square test, Spearman's correlation test, and log-rank test were used to determine statistically significant ($P < 0.05$) differences among variables. Cox's proportional hazards model was used to assess patient relative risk and calculate 95% confidence intervals (95% CIs). The efficacy of the two modified Gleason systems was compared using receiver operating characteristic (ROC) curve analysis, and differences in the area under the ROC curves (AUCs) were computed using the Z-test and MedCalc version 11.4.2.0 software (MedCalc Software, Ostend, Belgium).[9] SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for other statistical analyses.

RESULTS

The baseline characteristics of the 568 patients included in the study are presented in **Table 1**. The median age was 71 years (range 39–91 years). In total, 314/568 (55.3%) patients developed CRPC and 240/568 (42.3%) patients died. The median CFS and OS were 36 and 54 months, respectively. The 2-year CFS and OS rates were 64% and 79%, respectively; the 5-year CFS and OS rates were markedly decreased at 38% and 47%, respectively. The survival rates stratified by GS are shown in **Table 2**. According to the 2005 ISUP grading criteria, 30/568 (5.3%), 197/568 (34.7%), and 341/568 (60.0%) of the needle biopsy samples were categorized as GS 6, GS 7, and GS 8–10, respectively. When the samples were reexamined using the 2014 ISUP criteria, none of the tumor sample GS grades increased; using the

2014 ISUP criteria 30/568 (5.3%), 71/568 (12.5%), 126/568 (22.2%), 123 (21.6%), and 218/568 (38.4%) of the tumor samples were classified as Group 1, 2, 3, 4, and 5, respectively. The GS was correlated with age ($P = 0.121$) and was positively associated with the baseline PSA and clinical T stage ($P = 0.004$ and $P < 0.001$, respectively; **Table 1**).

Univariate analyses indicated that baseline PSA, the 2005 ISUP grading, and the 2014 ISUP grading were strongly associated with the occurrence of CRPC and overall mortality. However, clinical T stage, patient age, and ECOG status at the time of diagnosis could not predict progression of metastatic PCa (**Table 3** and **Figure 1**). Cox regression models indicated that of all the pretreatment parameters, only the 2005 ISUP grading was an independent prognostic indicator of a shorter time to CRPC occurrence and a poorer OS (CFS: hazard ratio [HR] = 2.843, 95% CI: 1.184–3.871, $P = 0.022$; OS: HR = 2.688, 95% CI: 1.102–4.385, $P = 0.054$). The 2014 ISUP grading was not an independent prognostic indicator.

Using the 2005 ISUP criteria, the probability of CFS for patients with GS 6, GS 7, and GS 8–10 tumors was 84.7%, 53.8%, and 35.3%, respectively. The probability of OS for patients with GS 6, GS 7, and GS 8–10 tumors was 87.5%, 67.0%, and 49.6%, respectively. Univariate analyses indicated that the differences between GS 6 and GS 7, GS 6 and GS 8–10, and GS 7 and GS 8–10 tumors were statistically significant (**Table 4**). The risk of CRPC occurrence and death was much higher for patients with GS 7 and GS 8–10 than those with GS 6 (CFS: HR = 5.07-fold and 8.26-fold, respectively, [$P = 0.006$ and $P < 0.001$]; OS: HR = 3.36-fold and 5.74-fold, respectively [$P = 0.040$ and $P = 0.003$]) (**Table 4**).

Using 2014 ISUP grading criteria, between-group comparisons indicated that the proportion of patients who experienced CFS and OS appeared to decrease as the cancer grade increased. The CFS rates of patients in Group 1, 2, 3, 4, and 5 were 84.7%, 54.9%, 53.2%, 35.8%, and 35.0%, respectively. The OS of patients in Group 1, 2, 3, 4, and 5 was 87.5%, 67.6%, 66.7%, 52.3%, and 44.7%, respectively. In accordance with the 2005 ISUP criteria, the 2014 ISUP criteria were able to distinguish the clinical outcome of patients with GS 6, GS 7, and GS 8–10 tumors. However, it is noteworthy that, even visually, the survival curves and survival outcomes of Groups 2 (GS 3 + 4) and 3 (GS 4 + 3) and Groups 4 (GS 8) and 5 (GS 9–10) were similar, and the survival curves overlapped (**Figure 1c** and **1d**). Statistical analyses indicated that there were no significant differences between Groups 2 and 3 and Groups 4 and 5 (**Table 4**). This implies that the 2014 ISUP grading system cannot discriminate GS 3 + 4 from GS 4 + 3 nor GS 8 from GS 9–10 in patients initially diagnosed with metastatic PCa with bone metastasis.

We had anticipated that the 2014 ISUP grading system would improve the discriminative ability of models based on the previous 2005 ISUP criteria. We compared the two grading systems using ROC curves (**Figure 2**). The AUCs for CFS and OS prediction were highly consistent between the two grading systems. When stratified using the 2005 ISUP criteria, the AUCs predicting CFS and OS were 0.666 (95% CI: 0.61–0.71) and 0.625 (95% CI: 0.58–0.67), respectively; using the 2014 ISUP grading system for stratification, the AUCs for CFS and OS were 0.667 (95% CI: 0.61–0.71) and 0.613 (95% CI: 0.58–0.66), respectively. No significant difference in the predictive ability of the 2005 and 2014 ISUP grading systems was observed ($P > 0.05$).

Our analysis has shown that the 2014 ISUP grading system cannot accurately subdivide GS 7 and GS 8–10 metastatic PCa patients into different prognostic groups. Interestingly, the predictive ability of 2005 ISUP criteria is, at least, noninferior to the updated 2014 ISUP grading system.

Table 1: Baseline characteristics of patients with initial diagnosed prostate cancer with bone metastasis

| | n | GS groups | | | | | | P |
		6	3+4	4+3	8	9	10	
Patients (%)	568	30 (5.3)	71 (12.5)	126 (22.2)	123 (21.6)	172 (30.3)	46 (8.1)	
Age (years) (median)	71	77	72	72	70	70	76	
<70	238	23	27	48	59	75	6	0.121
≥70	230	7	44	78	64	97	40	
ECOG score								
0–1	520	26	64	117	113	159	41	0.385
≥2	48	4	7	9	10	13	5	
Baseline PSA (ng ml⁻¹)								
Median (ng ml⁻¹)	72.1	21.56	47.0	70.51	79.84	92.46	103.0	0.004
<50	212	20	41	46	39	49	17	
≥50	355	10	30	80	83	122	26	
Clinical T staging								
<3	141	10	48	63	12	5	3	<0.001
3–4	423	20	21	62	111	166	43	

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen; GS: Gleason score

Table 2: 2-year and 5-year CFS and OS ratio of patients with metastatic prostate cancer stratified by Gleason scores

| GS | Patients | 2-year survival (%) | | 5-year survival (%) | |
		CFS	OS	CFS	OS
6	30	87	93	83	81
7	197	68	81	47	61
3+4	71	68	85	52	64
4+3	126	68	79	42	59
8–10	341	57	72	29	38
8	123	58	75	25	41
9	172	61	72	31	44
10	46	36	71	23	34
Total	568	64	79	38	47

GS: Gleason score; CFS: castration-resistant prostate cancer-free survival; OS: overall survival

DISCUSSION

Using the 2005 ISUP grading criteria, various GS-based prognostic models have been developed to predict the survival of PCa patients following RP.[10–13] Almost all of these have shown that the GS is an independent prognostic factor for predicting biochemical failure-free survival and cancer-specific survival. However, an absence of uniform GS groupings has made it difficult to evaluate the prognostic accuracy of the Gleason grading system. Since 2009, Stark and colleagues have voiced doubts regarding the different clinical outcomes of RP patients with GS 4 + 3 and GS 3 + 4,[14] and a growing body of evidence demonstrates that the prognosis of patients with GS 3 + 4 is different to those with GS 4 + 3.[15–19] Recently, Tsao *et al.* reported that patients who underwent RP with a GS 9–10 had a significantly worse outcome than those with GS 8.[20]

Although GS upgrading and downgrading from needle biopsy is inevitable, the biopsy GS remains the single most powerful prognostic tool in PCa.[21,22] However, to date, it has not been determined whether 2014 ISUP grading system is as powerful a prognostic indicator for metastatic PCa as it is for localized disease.

In this retrospective study, the predictive ability of the 2014 ISUP grading system for patients initially diagnosed with hormone-sensitive bone metastatic PCa was assessed using data from almost 600 patients. When stratified according to the 2005 and 2014 ISUP grading criteria, the majority of the patients in our study were GS ≥7, and more than

60% were GS ≥8. A number of studies have indicated that PCa patients with GS ≤6 have a very low-risk (0.2%–3%) of metastasis.[23–27] Epstein and colleagues have even argued that the primary reason for metastasis in GS ≤6 patients is under-grading at diagnosis.[28] They showed that if GS 6 cases were reviewed using the 2005 ISUP grading system, none of metastatic cases would have been reassigned to GS ≤6 upon RP. Epstein and colleagues, therefore, concluded that PCa prostatectomy specimens with a GS ≤6 have virtually no potential for metastasis. Needle prostate biopsies are limited in accuracy, and initially diagnosed metastatic PCas with GS 6 are still reported, albeit at a low rate.[21]

In accordance with previous studies, the proportion of GS 6 cases was very low in the present study; more than 80% of cases presented a primary Gleason pattern 4 or 5. The presence of metastatic cases with GS 6 is most likely related to needle prostate biopsy-associated under-grading. It should be noted that the dominant pattern in these cases was at least pattern 3; however, secondary or tertiary patterns, which could have been pattern 4 or 5, might have been overlooked due to the random nature of biopsy; this could account for distant metastasis in these cases. Regardless, our survival analysis indicated that the metastatic GS 6 cases in the present study had relatively low levels of disease progression and a favorable prognosis.

In this study, we anticipated validating the predictive efficacy of the 2014 ISUP grading system and compared the criteria to those proposed in 2005. Among various variables at the time of diagnosis, the baseline PSA level, 2005 ISUP GS grade, and 2014 ISUP GS grade were strongly associated with the occurrence of CRPC and OS in patients initially diagnosed with metastatic PCa. Both of the ISUP criteria sets could discriminate the prognosis of patients with GS 6, GS 7, and GS 8–10. However, further comparisons of the predictive ability of the two criteria sets indicated that the latest 2014 criteria could not distinguish the outcome of patients with GS 3 + 4 and GS 4 + 3 even though the new criteria have shown superior predictive efficacy for patients with localized PCa.

Furthermore, the 2014 ISUP criteria also failed to distinguish the outcome of patients with GS 8 and GS 9–10. There are a number of possible explanations for this, including (1) miscellaneous risk factors, such as poor ECOG status, older age, higher PSA level, or later T stage, even comorbidities and tumor burden, might have interfered with the predictive value of the 2014 ISUP GSs in patients without organ confined disease. To address this, the Japan Cancer of the Prostate Risk

Assessment has enrolled several prognosticators to predict the clinical outcome of patients who undergo androgen deprivation therapy.[29]

Table 3: Univariate analysis of survival in patients with bone metastatic prostate cancer

Grouping	n	CFS (months) (mean±s.d.)	P Log-rank test	OS (months) (mean±s.d.)	P Log-rank test
Age (years)					
<70	238	47.23±1.66	0.342	54.69±1.69	0.430
≥70	230	43.22±2.31		53.47±2.47	
ECOG score					
0–1	520	45.98±1.41	0.656	55.06±1.49	0.180
≥2	48	40.71±3.71		44.06±3.35	
Clinical T staging					
<3	141	43.09±1.99	0.137	59.69±2.71	0.303
3–4	423	44.49±1.56		52.31±1.51	
Baseline PSA (ng ml⁻¹)					
<50	212	50.86±1.73	<0.001	60.55±1.73	<0.001
≥50	355	39.94±1.64		48.18±1.74	
2005 ISUP grading criteria					
≤6	30	52.96±2.22	<0.001	67.18±2.37	<0.001
7	197	44.27±1.68		62.52±2.31	
8–10	341	39.64±1.66		48.82±1.68	
2014 ISUP grading criteria					
Group 1 (GS ≤6)	30	50.46±2.69	<0.001	67.18±2.37	0.001
Group 2 (GS=3+4)	71	46.79±2.62		64.29±3.57	
Group 3 (GS=4+3)	126	43.77±2.25		61.36±3.03	
Group 4 (GS=8)	123	41.27±1.34		50.51±2.14	
Group 5 (GS=9–10)	218	36.88±2.12		46.78±2.02	

CFS: castration-resistant prostate cancer-free survival; OS: overall survival; ECOG: Eastern Cooperative Oncology Group; GS: Gleason score; ISUP: International Society of Urological Pathology; PSA: prostate-specific antigen; s.d.: standard deviation

(2) Under- or over-grading of GSs could have occurred due to the random nature of biopsies, and this could have introduced bias; all of the pathological evidence for the metastatic PCa patients included in this study was obtained from needle prostate biopsy specimens. (3) Differential therapeutic regimens could have impacted the final clinical outcome. Initially, all of the patients were treated with standard MAB, and following disease progression, only a small subset of patients were given sequential therapies, including chemotherapy and novel antiandrogen receptor inhibitors.

In the case of localized PCa after RP, distinguishing patients with GS 4 + 3 and GS 3 + 4, or GS 8 and GS 9–10 is particularly important because it would most probably affect the adjuvant therapeutic strategy employed.[14,20,30,31] However, for metastatic PCa, distinguishing GS 3 + 4 from GS 4 + 3, or GS 8 from GS 9–10 is probably less important because it would not impact clinicians' therapeutic decision; these patients would undoubtedly be treated with antiandrogen deprivation therapy.

Our study indicates that the 2005 ISUP criteria have not lost their important role in metastatic PCa. The complexity of the 2014 ISUP classification, such as dividing GS 7 into 3 + 4 and 4 + 3 groups, might have reduced its prognostic accuracy in metastatic PCa patients. As such, we recommend that patients initially diagnosed with metastatic prostate cancer are suitable for both 2005 and 2014 ISUP grading criteria.

There are several potential limitations to our study. First, this is a retrospective study, and therefore, biases such as treatment selection are unavoidable. For example, the clinical therapeutic strategy and the duration of treatment can affect outcome. Second, all of our results are based on a cohort of patients treated at a single, tertiary referral center. As such, they may not be representative of the general population.

CONCLUSIONS
The new 2014 ISUP grading system has primarily been validated and shown to be efficacious in patients following RP. However, to the best of our knowledge, ours is the first comparison of the 2014 and 2005

Table 4: Kaplan–Meier survival probabilities and adjusted hazard ratios by the 2005 and 2014 ISUP grading criteria for each endpoint

	CFS			OS		
	Survival probability (%)	HR (95% CI)	P	Survival probability (%)	HR (95% CI)	P
2005 ISUP						
6[a]	84.7	1	-	87.5	1	-
7	53.8	5.07 (1.61–16.03)	0.006	67.0	3.36 (1.06–10.70)	0.040
8–10	35.3	8.26 (2.65–25.84)	<0.001	49.6	5.74 (1.84–18.00)	0.003
2005 ISUP						
7[a]	53.8	1		67.0	1	-
8–10	35.3	1.63 (1.27–2.08)	<0.001	49.6	1.71 (1.28–2.27)	<0.001
2014 ISUP						
6[a]	84.7	1		87.5	1	-
3+4	54.9	4.65 (1.43–15.21)	0.011	67.6	3.16 (0.95–10.54)	0.04
4+3	53.2	5.33 (1.67–17.02)	0.005	66.7	3.47 (10.8–11.21)	0.037
8	35.8	8.44 (2.67–26.76)	<0.001	52.3	5.31 (1.69–16.70)	0.001
9–10	35.0	8.16 (2.60–25.64)	<0.001	44.7	6.52 (2.05–20.75)	0.004
2014 ISUP						
3+4[a]	54.9	1	-	67.6	1	-
4+3	53.2	1.15 (0.75–1.76)	0.471	66.7	1.10 (0.66–1.83)	0.709
2014 ISUP						
8[a]	35.8	1	-	52.3	1	-
9–10	35.0	0.97 (0.73–1.27)	0.801	44.7	1.25 (0.89–1.99)	0.156

[a]Reference group. CI: confidence interval; HR: hazard ratio; ISUP: International Society of Urological Pathology; CFS: castration-resistant prostate cancer-free survival; OS: overall survival
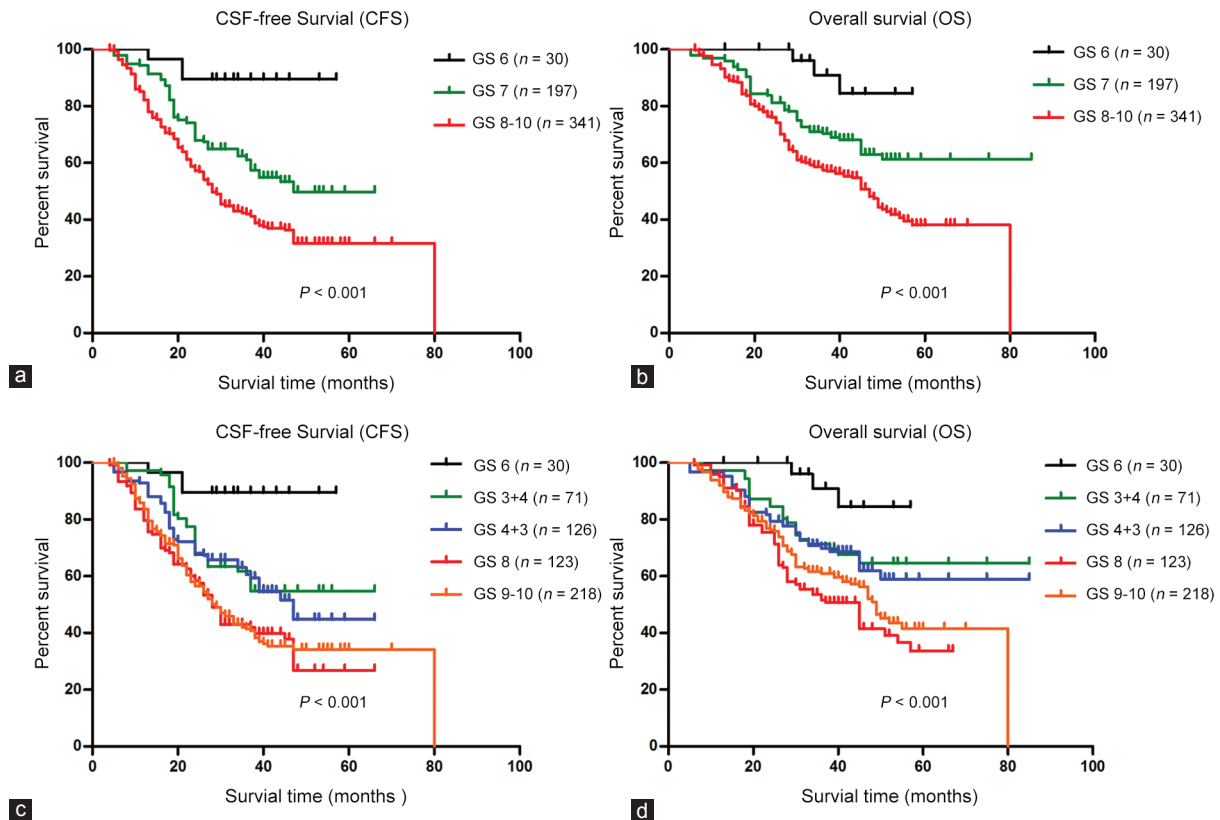
Figure 1: Kaplan–Meier estimates for CRPC-free survival (CFS) and overall survival (OS) stratified by 2005 and 2014 ISUP grading systems. **(a)** CFS stratified by 2005 ISUP grading system, **(b)** OS stratified by 2005 ISUP grading system, **(c)** CFS stratified by 2014 ISUP grading system, **(d)** OS stratified by 2014 ISUP grading system. GS: Gleason score.
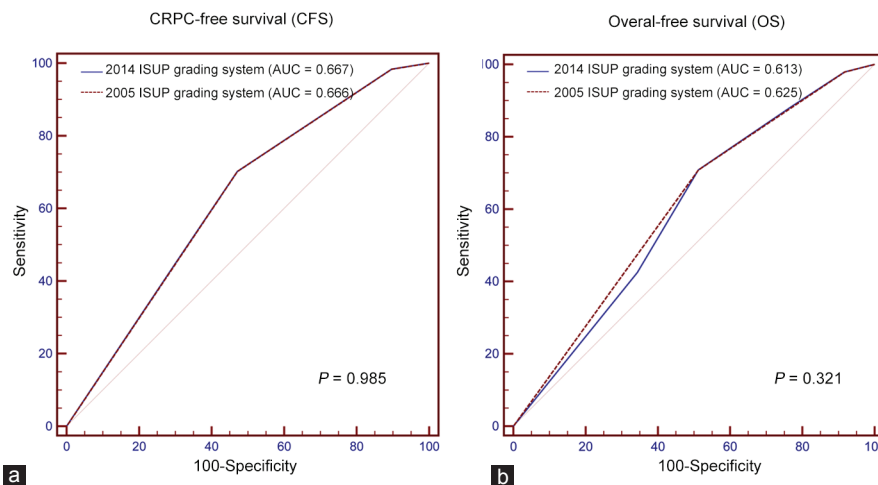

Figure 2: Comparisons between the 2005 and 2014 ISUP grading systems using ROC curve for predicting **(a)** CRPC-free survival (CFS) and **(b)** overall survival (OS) in patients with initially diagnosed prostate cancer with bone metastasis.

ISUP grading systems in patients initially diagnosed with PCa with bone metastasis. Our results indicate that the new 2014 system failed to improve the predictive efficacy for patients with metastatic PCa. Our results imply that it may not be necessary to use the newly refined 2014 ISUP grading system to predict the prognosis of metastatic PCa. Given the relatively small population that uses our medical center, further studies in larger cohorts are required to determine the clinical usefulness of the 2014 criteria. At present, we recommend that both

the 2005 ISUP grading criteria and the 2014 updated criteria are useful prognostic indicators in patients with metastatic PCa.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Bailar JR, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation-preliminary report. *Cancer Chemother Rep* 1966; 50: 129–36.
2. Epstein JI, Allsbrook WJ, Amin MB, Egevad LL. 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. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, *et al*. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011; 59: 88–95.
4. Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, *et al*. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. *BMJ* 2014; 348: g1502.
5. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, *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.
6. Samaratunga H, Delahunt B, Gianduzzo T, Coughlin G, Duffy D, *et al*. The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. *Pathology* 2015; 47: 515–9.
7. Delahunt B, Egevad L, Srigley JR, Steigler A, Murray JD, *et al*. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data. *Pathology* 2015; 47: 520–5.
8. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, *et al*. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol* 2016; 69: 428–35.
9. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143: 29–36.
10. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, *et al*. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013; 368: 436–45.
11. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, *et al*. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; 367: 203–13.
12. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014; 370: 932–42.
13. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; 280: 969–74.
14. Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, *et al*. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? *J Clin Oncol* 2009; 27: 3459–64.
15. 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.
16. Wright JL, Salinas CA, Lin DW, Kolb S, Koopmeiners J, *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.
17. Zumsteg ZS, Spratt DE, Pei I, Zhang Z, Yamada Y, *et al*. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013; 64: 895–902.
18. Spratt DE, Zumsteg Z, Ghadjar P, Pangasa M, Pei X, *et al*. Prognostic importance of Gleason 7 disease among patients treated with external beam radiation therapy for prostate cancer: results of a detailed biopsy core analysis. *Int J Radiat Oncol Biol Phys* 2013; 85: 1254–61.
19. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, *et al*. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol* 2015; 28: 457–64.
20. Tsao CK, Gray KP, Nakabayashi M, Evan C, Kantoff PW, *et al*. Patients with biopsy Gleason 9 and 10 prostate cancer have significantly worse outcomes compared to patients with Gleason 8 disease. *J Urol* 2015; 194: 91–7.
21. Rusthoven CG, Carlson JA, Waxweiler TV, Yeh N, Raben D, *et al*. The prognostic significance of Gleason scores in metastatic prostate cancer. *Urol Oncol* 2014; 32: 707–13.
22. Kambara T, Oyama T, Segawa A, Fukabori Y, Yoshida K. Prognostic significance of global grading system of Gleason score in patients with prostate cancer with bone metastasis. *BJU Int* 2010; 105: 1519–25.
23. Abdollah F, Schmitges J, Sun M, Thuret R, Djahangirian O, *et al*. Head-to-head comparison of three commonly used preoperative tools for prediction of lymph node invasion at radical prostatectomy. *Urology* 2011; 78: 1363–7.
24. Birkhahn M, Penson DF, Cai J, Groshen S, Stein JP, *et al*. Long-term outcome in patients with a Gleason score </=6 prostate cancer treated by radical prostatectomy. *BJU Int* 2011; 108: 660–4.
25. Boorjian SA, Thompson RH, Siddiqui S, Bagniewski S, Bergstralh EJ, *et al*. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 2007; 178: 864–70, 870–1.
26. Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE. Is pelvic lymph node dissection necessary in patients with a serum PSA<10ng/ml undergoing radical prostatectomy for prostate cancer? *Eur Urol* 2006; 50: 272–9.
27. Weckermann D, Goppelt M, Dorn R, Wawroschek F, Harzmann R. Incidence of positive pelvic lymph nodes in patients with prostate cancer, a prostate-specific antigen (PSA) level of < or =10 ng/mL and biopsy Gleason score of < or =6, and their influence on PSA progression-free survival after radical prostatectomy. *BJU Int* 2006; 97: 1173–8.
28. Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, *et al*. Do adenocarcinomas of the prostate with Gleason score (GS) </=6 have the potential to metastasize to lymph nodes? *Am J Surg Pathol* 2012; 36: 1346–52.
29. Cooperberg MR, Hinotsu S, Namiki M, Ito K, Broering J, *et al*. Risk assessment among prostate cancer patients receiving primary androgen deprivation therapy. *J Clin Oncol* 2009; 27: 4306.
30. Alenda O, Ploussard G, Mouracade P, Xylinas E, de la Taille A, *et al*. Impact of the primary Gleason pattern on biochemical recurrence-free survival after radical prostatectomy: a single-center cohort of 1,248 patients with Gleason 7 tumors. *World J Urol* 2011; 29: 671–6.
31. Jackson W, Hamstra DA, Johnson S, Zhou J, Foster B, *et al*. Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. *Cancer* 2013; 119: 3287–94.