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

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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.

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INTRODUCTION

The Gleason score (GS) system, first described by Gleason in 1966, 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. 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 PCa. 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). Subsequent studies have tentatively validated and confirmed the accuracy of the new 2014 grading system in predicting PCa patient prognosis. 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.

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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. 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 orchietomy (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). 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.
DISCUSSION

Using the 2005 ISUP grading criteria, various GS-based prognostic models have been developed to predict the survival of PCa patients following RP.\textsuperscript{16–19} 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,\textsuperscript{1} and a growing body of evidence demonstrates that the prognosis of patients with GS 3 + 4 is different to those with GS 4 + 3.\textsuperscript{14} 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.\textsuperscript{28}

Although GS upgrading and downgrading from needle biopsy is inevitable, the biopsy GS remains the single most powerful prognostic tool in PCa.\textsuperscript{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.\textsuperscript{23–27} Epstein and colleagues have even argued that the primary reason for metastasis in GS ≤6 patients is under-grading at diagnosis.\textsuperscript{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.\textsuperscript{29}

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

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

|                  | n     | 6        | 3+4      | 4+3      | 8        | 9        | 10       | P     |
|------------------|-------|----------|----------|----------|----------|----------|----------|-------|
| 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       | 76       |       |
| ≥70              | 230   | 7        | 44       | 78       | 64       | 97       | 40       |       |
| ECOG score       |       |          |          |          |          |          |          |       |
| 0–1              | 520   | 26       | 64       | 117      | 113      | 159      | 41       | 0.121 |
| ≥2               | 48    | 4        | 7        | 9        | 10       | 13       | 5        | 0.385 |
| 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       | 0.041 |
| ≥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      | GS                  | 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
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) | OS (months) | P (Log-rank test) | P (Log-rank test) |
|----------|----|--------------|-------------|------------------|------------------|
| Age (years) |    |              |             |                  |                  |
| <70      | 238 | 47.23±1.66   | 54.69±1.69  | 0.342            | 0.430            |
| ≥70      | 230 | 43.22±2.31   | 53.47±2.47  |                  |                  |
| ECOG score |    |              |             |                  |                  |
| 0–1      | 520 | 45.98±1.41   | 55.06±1.49  | 0.656            | 0.180            |
| ≥2       | 48  | 40.71±3.71   | 44.06±3.35  |                  |                  |
| Clinical T staging |    |              |             |                  |                  |
| <3       | 141 | 43.09±1.99   | 59.69±2.71  | 0.137            | 0.303            |
| 3–4      | 423 | 44.49±1.56   | 52.31±1.51  |                  |                  |
| Baseline PSA (ng ml\(^{-1}\)) |    |              |             |                  |                  |
| <50      | 212 | 50.86±1.73   | 60.55±1.73  | <0.001           | <0.001           |
| ≥50      | 355 | 39.94±1.64   | 48.18±1.74  |                  |                  |
| 2005 ISUP grading criteria |    |              |             |                  |                  |
| ≤6       | 30  | 52.96±2.22   | 67.18±2.37  | <0.001           | <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 | 67.18±2.37 | <0.001 | 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; CFS: castration-resistant prostate cancer-free survival; OS: overall survival.

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

| ISUP     | Survival probability (%) | HR (95% CI) | P   | Survival probability (%) | HR (95% CI) | P   |
|----------|--------------------------|-------------|-----|--------------------------|-------------|-----|
| 2005 ISUP |                          |             |     |                          |             |     |
| 6        | 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        | 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        | 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      | 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        | 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 |

Reference group. CI: confidence interval; HR: hazard ratio; ISUP: International Society of Urological Pathology; CFS: castration-resistant prostate cancer-free survival; OS: overall survival.
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
GX, PFS, and XMZ participated in data interpretation, statistical analysis and drafted the manuscript. NC and HZ revised the paper. JG, HJG, KPS, JDL, JGZ, YJY, and XQC also participated in data acquisition.

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.

GX Sun et al
The 2014 Gleason grading system in mPCa
Asian Journal of Andrology
577
COMPETING INTERESTS

The authors declared that they have no competing interests.

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