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Original Article

Significant prognostic difference between Grade Group 4 and 5 in the 2014 International Society of Urological Pathology Grading System for High Grade Prostate Cancer with Bone Metastasis

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ABSTRACT

Background: To investigate prognostic difference between Gleason Score (GS) 8 and 9–10, as the 2014 International Society of Urological Pathology Gleason Grading Systems proposed, in patients with prostate cancer (PCa) with bone metastasis.

Materials and methods: We retrospectively reviewed data on 106 patients with GS 8–10 between 2006 and 2016. All patients received androgen deprivation therapy immediately. We validated biochemical recurrence, PCa-specific survival, and overall survival, and analyzed the predictive value for overall survival.

Results: Patients with GS 9–10 had significantly lower PCa-specific survival (50.5% vs. 83.4%, $P = 0.01$) and overall survival (38.8% vs. 66.3%, $P = 0.04$) at 5 years than those with GS 8, while biochemical recurrence rate was not significantly different ($P = 0.26$). Furthermore, these significant differences between GS 8 and 9–10 were also observed among high-risk groups proposed in Japan Cancer of the Prostate Risk Assessment Stratification (prostate cancer-specific survival: $P = 0.03$, overall survival: $P = 0.04$, respectively). Pathological GS 9–10 was an independent prognostic factor for overall survival (hazard ratio = 1.97, $P = 0.04$) in multivariable cox proportional hazard regression analysis. Among patients with GS 9–10, albumin level was an only prognostic factor for overall survival (hazard ratio = 0.33, $P < 0.01$).

Conclusion: Pathological GS 9–10 predicts significantly worse outcomes than GS 8 in Japanese PCa patients with bone metastasis. Our data indicated clinical significance of discriminating the 2014 International Society of Urological Pathology Gleason Grading Group 4 and 5 among high-risk PCa patients with bone metastasis.

1. Introduction

According to Global Cancer Statistics, in 2008, ~900,000 individuals were diagnosed with prostate cancer (PCa) worldwide. PCa accounts for 14% of all cancer cases in men, making it the second most common after lung cancer.[1] Recently, results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) have shown that PCa-related death has decreased by ~21% among men aged 55–69 years thanks to prostate-specific antigen (PSA) screening, and that the significance of PSA screening has become more important.[2,3] In the United States, where PSA screening is common, with 70–80% of all men undergoing screening, the prevalence of metastatic PCa at diagnosis is < 5% and the mortality rate has been trending lower since 1993.[4] By contrast,

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diagnosis of metastatic PCa remains high in countries where PSA screening is less common than that in the United States and PCa mortality has been on the rise. In Japan, the exposure rate of PSA screening is estimated to be 5–10% and the frequency of metastatic PCa is ~30%.[5] The number of deaths from PCa continues to increase, reaching > 10,000 in 2010. Treatment for localized PCa, including surgery, radiotherapy, and androgen deprivation therapy (ADT), often provide an excellent prognosis. ADT has been used for the initial treatment of metastatic PCa since the 1940s, but castration resistance frequently occurs with unsatisfactory outcome in patients with high-risk PCa.

Different classification systems, such as the D'Amico[6] and that of the National Comprehensive Cancer Network, suggest that stratification of PCa patients according to Gleason Score (GS) $\leq$ 6, 7, and 8–10. However, several reports have indicated that this is not always sufficient for prognosis prediction.[7,8] The International Society of Urological Pathology (ISUP) meeting in 2014 suggested the following stratification: GS $\leq$ 6, 3+4, 4+3, 8, and 9–10 (Gleason Grading Group 1, 2, 3, 4, and 5, respectively) for localized PCa.[8] However, most of the previous studies validated the prognosis of GS in localized cancer.[9,10] Thus, the prognostic stratification by GS for PCa with bone metastasis (PCaBM) has rarely been validated.

In the present study, we validated the impact of GS and other clinical factors on prognosis of PCaBM. According to the Surveillance, Epidemiology, and End Results (SEER) database, most metastatic PCa patients have GS $\geq$8.[11] Therefore, we focused on the prognostic differences in PCaBM patients with GS 8 and those with GS 9–10 and examined the prognostic significance of Gleason Grading Group 4 and 5 proposed in ISUP 2014 among metastatic PCa patients.

2. Materials and methods

2.1. Patients and clinical variables

The present retrospective study included 106 men diagnosed with PCaBM with GS 8–10 at our institution between 2006 and 2012. The median observation period was 39 months. Patients with or without lymph node metastasis were included. Clinical tumor–node–metastasis classification based on National Comprehensive Cancer Network 2014 guidelines was determined via computed tomography and bone scintigraphy findings. Bone metastasis was classified according to the extent of disease score. All patients received ADT immediately after diagnosis. Patient characteristics including age, body mass index, initial PSA levels, total prostate volume, PSA density, GS, positive-to-total biopsy cores ratio, tumor–node–metastasis classification, laboratory results, and whether high volume PCa or not were collected. Laboratory results collected at diagnosis included white blood cell count, hemoglobin level, platelet count, alkaline phosphatase level, and albumin level. The Gleason Grading System based on the 2005 ISUP consensus was used to confirm GS at biopsy. All biopsy specimens were obtained via the transperineal approach, and 10-core biopsies were performed at the apex, middle, and base of the peripheral zone and in the middle of the transitional zone of the prostate.

We validated clinical outcomes [biochemical recurrence (BCR), PCa-specific survival (PCSS), and overall survival (OS)] in patients with GS 8 versus those with GS 9–10 at biopsy and analyzed the predictive value for OS with other clinical factors.

2.2. Definition of BCR

BCR was defined as PSA level > 2 ng/mL above the nadir. For these measurements, the increase had to be $\geq$ 25% above the nadir and confirmed by a second PSA test performed $\geq$ 3 weeks later.

2.3. Definition of high-volume tumor

High-volume PCa was defined as visceral metastases and/or $\geq$ 4 bone metastases.[12]

2.4. Statistical analysis

Mann–Whitney *U* test, χ^2 test, Kaplan–Meier method (log-rank test), and Cox proportional hazard model were used to assess the association between patients with GS 8 and 9–10 and clinical outcomes. Statistical analysis was performed using JMP version 11.0.0 (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

3. Results

The clinical characteristics of 106 enrolled patients are presented in Table 1. Of these, 33 (31.1%) patients had GS 8, and 73 (68.9%) patients had GS 9–10 at biopsy. There was only one patient with GS 3+5 in this study. The median patient age was 74 years and median PSA level was 457.3 ng/mL. Visceral metastases were observed in 17 patients (16%). There were no statistically significant differences in age, PSA, total prostate volume, PSA density, lymph node metastasis status, high-volume status, extent of disease score, and initial treatment between patients with GS 8 and those with GS 9–10. However, patients with GS 9–10 had a higher positive-to-total biopsy core ratio and clinical T stage. Visceral metastases were significantly more common in patients with GS 8.

Of the enrolled patients, 79 (74.5%) had BCR and 41 (38.7%) succumbed to PCa-specific death during the observation period. Overall, 58 (54.7%) patients had died by the time of this analysis. PSA progression-free survival rate was not significantly different between PCaBM patients with GS 8 and those with GS 9–10 ($P = 0.25$, Fig. 1A) in Kaplan–Meier analysis (log rank test). The 3- and 5-year PCSS was 70.1% and 59.6%, respectively, whereas the 3- and 5-year OS was 61% and 46.3%, respectively, in the overall cohort. Kaplan–Meier analyses revealed that patients with GS 9–10 had significantly lower PCSS (50.5% vs. 83.4% at 5 years, $P = 0.01$, Fig. 1B) and OS (38.8% vs. 66.3% at 5 years, $P = 0.04$, Fig. 1C) than those with GS 8.

Univariable and multivariable Cox proportional hazard regression analyses were performed for OS in PCaBM patients with GS 8–10 (Table 2). In the univariable analysis, age, hemoglobin level, albumin level, and GS 9–10 were significant predictive factors for OS ($P = 0.01$, $P = 0.04$, $P < 0.01$ and $P = 0.04$, respectively). The multivariable analysis identified albumin level and GS 9–10 as significant factors for OS with hazard ratios (HRs) of 0.55 and 1.97, respectively (both $P = 0.04$). We also validated the best cut-line of GS for prognosis in PCaBM patients among those with GS 8–10. GS 9–10 distinguished prognosis from GS 8 significantly, unlike GS 8/4+5 versus 5+4/10 and GS8/9 versus 10 (Table 2). This cutoff was identical to the cutoff of the Gleason Grading Group between 4 and 5 proposed in ISUP 2014.

In addition, we validated the prognosis of PCaBM patients with GS 8 and GS 9–10 using J-CAPRA (Japan Cancer of the Prostate Risk Assessment) risk stratification.[13] We compared PCaBM patients with GS 8 and those with GS 9–10 among high-risk group (scoring 8–12 points) proposed in J-CAPRA risk stratification. PCaBM patients with GS 9–10 had worse PCSS ($P = 0.03$) and OS ($P = 0.04$) than those with GS 8 among the high-risk group (Fig. 2A, B). Significant prognostic difference between GS 8 and GS 9–10 were observed among the high-risk group in J-CPRA risk stratification. These data indicated clinical significance of discriminating Grade Group 5 (GS 9–10) from Grade Group 4 (GS 8), even among the high-risk group in J-CPRA risk stratification.

Table 1
Patient characteristics.

	Total	GS 8	GS 9–10	*P*
No. of patients	106	33 (31.1)	73 (68.9)	—
Age (yr)	74 (50–93)	74 (50–93)	75 (57–90)	0.45
BMI (kg/m^2)	21.95 (14.1–36.1)	21.8 (16.1–30.4)	21.9 (14.1–36.1)	0.41
PSA (ng/mL)	457.3 (3.4–24,913.3)	239.5 (9.3–24,913.3)	552.6 (3.4–14,957.3)	0.48
Prostate volume (mL)	35.9 (9.9–423.9)	36 (20.2–423.9)	35.3 (9.9–151.8)	0.59
PSAD (ng/mL/cm^3)	9.9 (0.1–513.7)	5.4 (0.3–151.1)	14.9 (0.1–513.7)	0.25
Positive/total biopsy core (%)	90 (10–100)	70 (10–100)	90 (20–100)	< 0.01
Gleason score				—
4 + 4/3 + 5	32/1 (31.1)	32/1 (100)	0	
4 + 5/5 + 4	34/28 (58.5)	0	34/28 (84.9)	
5 + 5	11 (10.4)	0	11 (15.1)	
Clinical T stage				0.02
≤ T3a	26 (24.5)	13 (39.4)	13 (17.8)	
≥T3b	80 (75.5)	20 (60.6)	60 (82.2)	
Lymph node metastasis	76 (71.7)	21 (63.6)	55 (75.3)	0.22
Visceral metastasis	17 (16)	9 (27.3)	8 (10.9)	0.03
High volume	74 (69.8)	23 (69.7)	51 (69.9)	0.99
EOD score				0.63
≤2	56 (52.8)	17 (51.5)	39 (53.4)	
≥ 3	46 (43.4)	16 (48.5)	30 (41.1)	
Unknown	4 (3.8)	0 (0)	4 (5.5)	
Initial treatment				0.81
Orchiectomy + antiandrogen	82 (77.4)	26 (78.8)	56 (76.7)	
LH-RH agonist + antiandrogen	24 (22.6)	7 (21.2)	17 (23.3)	

Data are presented as median (range) or *n* (%).
BMI, body mass index; EOD, extent of disease; GS, Gleason score; LH-RH, luteinizing hormone - releasing hormone; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

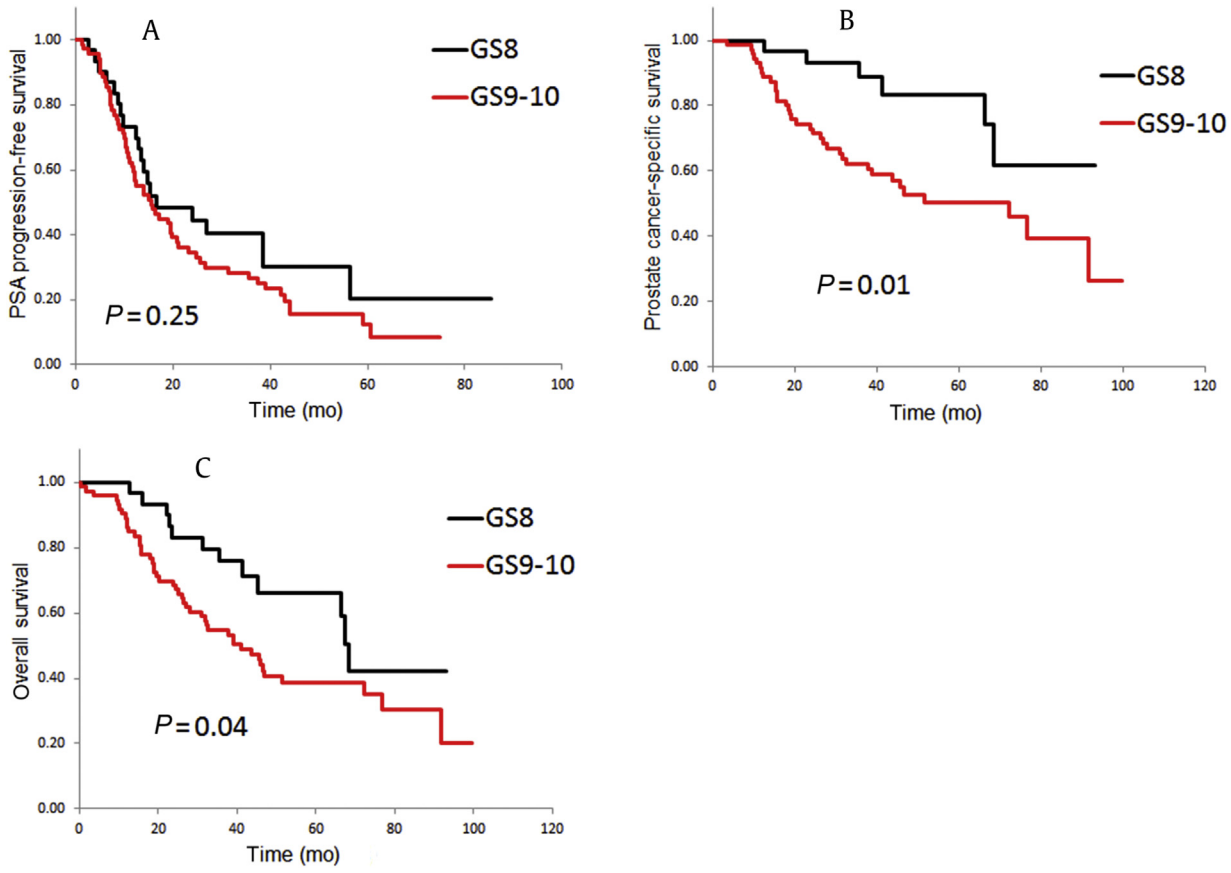

Fig. 1. Kaplan–Meier curves show patients with GS 8 and 9–10. (A) PSA progression-free survival rate for initial androgen deprivation therapy ($P = 0.25$). (B) Prostate cancer-specific survival rate ($P = 0.01$). (C) Overall survival rate ($P = 0.04$). GS, Gleason Score; PSA, prostate-specific antigen.

Table 2
Univariable and multivariable Cox proportional hazard regression models for OS in PCaBM with GS 8–10.

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (>74 yrs)[a]	1.96	1.15–3.31	0.01	1.54	0.86–2.76	0.15
BMI (>22)[a]	0.67	0.40–1.13	0.13	—	—	—
PSA (> 458 ng/mL)[a]	0.93	0.56–1.55	0.78	—	—	—
Total prostate volume (> 35 mL)[a]	0.84	0.48–1.45	0.53	—	—	—
PSA density (> 10)[a]	0.78	0.45–1.35	0.37	—	—	—
Positive/ total biopsy core (≥ 0.9)[a]	1.58	0.93–2.7	0.09	—	—	—
WBC (> 860/μL)[b]	1.07	0.57–1.99	0.83	—	—	—
Hb (> 13 g/dL)[b]	0.57	0.33–0.97	0.04	1.01	0.34–3.01	0.55
Plt (> 35 × 10^4/μL)[b]	1.07	0.38–2.97	0.89	—	—	—
NLR (> 2.7)[a]	1.32	0.78–2.23	0.3	—	—	—
ALP (> 320 U/L)[b]	1.49	0.86–2.59	0.15	—	—	—
Alb (> 4 g/dL)[b]	0.49	0.29–0.83	< 0.01	0.55	0.31–0.99	0.04
≥ T3b	1.59	0.84–3	0.16	—	—	—
Lymph node metastasis	1.41	0.77–2.57	0.27	—	—	—
Visceral metastasis	0.7	0.3–1.63	0.41	—	—	—
High volume	1.67	0.93–3.02	0.08	—	—	—
EOD ≥ 3	1.71	0.99–2.72	0.05	—	—	—
GS 9–10 (vs. GS 8)	1.9	1.01–3.59	0.04	1.8	1.01–3.08	0.04
GS 5+4, 10 (vs. GS 8, 4+5)	1.24	0.73–2.1	0.42	—	—	—
GS 10 (vs. GS 8–9)	0.99	0.42–2.32	0.98	—	—	—

Alb, albumin; ALP, alkaline phosphatase; CI, confidence interval; EOD, extent of disease; GS, Gleason Score; Hb, hemoglobin; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PCaBM, prostate cancer with bone metastasis; Plt, platelets; PSA, prostate-specific antigen; WBC, white blood cell.
[a] Median.
[b] Normal or abnormal value.

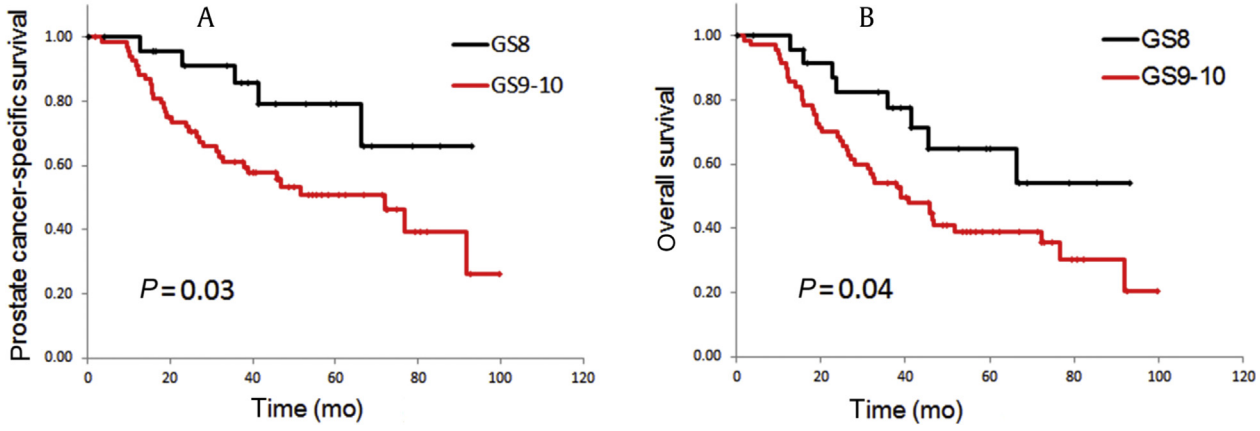

Fig. 2. Kaplan–Meier curves show patients with GS 8 and 9–10 among high-risk group in J-CAPRA risk stratification. (A) Prostate cancer-specific survival rate ($P = 0.03$). (B) Overall survival rate ($P = 0.04$). GS, Gleason Score; J-CAPRA, Japan Cancer of the Prostate Risk Assessment.

We performed Cox proportional hazard regression analyses for OS in PCaBM patients with focus on the GS 9–10 group. In multivariable analysis, albumin level was the only predictive factor for OS (Table 3, $P < 0.01$, HR = 0.33). The evident difference in OS between patients with albumin level < 4 g/dL and those with > 4 g/dL were seen in the GS 9–10 group with median OS periods of 19.3 months and 46.2 months, respectively ($P < 0.01$, Fig. 3A). By contrast, among PCaBM patients with GS 8, albumin level was not a significant predictive factor for OS by Kaplan–Meier analysis ($P = 0.51$, Fig. 3B). Furthermore, PCaBM patients with GS 9–10 and albumin level > 4 g/dL demonstrated a similar OS rate compared to that of the GS 8 group, which indicated clinical significance of albumin level among Grade Group 5 patients (GS 9–10) ($P = 0.88$, Fig. 3C).

Table 3
Univariable and multivariable Cox proportional hazard regression models for OS in PCaBM with GS 9–10.

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (>74 yrs)[a]	2.05	1.13–3.73	0.02	—	—	n.s.
Hb (>13g/dL)[b]	0.49	0.27–0.89	0.02	—	—	n.s.
Alb (>4g/dL)[b]	0.33	0.18–0.61	< 0.01	0.33	0.18-0.61	< 0.01

Alb, albumin; CI, confidence interval; GS, Gleason score; Hb, hemoglobin; HR, hazard ratio; n.s., not significant; OS, overall survival; PCaBM, prostate cancer with bone metastasis.
[a] Median.
[b] Normal or abnormal value.

4. Discussion

In the present study, we validated the difference in prognosis between PCaBM patients with GS 8 and GS 9–10, and demonstrated that pathological GS 9–10 at biopsy was a significant predictor for PCSS and OS in PCaBM patients with GS 8–10. Furthermore, GS 9–10 was a significant prognostic factor among

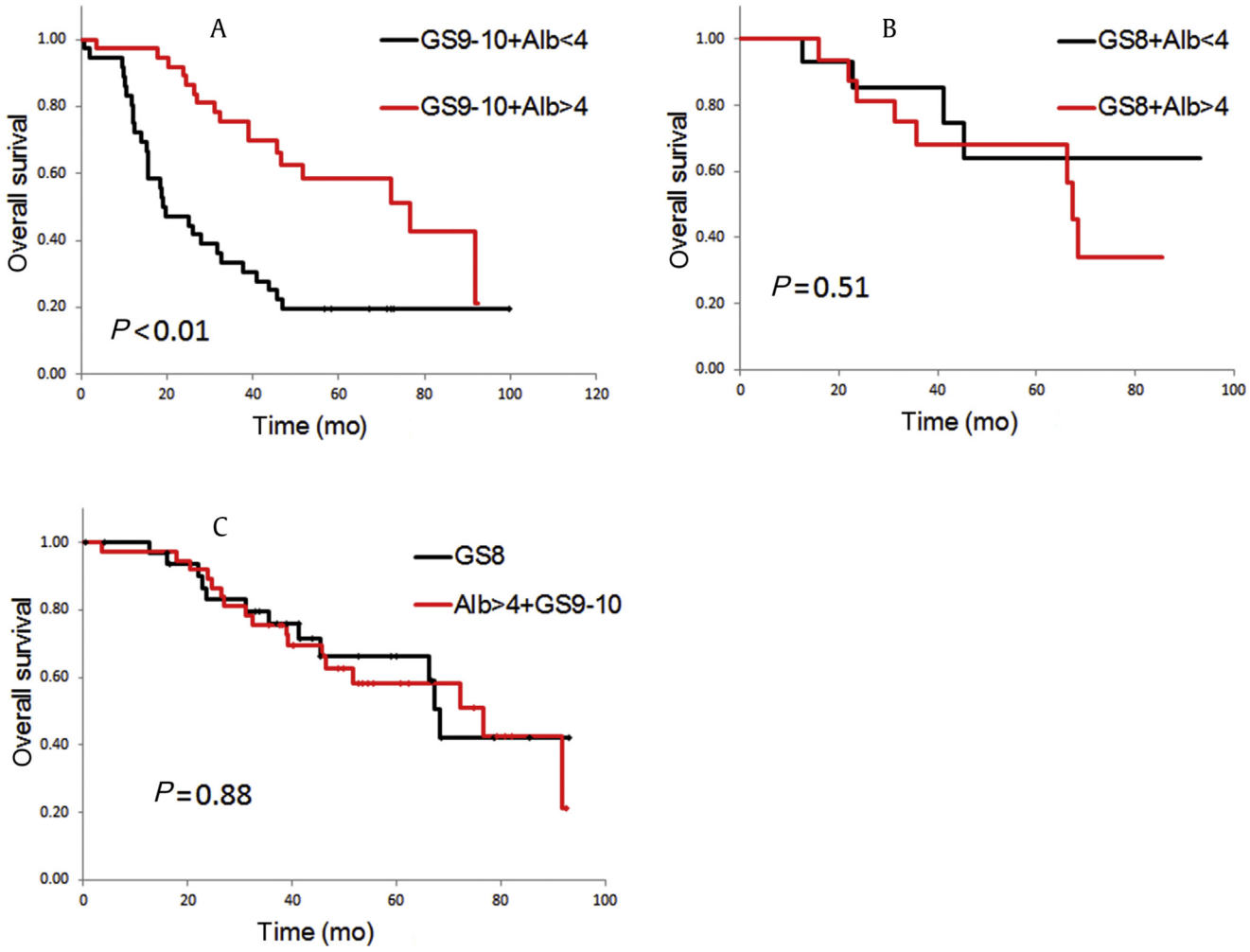

Fig. 3. Kaplan–Meier curves show overall survival according to Alb level. (A) Overall survival rate in patients with albumin level < 4 g/dL and > 4 g/dL with GS 9–10 ($P < 0.01$). (B) Overall survival rate in patients with albumin level < 4 g/dL and > 4 g/dL with GS 8 ($P = 0.51$). (C) Overall survival rate in patients with GS 8 and Alb level > 4 g/dL and GS 9–10 ($P = 0.88$). Alb, albumin; GS, Gleason Score.

the high-risk group in J-CAPRA risk stratification. Moreover, we found that albumin level could be a useful prognostic marker in PCaBM patients with GS 9–10. To the best of our knowledge, this study is the first report to show the clinical significance of the 2014 ISUP Gleason Grading Systems in Japanese men with PCaBM. Since a significantly worse outcome was observed in Grade Group 5 (GS 9–10) treated with standard hormonal therapy, our study suggested the need for a different treatment strategy, such as upfront docetaxel plus ADT in this group of patients.

The original Gleason Grading System was improved in 2005 with modifications by the ISUP, recommending that a higher grade should be considered regardless of tumor volume at biopsy.[14] Furthermore, the ISUP meeting in 2014 suggested the following stratification: GS $\leq$ 6, 3+4, 4+3, 8, and 9–10 for localized PCa, which represents Gleason Grading Group 1, 2, 3, 4, and 5, respectively.[8] However, the prognostic stratification by GS for metastatic PCa has rarely been validated. In the present study, we found a significant difference in PCSS and OS between PCaBM patients with GS 8 and those with GS 9–10.

Tsao et al[9] reported that patients with GS 9–10 treated with definitive local treatment (radiotherapy or radical prostatectomy) had worse outcomes than those with GS 8, thus, they recommended clinical trials for novel approaches of treating PCa patients with GS 9–10. This report supports the prognostic significance of 2014 ISUP Gleason Grading Systems in high-risk patients with localized PCa. In our study, PCaBM patients with GS 9–10 also had worse outcome than those with GS 8. Therefore, our results suggested that the ISUP Gleason Grading System, especially Groups 4 and 5, could be applied not only in localized PCa but also advanced PCa with bone metastasis.

Pathological GS 9–10 contains Gleason Pattern 5. Therefore, we considered that the presence of Gleason Pattern 5 might affect metastatic PCa prognosis. Several authors have reported the impact of Gleason Pattern 5 and GS $\geq$ 9 on PCa prognosis[15–18] and Gleason Pattern 5 might affect prognosis even if it is a tertiary pattern in localized PCa.[19] These reports are mainly for localized PCa with definitive treatment. In our cohort, there was only one patient with GS 3+5 or 5+3, and thus we could not investigate the difference between GS 4+4 and 3+5, or 5+3. Whether pathological GS 3+5 and 5+3 should be discriminated from GS 4+4 warrants further discussion.

Regarding response to initial ADT, patients with GS 9–10 did not have significantly higher BCR rate than those with GS 8 (Fig. 1A). However, PCaBM patients with GS 9–10 had significantly lower PCSS and OS than those with GS 8 (Fig. 1B,C). These results suggested that patients with GS 9–10 would be more likely to exhibit resistance to subsequent sequential therapy than those with GS 8. Actually, regarding PSA response of sequential hormonal therapy

(not chemotherapy), patients with GS 9–10 had a lower rate than those with GS 8 (64.4% vs. 80%, $P = 0.19$) in the present study, although it was not significant. These resistances to sequential hormonal treatments may cause unfavorable PCSS. In the CHAARTED (ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial, significant survival benefit was clinically identified in patients with high-volume PCa treated with ADT plus docetaxel compared with ADT alone.[12] Upfront docetaxel plus ADT should be considered for PCa with a high tumor burden.[12,20] We demonstrated that PCaBM with GS 9–10 had worse outcome even compared to those with GS 8, regardless of tumor burden when treated with primary ADT. Thus, PCaBM with GS 9–10 may be a good candidate for upfront docetaxel plus ADT.

In our study, PCaBM patients with GS 9–10 and albumin level > 4 g/dL had significantly higher OS than those with GS 9–10 and Alb level < 4 g/dL (Fig. 3A). Furthermore, PCaBM patients with GS 9–10 and albumin level > 4 g/dL had equal OS rate to those with GS 8 (Fig. 3C). Thus, PCaBM patients who have good nutrition can be expected to have a certain survival advantage, even though patients are classified into a high-risk group. Albumin level could be an index biomarker for predicting survival among PCaBM patients with GS 9–10. Some authors have reported the significance of albumin level as a predictive indicator for prognosis in patients with metastatic PCa.[21] Among patients with various malignancies, Glasgow Prognostic Scale was proposed as a predictive indicator for prognosis[22] and nutritional status has recently been considered a significant factor for survival. In our study, body mass index was not a significant predictive factor but albumin level was an independent predictive factor for OS (Table 2). This result indicates that albumin level could predict life prognosis before patients lapse into a cachectic condition. It is also reported that hypoalbuminemia in malignant tumor patients relates to chronic inflammation and could be the result of cytokine-induced immune suppression.[23,24] In addition, it is reported that a high Glasgow Prognostic Scale score, indicating high C-reactive protein level and hypoalbuminemia, is significantly correlated with worse performance status (PS).[22] To date, some authors have reported that worse PS is significantly associated with worse prognosis in advanced PCa.[25] Thus, hypoalbuminemia is considered to represent worse PS and cause worse prognosis. The association between cancer progression and hypoalbuminemia is expected to be investigated further.

The present study had some limitations. First, our cohort size was small due to the lower prevalence of PCaBM at diagnosis compared to localized PCa. Second, our study was a retrospective database analysis. Third, biopsy specimens were not diagnosed by one pathologist.

In conclusion, PCaBM patients with GS 9–10 had significantly worse outcome than those with GS 8, which indicated prognostic significance of ISUP Gleason Grading Group 4 and 5, even in patients with bone metastatic PCa. Furthermore, albumin level could be a strong prognostic factor among PCaBM patients with GS 9–10. Treatment strategy may be considered based on the GS as well as albumin level among PCaBM patients with GS 8–10.

Conflict of interests

The authors have no conflicts of interest to declare.

Acknowledgments

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