Original Article

Prognostic factors in Japanese men with high-Gleason metastatic castration-resistant prostate cancer

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Background: Several therapeutic agents are available for metastatic castration-resistant prostate cancer (CRPC). However, prognosis is still not well developed. The Gleason score (GS) is a prognostic factor available for patients with metastatic CRPC. GSs ranging from 6 to 10 and GSs ≥8 are usually categorized as single prognostic factors. In this study, we evaluated the prognosis of high-GS metastatic CRPC in Japanese men.

Methods: Overall, 105 patients with metastatic CRPC with a GS ≥8 were retrospectively analyzed. Multivariate analyses of patient age, GS, and Eastern Cooperative Oncology Group performance status (ECOG-PS) were performed using Cox proportional hazards analysis to predict overall survival (OS).

Results: GS 8 had all Gleason patterns of 4+4. Thirty patients (28.6%) had GS of 8, and 75 (71.4%) had GS of 9 or 10. As a first-line treatment for metastatic CRPC, 42 patients (40%) received abiraterone, 35 (33.3%) received enzalutamide, and 26 (24.8%) received docetaxel. The 5-year OS in patients with GS of 8 was 65.0% [95% confidence interval (CI): 43.07–86.82%], while the 5-year OS in patients with GS of 9 or 10 was 37.0% (95% CI: 24.41–56.11%). There was a significant difference in OS between the GS 8 and GS 9–10 groups (log-rank test, P=0.038). Multivariate analysis showed that GS and ECOG-PS were significant prognostic factors for OS.

Conclusions: Patients with metastatic CRPC with GS 9–10 had poor prognoses, suggesting the need for additional treatment options.

Keywords: Gleason score (GS); overall survival (OS); high-volume mCRPC; taxane

Submitted Feb 17, 2022. Accepted for publication Jun 06, 2022.
doi: 10.21037/tcr-22-375
View this article at: https://dx.doi.org/10.21037/tcr-22-375

Introduction

The U.S. Preventive Services Task Force recommends against prostate-specific antigen (PSA)-based screening for prostate cancer in men aged ≥70 years; however, the incidence of metastatic prostate cancer has been increasing rapidly since 2012 (1). Accordingly, the incidence of metastatic castration-resistant prostate cancer (CRPC) will increase. First-line treatments for CRPC are docetaxel or the next-generation antiandrogens and CYP17 inhibitors. Patients with metastatic CRPC prefer androgen receptor signaling inhibitors (ARSIs) to docetaxel because of their severe side effects and worse quality of life (2,3).

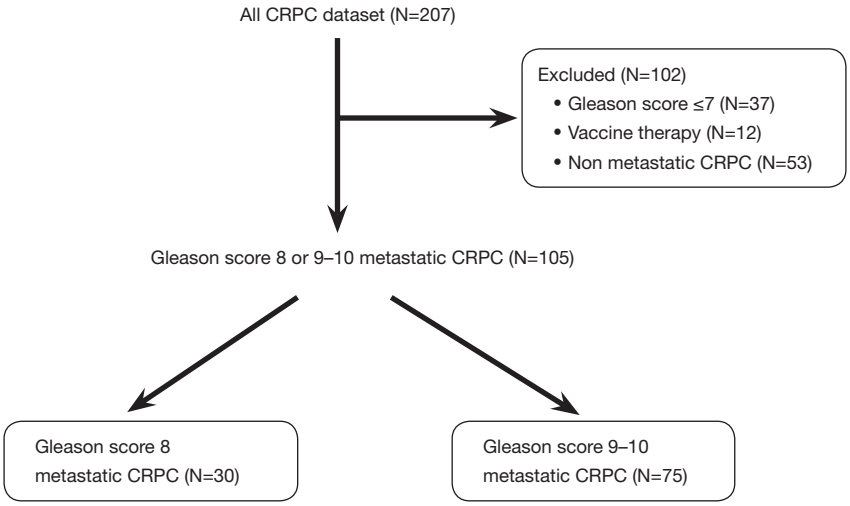

Figure 1 Flowchart of CRPC dataset. CRPC, castration-resistant prostate cancer.

The Gleason score (GS) classifies biopsy tissues by their visual similarity to healthy and cancerous tissues and is a prognostic factor for survival. Biochemical recurrence-free survival (BFS) rates are consistent with the comparison of pathological stage, with a higher GS corresponding to worse BFS (4,5). In most clinical studies, a GS of 8 or more was categorized as high (6,7). Typical GSs range from 6 to 10. The higher the GS, the more likely it is for the cancer to grow and spread quickly. A score of 6 indicates cancer cells that look similar to normal cells and suggests that the cancer is likely to grow slowly. A Gleason pattern 5 is pathologically different from Gleason pattern 4. Gleason pattern 5 is characterized by the complete loss of glandular lumina, whereas Gleason pattern 4 is characterized by fused glands or cribriform patterns (8). Because the microscopic characteristics of Gleason patterns 4 and 5 are different, the aggressiveness and responsiveness to therapeutic agents for a GS of 9, which includes Gleason pattern 5, could be different from those for a GS of 8.

In this study, we retrospectively analyzed the prognostic factors in Japanese men diagnosed with metastatic CRPC with a GS ≥8. We present the following article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-375/rc).

Methods

The patients included in this study were diagnosed with metastatic CRPC at Kindai University Hospital and Kindai University Nara Hospital between 2011 and 2019. All CRPC datasets are shown in *Figure 1*. The Gleason classification, revised at the consensus meeting of the International Society of Urologic Pathology (ISUP) 2005 was used to calculate and assign GS. Patients with a GS of 7, vaccine therapy, and non-metastatic prostate cancer were excluded. Overall, 105 patients with metastatic CRPC with a GS ≥8 were retrospectively analyzed. The following clinical and pathological data were obtained from medical records: age, initial PSA, Eastern Cooperative Oncology Group performance status (ECOG-PS), pathological reports of transrectal ultrasound-guided needle prostate biopsy, follow-up data, and overall survival (OS). The patients were followed up every 3 months. CRPC was diagnosed based on the definition of the Prostate Cancer Working Group 2 as a confirmed relative increase in the PSA level from the nadir value by ≥50% and by ≥2 ng per milliliter under the serum testosterone levels less than 50 ng/dL. The site of metastasis was evaluated using computed tomography and bone scintigraphy. The extent of disease (EOD) score was used to classify bone metastases (9). Treatment resistance is defined as 25% and +2 increase of PSA levels from the nadir point. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of Kindai University (No. R02-247). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Table 1 Patient characteristics

Characteristics	Gleason score 8	Gleason score 9–10	P value
n (%)	30 (28.6)	75 (71.4)	
Age (years), median [range]	71.5 [55–80]	72 [49–88]	0.56
Time to CRPC (months), median [range]	30 [7–103]	17 [1–156]	0.22
Age of CRPC (years), median [range]	73.5 [61–85]	75 [52–90]	0.86
PSA of CRPC (ng/mL), median [range]	7.35 [0.3–285.8]	11 [0.02–3,123]	0.49
ECOG-PS, n (%)			0.47
0–1	29 (96.6)	72 96.0)	
≥2	1 (3.4)	3 (4.0)	
Lymph node metastasis, n (%)			
N1	9 (30.0)	30 (40.0)	0.34
Distant metastasis, n (%)			
M1a	6 (20.0)	26 (34.7)	0.84
M1b	29 (96.7)	70 (93.3)	0.51
M1c	3 (10.0)	10 (13.3)	0.64
Extent of disease, n (%)			0.28
EOD 0	4 (13.8)	5 (7.1)	
EOD 1	16 (55.2)	38 (54.3)	
EOD 2	7 (24.1)	19 (27.1)	
EOD 3	2 (6.9)	8 (11.4)	

CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; EOD, extent of disease.

Statistical analysis

Results are presented as median values (range). The comparison of the 2 groups (GS 8 and GS 9–10) was conducted using the Mann-Whitney U-test and the χ^2-test. The Kaplan-Meier estimate of the survival curve and log-rank test were used to explore the association between the parameters and patient survival. Multivariate analyses of patient age, GS, and ECOG-PS were performed using Cox proportional hazards analysis to predict OS. All statistical tests were performed using SPSS version 11.02 (SPSS, Chicago, IL, USA) and GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA) software. All P values were two-sided, and statistical significance was set at $P<0.05$.

Results

Patient characteristics are summarized in *Table 1*. All patients underwent 12 or 16 echo-guided transperineal needle biopsies at diagnosis. Group of GS 8 had all GS 4+4, did not have Gleason pattern 5. Two distinct groups of patients, 30 with GS 8 and 75 with GS 9–10 were categorized for further analysis. There was no significant difference in age at the time of diagnosis of prostate cancer, time to CRPC, or PSA levels at the time of diagnosis of CRPC between patients with GS 8 and GS 9–10. There were also no significant differences in the N stage, M stage, or EOD score at the diagnosis of CRPC between the 2 groups. Treatment changes were at the discretion of the attending physicians. Primary and secondary treatments are summarized in *Table 2*. Fifteen patients (50.0%) with GS 8 received abiraterone acetate, 14 (46.7%) received enzalutamide, and none (0%) received docetaxel as the first-line therapy for CRPC, while 27 (36.0%) with GS 9–10 received abiraterone acetate, 21 (28.0%) received enzalutamide, and 26 (34.7%) received docetaxel. There

Table 2 Primary and secondary treatments for mCRPC

Treatment for mCRPC	Gleason score 8, n (%)	Gleason score 9–10, n (%)
First line		
Abiraterone acetate	15 (50.0)	27 (36.0)
Enzalutamide	14 (46.7)	21 (28.0)
Docetaxel	0 (0)	26 (34.7)
Apalutamide	1 (0.3)	1 (1.3)
Second line		
Abiraterone acetate	6 (31.6)	16 (30.2)
Enzalutamide	4 (21.0)	23 (43.4)
Docetaxel	8 (42.0)	5 (9.4)
Cabazitaxel	0 (0)	8 (15.1)
Apalutamide	0 (0)	1 (1.9)
Ra-223	4 (13.3)	9 (12.0)
Others	1 (5.3)	0 (0)

mCRPC, metastatic castration-resistant prostate cancer.

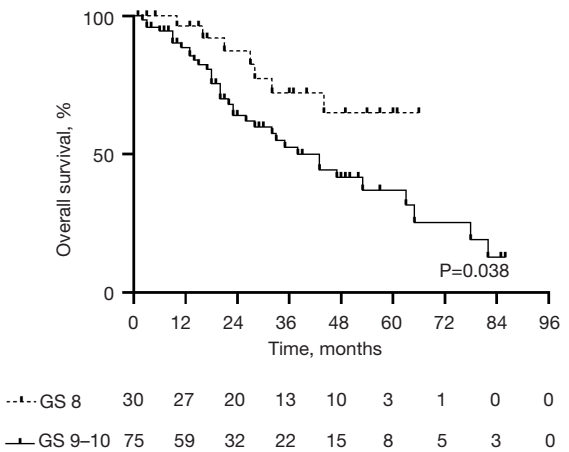

Figure 2 Overall survival in 105 patients with mCRPC based on Gleason Score (8 *vs.* 9–10). GS, Gleason score; mCRPC, metastatic castration-resistant prostate cancer.

was no significant difference in first- and second-line taxane treatment use between the GS 8 group (26.7%) and the GS 9–10 group (41.3%) (P=0.38). The median follow-up duration was 22 months (range, 1–86 months). Of the 105 patients, 43 (41.0%) died during the follow-up. In the overall cohort, the 5-year OS rate was 45.0% [95% confidence interval (CI): 29.6–64.3%]. *Figure 2* shows the Kaplan-Meier curves of the OS of GS 8 and GS 9–10. The 5-year OS rate in patients with GS 8 was 65.0% (95% CI: 43.0–86.8%), while the 5-year OS rate in patients with GS 9–10 was 37.0% (95% CI: 24.4–56.1%).

There was a significant difference in OS between the GS 8 group and GS 9–10 groups (log-rank test, P=0.038). When patients were divided into 2 cohorts, patients treated during 2011–2015 and those during 2016–2019, no significant differences regarding OS were observed (P=0.37).

Table 3 shows the univariate and multivariate Cox proportional hazards analyses for OS prediction. In the univariate analysis, the following were statistically significantly associated with OS: PSA more than 10 ng/mL at the time of CRPC diagnosis (HR, 2.27; 95% CI: 1.23–4.32; P=0.008), GS 9–10 (HR, 2.31; 95% CI: 1.08–5.70; P=0.028), EOD score ≥2 (HR, 2.23; 95% CI: 1.21–4.14; P=0.010), and visceral metastasis (HR, 2.71; 95% CI: 1.15–5.66; P=0.024). The use of taxane in first- and second-line treatments was not associated with OS (HR, 1.324; 95% CI: 0.70–2.48; P=0.38). In the multivariate analysis, GS 9–10 (HR, 2.90; 95% CI: 1.28–7.64; P=0.009) and ECOG-PS at the diagnosis of CRPC (HR, 8.24; 95% CI: 1.17–37.1; P=0.036) were significantly associated with OS.

Discussion

In this study, we found that patients with metastatic CRPC with GS 9–10 had a poor prognosis compared to patients with GS 8 (Gleason pattern 5 was not included); and early (primary and secondary) taxane treatments did not contribute to improved OS.

In recent years, the Gleason Grade classification is often used in ISUP 2005. On the other hand, it is also true that the GS classification is still often used in many clinical trials. Thus, we used the GS classification in this study. In 1974, Gleason *et al.* proposed the 2 most common grade patterns as a grading system for prostate cancer (10). The predominant pattern (by area) was designated as the primary pattern and the lesser pattern (by area) as the secondary pattern. After several modifications of the grading systems, GS was found to be one of the strongest prognostic factors of prostate cancer (11-13). GS pattern 5 is different from GS patterns 3 and 4 in both morphology and gene mutations. Primary Gleason pattern 5 prostate cancer has a higher incidence of mutated DNA repair pathway genes (14). Stenmark *et al.* reported that GP5 has a worse prognosis than GP4 in patients with high-risk prostate

Table 3 Cox-proportional hazards analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.01	0.96, 1.06	0.53	1.03	0.97, 1.10	0.25
PSA of CRPC (ng/mL)						
<10	1.00			1.00		
≥10	2.27	1.23, 4.32	0.008	2.09	0.98, 4.34	0.056
Gleason score						
8	1.00			1.00		
9–10	2.31	1.08, 5.70	0.028	2.90	1.28, 7.64	0.009
ECOG PS						
0–1	1.00			1.00		
≥2	2.50	0.40, 8.27	0.27	8.24	1.17, 37.1	0.036
EOD						
0–1	1.00			1.00		
≥2	2.23	1.21, 4.14	0.010	1.49	0.69, 3.17	0.29
Site of metastasis						
Bone only	1.00			1.00		
Visceral metastasis	2.71	1.15, 5.66	0.024	1.79	0.66, 4.46	0.23
First-second line taxane use						
Without taxane	1.00			1.00		
With taxane	1.32	0.70, 2.48	0.38	1.13	0.48, 2.66	0.76

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; CRPC, castration-resistant prostate cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; EOD, extent of disease.

cancer treated with dose-escalated external-beam radiation therapy and androgen deprivation (15). In the retrospective analysis of 20,139 men from the National Cancer Database with localized or locally advanced Gleason 8–10 prostate cancer who received the external beam radiation therapy, the significant survival advantage of androgen deprivation therapy (ADT) was found in patients with Gleason 8 prostate cancer but not in those with Gleason 9–10 prostate cancer (16). In the retrospective analysis of 605 patients with metastatic hormone-sensitive prostate cancer who received ADT or combined androgen blockade, a GS 9 or higher was a prognostic factor of both CRPC-free survival and OS (17). In a report of 85 patients treated with docetaxel or ARSIs with propensity score matching, the median OS was 38.2 months for docetaxel *vs.* 58.3 months for ARSIs (18). However, no treatment beyond the first line was mentioned. Angelergues *et al.* reported that 574 patients with high GS CRPC had poor OS after treatment with docetaxel, cabazitaxel, and ARSIs (19). Two prognostic factors were noted in the multivariate analysis: length of first-line ADT for less than or more than 12 months and PSA level at the time of CRPC diagnosis (19). Chen *et al.* reported that ECOG performance status was identified as a significant prognostic factor in CRPC patients (20). Our univariate analysis showed that PSA level at the time of CRPC diagnosis was a prognostic factor for OS using PSA levels of 10 ng/mL at the time of CRPC diagnosis as a cutoff value, but the multivariate analysis did not show any significance. When PSA values were analyzed in continuous form, univariate analysis showed a significant difference, but not in multivariate analysis. This discrepancy might be due to the small sample size.

Our results suggest that patients with Gleason 9–10 metastatic CRPC have a poor prognosis compared to

patients with Gleason 8, even with the new ARSI or taxane. More researches in predictive markers are needed in this group of patients with GS 9–10. Based on this study, in the case of GS 8, we consider using ARSI as 1st line treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). If the patient is refractory to treatment with 1st line ARSI, other ARSI or taxane should be considered for the 2nd line. On the other hand, taxane as 1st -2nd line was not effective in patients with GS 9–10. However, de Leeuw *et al.* reported that loss of retinoblastoma (RB) function induces sensitization to taxanes. Thus, patients with mutated *RB* could benefit from taxane treatment (21). Therefore, we believe that genetic testing early in treatment may be useful to better strategize treatment regimens.

This study had several limitations. First, it was a very small-scale retrospective study. The cohort was inhomogeneous, and each physician independently decided the course of treatment. Although we performed multivariate analysis, other confounding factors affecting survival, such as tumor volume, PSA, localization of metastasis, might have existed. For example, Choy *et al.* reported the presence of cribriform architecture may affect prognosis (22). However, we did not assess the presence of cribriform architecture in biopsy specimens. Therefore, further large-scale studies are required.

Conclusions

Patients with metastatic CRPC with GS 9–10 who received ARSIs or taxane had a poor prognosis compared with patients with GS 8.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-375/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-375/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-375/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-375/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Kindai University (No. R02-247) and individual consent for this retrospective analysis was waived.

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Cite this article as: Nishimoto M, Fujita K, Yamamoto Y, Hashimoto M, Adomi S, Banno E, Saito Y, Shimizu N, Mori Y, Minami T, Nozawa M, Nose K, Hirayama A, Yoshimura K, Uemura H. Prognostic factors in Japanese men with high-Gleason metastatic castration-resistant prostate cancer. Transl Cancer Res 2022;11(8):2681-2687. doi: 10.21037/tcr-22-375

