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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) ≤ 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 ≤ 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 ≥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 ≥ 25% above the nadir and confirmed by a second PSA test performed ≥ 3 weeks later.

2.3. Definition of high-volume tumor

High-volume PCa was defined as visceral metastases and/or ≥ 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.

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