

Spinal Instability as a Prognostic Factor in Patients With Spinal Metastasis of Castration-resistant Prostate Cancer

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Abstract. *Background/Aim:* To evaluate the Spinal Instability Neoplastic Score (SINS) for prediction of survival in patients with spinal column metastasis of castration-resistant prostate cancer (CRPC). *Patients and Methods:* A retrospective study of spinal instability was performed in patients with CRPC using SINS. Overall survival was evaluated starting from the time of SINS evaluation. The subjects were 42 patients with CRPC among 261 cases diagnosed with metastatic spinal tumors by radiologists, among 42,152 cases that underwent a body computed tomography scan at Kawasaki Medical School Hospital within 32 months from December 2013 to July 2016. *Results:* The median age was 78 (range=55-91 years), the median prostate-specific antigen (PSA) level at SINS evaluation was 42.1 (0.1-3,121.6) ng/ml, and 11 patients had visceral metastasis. The median periods from diagnosis of bone metastasis and development of CRPC to SINS evaluation were 17 (0-158) and 20 (0-149) months, respectively. The spine was stable in 32 cases (group S) and potentially unstable or unstable in 10 (24%) (group U). The median observation period was 17.5 (0-83) months and 36 patients died. The median survival period after SINS evaluation was longer in group S than that in

group U (20 vs. 10 months, $p=0.0221$). In multivariate analysis, PSA level, visceral metastasis, and spinal instability were significant prognostic factors. The hazard ratio for patients in group U was 2.60 (95%CI=1.07-5.93, $p=0.0345$). *Conclusion:* Spinal stability evaluated using SINS is a new prognostic factor for survival of patients with spinal metastasis of CRPC.

Prostate cancer often metastasizes to the bone, and bone metastasis is found at autopsy in $\geq 90\%$ of cases (1). Bone metastasis of castration-resistant prostate cancer (CRPC) has rates of 85-100% (2) and 80% (3) in the United States and Japan, respectively, and metastatic spinal tumors are associated with pain, paralysis, sensory loss, and a non-ambulatory status, resulting in decreased quality of life and death (4).

At Kawasaki Medical School Hospital, the Liaison Treatment Team for Metastatic Spinal Tumors was established in December 2013 for early intervention to prevent paralysis and gait inability of patients with spinal bone metastasis. This team is led by a spine surgeon. Radiologists first check for metastatic spinal tumors based on whole body CT images taken at the hospital. Spine surgeons then evaluate these images to evaluate spinal instability. Departments responsible for primary tumors (urology, breast surgery, thoracic surgery, etc.), oncology and palliative care (pain clinic, etc.) use this information to determine treatment plans, and discuss these plans at joint monthly conferences. In this study, we examined the influence of spinal instability on prognosis of patients with spinal metastasis of CRPC who were treated using this system.

Patients and Methods

A retrospective study was performed in 42 patients with spinal metastasis of CRPC. Whole body CT was recorded for 42,152 cases at our hospital within 32 months from December 1, 2013 to July 31, 2016. Among these cases, 261 patients were diagnosed with spinal metastasis, including 68 with prostate cancer (26.1%). These 68

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Key Words: Castration-resistant prostate cancer, spinal instability, SINS, spinal bone metastasis, overall survival.

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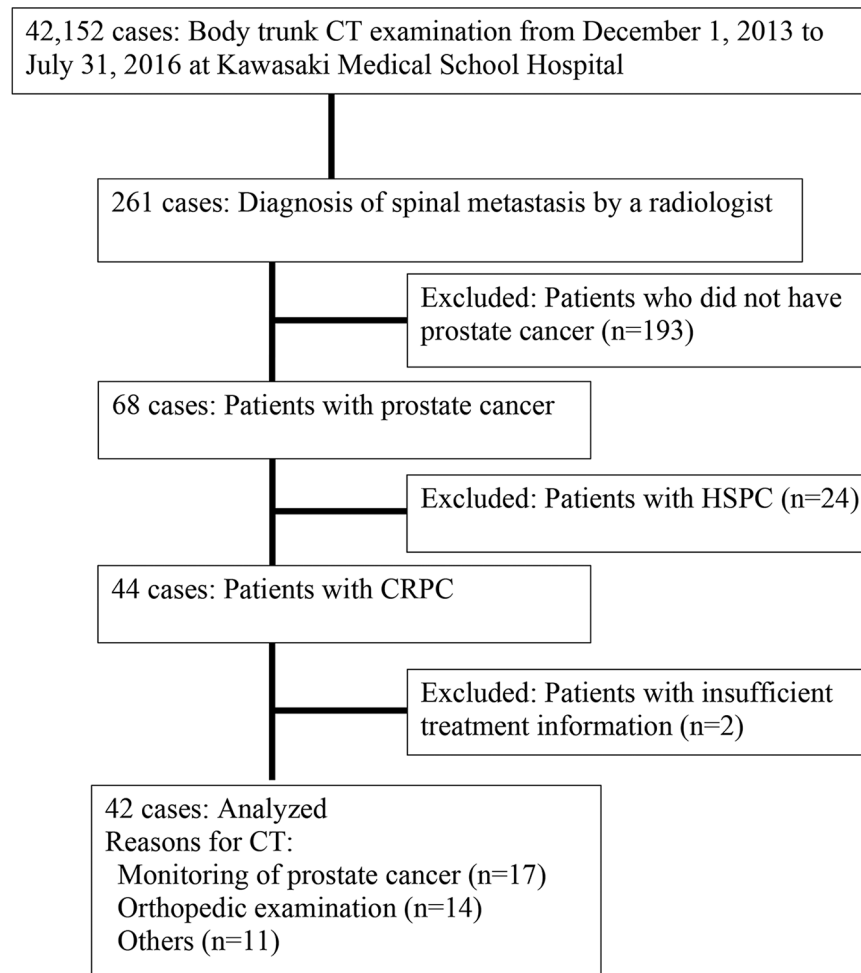


Figure 1. Flowchart of patient selection. CT: Computed tomography; CRPC: castration-resistant prostate cancer; HSPC: hormone-sensitive prostate cancer.

patients included 24 with hormone-sensitive prostate cancer (HSPC) and 44 with CRPC (64.7%). Two patients with CRPC were excluded due to a lack of clarity with treatment details because they were treated at other hospitals, leaving 42 patients for inclusion in the study (Figure 1).

Of the 42 patients, 17 (40%) underwent CT for monitoring of prostate cancer, including an increased prostate-specific antigen (PSA) level and a change of treatment; 14 (33%) for an orthopedic examination of bone metastasis and indication for palliative radiation, and 11 (26%) for other reasons, including fever, edema, decreased urinary volume, and examination for other malignant tumors. CRPC was defined as an increase in PSA of $\geq 25\%$ or to ≥ 2.0 ng/ml, even if testosterone was < 50 ng/dl. Electronic medical records were examined until February 6, 2021. All patients received treatment from several physicians according to guidelines used in Japan, the USA (National Comprehensive Cancer Network), and Europe. The study was approved by the ethics committee of Kawasaki Medical School and Hospital (No. 2037-2, and No. 3538).

Spinal instability neoplastic score (SINS). Spinal instability was evaluated using the Spinal Instability Neoplastic Score (SINS) defined by Fisher *et al.* (5). SINS includes six components of spinal instability: 1, spinal location (0-3 points); 2, type and presence of pain (0-3 points); 3, bone lesion quality (lytic or blastic) (0-2 points); 4, spinal alignment (0-4 points); 5, extent of vertebral body collapse (0-3 points); and 6, posterolateral involvement of the spinal element (0-3 points). Patients were initially divided into 3 groups based on total SINS scores of 0-6 (stable), 7-12 (potentially unstable) and 13-18 (unstable), but the final analysis used only two groups: SINS 0-6 (group S) and 7-18 (group U). All patients were evaluated by one spine surgeon (K.N.) within one month after a radiologist suggested the presence of spinal metastasis (Figure 2).

Bone scan index (BSI). Whole-body bone scintigraphy within 3 months before and after SINS evaluation was performed for 31 patients. Bone scans were evaluated quantitatively using a computer-aided diagnostic system (BONENAVI®, FUJIFILM

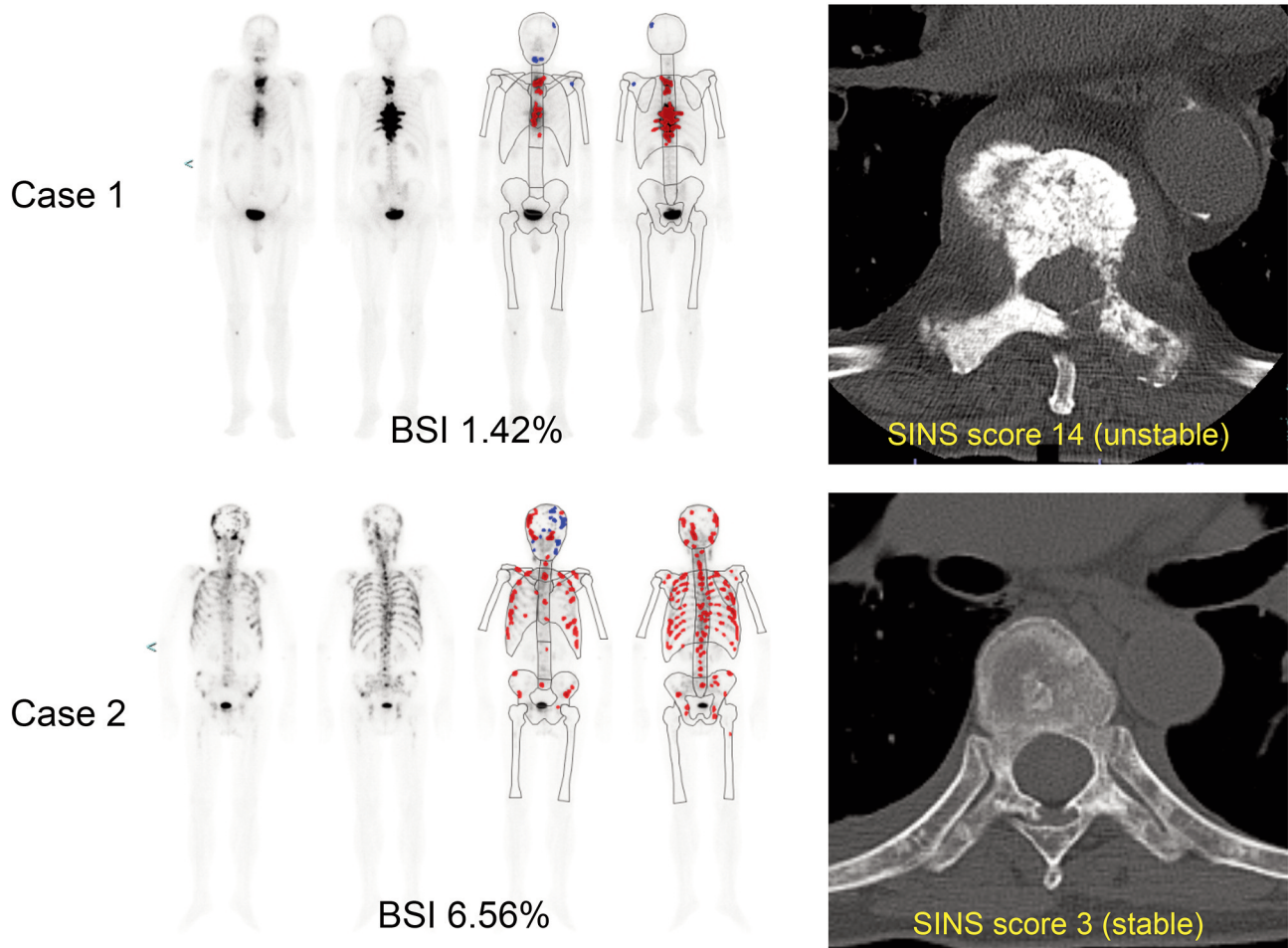


Figure 2. Spinal Instability Neoplastic Score (SINS) and bone scan index (BSI) in representative cases. Case 1. An 80-year-old patient with CRPC. BSI was 1.42%. Computed tomography (CT) showed a T11 lesion. SINS=Location: junctional (T11) spine (3 points); pain: yes (3 points); bone lesion; lytic (2 points); spinal alignment: de novo deformity (2 points); >50% vertebral body collapse (3 points); and unilateral posterolateral involvement (1 point). Total SINS=14 points (unstable). Case 2. A 79-year-old patient with CRPC. BSI was 6.56%. CT showed a T8 lesion. SINS=Location: semi-rigid (T8) spine (1 point); pain: occasional (1 point); bone lesion; mixed (lytic/blastic) (1 point); spinal alignment: normal (0 points); vertebral body collapse: none (0 points); and no posterolateral involvement of spinal elements (0 points). Total SINS=3 (stable).

Toyama Chemical Co. Ltd., Tokyo, Japan). The extent of the bone tumor was measured using the bone scan index (BSI) (6).

Statistical analysis. Descriptive statistics for continuous variables are presented as medians and ranges, and those for categorical variables are shown as frequencies and percentages. A Fisher exact, χ^2 , and Mann-Whitney *U*-tests were used as appropriate to evaluate group differences. Overall survival (OS) was defined as the period from SINS evaluation to death. Univariate and multivariate analyses of OS were performed using Cox proportional hazards regression models. Survival curves were determined using Kaplan-Meier estimates, and the difference between curves was analyzed by log-rank test. The Kaplan-Meier estimates were based on groups with SINS ≤ 6 (stability, group S) and SINS ≥ 7 (potential or determined instability, group U). The significance level was 5%. All analyses were performed using ©JMP v. 14.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of the 42 patients in the study are shown in Table I. The median age was 78 (range=55-91 years), the median observation period was 17.5 (range=0-83 months), and the median PSA level at the time of SINS evaluation was 42.1 (0.1-3,121.6) ng/ml. The median periods from diagnosis of bone metastasis and development of CRPC to SINS evaluation were 17 (0-158) and 20 (0-149) months, respectively. Eleven patients had visceral metastasis and 5 had a history of treatment with docetaxel. During the observation period, 36 patients died (34 from prostate cancer and two from other causes). The median OS was 18 months.

The 42 cases were classified into those with spinal stability (SINS 0-6, n=32) and those that were potentially

Table I. Characteristics of patients (n=42) at the time of Spinal Instability Neoplastic Score (SINS) scoring.

		Overall (n=42)	SINS≥7 (n=10)	SINS≤6 (n=32)	p-Value
Age (years)	Median (range)	78 (55-91)	76 (55-87)	78.5 (63-91)	0.6894
PSA level (ng/ml)	Median (range)	42.1 (0.1-3,121.6)	158.6 (1.6-3,121.6)	35.3 (0.1-1,004.8)	0.0982
Gleason grading group	≤3	10 (24)	1 (10)	9 (28)	0.4779
at diagnosis (n=39)	4	7 (17)	2 (20)	5 (16)	
	5	22 (52)	6 (60)	16 (50)	
Period from confirmation of bone metastasis	Median (range)	17 (0-158)	17 (0-78)	17 (0-158)	0.9527
Period from development of CRPC	Median (range)	20 (0-149)	19.5 (3-70)	20 (0-149)	0.9294
Object of CT	Prostate cancer monitoring	17 (40)	3 (30)	14 (44)	0.7395
	Orthopedic	14 (33)	4 (40)	10 (31)	
	Others	11 (26)	3 (30)	8 (25)	
Pain	None	15 (36)	1 (10)	14 (44)	0.1439
	NSAIDS	10 (24)	3 (30)	7 (22)	
	Opioids	17 (40)	6 (60)	11 (34)	
BSI (n=31)	Median (range)	1.87 (0.1-12.0)	3.64 (0.6-9.8)	1.69 (0.1-12.0)	0.2404
Bone modifying agents	None	16 (38)	3 (30)	13 (41)	0.5835
	Zoledronic acid	18 (43)	4 (40)	14 (44)	
	Denosumab	8 (19)	3 (30)	5 (16)	
Metastasis (other than bone metastasis)	Lymph node metastasis	21 (50)	6 (60)	15 (47)	0.4687
	Visceral metastasis	11 (26)	4 (40)	7 (22)	0.2552
Previous treatment line	1	5 (12)	0 (0)	5 (16)	0.5854
	2	5 (12)	1 (10)	4 (13)	
	3	11 (26)	3 (30)	8 (25)	
	≥4	21 (50)	6 (60)	15 (47)	
Prior docetaxel	No administered/administered	37/5	8 (80)/2 (20)	29 (91)/3 (9)	0.3651

PSA: Prostate specific antigen; CRPC: castration-resistant prostate cancer; CT: computed tomography; BSI: bone scan index; NSAIDS: non-steroidal anti-inflammatory drugs.

Table II. Demographics of patients (n=42) based on Spinal Instability Neoplastic Score and bone treatment.

	Total score	Number of patients	Number	PLF+RT (n=3)	PLF+Decompression+RT (n=1)	RT only (n=6)	Radium-223 (n=7)
Stability (0-6 points)	2	32	1	0	0	0	0
	3		8	1	0	0	3
	4		9	0	1	1	1
	5		6	0	0	2	2
	6		8	0	0	1	1
Potentially unstable (7-12 points)	7	9	5	0	0	1	0
	8		2	0	0	0	0
	9		2	1	0	1	0
Unstable (13-18 points)	14	1	1	1	0	0	0

PLF: Posterior lumbar fusion; RT: radiation therapy.

unstable or unstable (SINS ≥7, n=10) (Table II). PSA showed a tendency to be higher in group U compared with group S, but the difference was not significant ($p=0.0982$). BSI and the periods from development of bone metastasis and development of CRPC to SINS evaluation did not differ significantly between the two groups (Table I).

In bone treatment after SINS evaluation, 10 patients received local treatment, including a combination of posterior lumbar fusion (PLF) and radiotherapy (n=3), a combination of PLF, decompression, and radiotherapy (n=1), and radiotherapy alone (n=6). Radium-223 was administered to 7 patients in group S (SINS 0-6) (Table II). There was no

Table III. Exploratory analysis of overall survival in patient groups.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age ≥ 78 vs. < 78	1.55	0.78-3.16	0.2154	–	–	–
Gleason grade 5 vs. ≤ 4	0.73	0.36-1.49	0.3888	–	–	–
PSA ≥ 42.1 vs. < 42.1 ng/ml	3.66	1.73-8.04	0.0007	4.46	2.07-10.01	0.0001
Time after CRPC diagnosis ≥ 20 vs. < 20	1.60	0.81-3.17	0.1749	–	–	–
Time after bone metastasis diagnosis ≥ 17 vs. < 17	0.76	0.38-1.50	0.4308	–	–	–
SINS ≥ 7 vs. ≤ 6	2.44	1.04-5.26	0.0402	2.60	1.07-5.93	0.0345
Visceral metastasis BSI ≥ 1.87 vs. < 1.87	3.42	1.37-8.33	0.0095	5.59	2.34-13.31	0.0002
Pain	1.55	0.73-3.31	0.2542	–	–	–
Docetaxel	1.67	0.84-3.50	0.1437	–	–	–
	2.86	0.81-8.03	0.0968	–	–	–

PSA: Prostate specific antigen; CRPC: castration-resistant prostate cancer; SINS: Spinal Instability Neoplastic Score; BSI: bone scan index; HR: hazard ratio; CI: confidence interval. Significant *p*-values are shown in bold.

significant difference in OS between patients with and without spine treatment ($p=0.8333$), or between those in group S who did and did not receive radium-223 ($p=0.2498$).

PSA level at the time of SINS evaluation, development of visceral metastasis, and SINS were significant prognostic factors for OS in univariate analysis. These three factors remained significant in multivariate analysis, and patients with SINS ≥ 7 had a hazard ratio (HR) of 2.60 (95%CI=1.07-5.93, $p=0.0345$) (Table III). In Kaplan-Meier analysis (Figure 3), there was a significant difference in median OS after SINS evaluation in patients in group S (SINS 0-6) and group U (SINS ≥ 7) (20 vs. 10 months, $p=0.0221$).

Discussion

Therapeutic strategies for advanced prostate cancer have progressed with introduction of new drugs that have significantly improved survival (7-9). However, the prognosis of metastatic CRPC is still unfavorable and annual mortality in the US is 56% (10). The median OS of patients with CRPC has been found to be 3-4 years in Japanese subjects who respond well to hormone therapy (11). Bone metastasis is a well-known prognostic factor in untreated metastatic prostate cancer patients, and extent of disease (EOD) in initial bone scintigraphy (12) and BSI in computer-aided diagnosis are useful measurements (13, 14). PSA level, visceral metastasis (especially hepatic metastasis), hemoglobin, alkaline phosphatase, and pain have also been reported as prognostic factors in CRPC (11, 15, 16). On-treatment change in BSI is a response indicator for metastatic CRPC (17, 18). However, bone metastasis itself is not a

useful prognostic factor in metastatic CRPC because most cases have this metastasis (2, 3).

Patients with a malignant tumor often develop paralysis and gait difficulty caused by progression of spinal metastasis, and this has a large impact on life prognosis. A combination of surgical treatment, such as decompression and fixation, and radiotherapy is useful for maintaining neurologic functions and for pain relief (19, 20). Thus, such treatment is offered in combination by medical oncologists, radiation oncologists, and spine surgeons. For this purpose, SINS was developed as an index for appropriate therapeutic intervention (5), as a simple method to evaluate spinal instability based on CT images, and as a valid tool with high reliability and reproducibility in diagnosis (scoring) by radiation oncologists. This method has also been suggested to be useful in determining the indication for surgery (21).

In a retrospective study of 27 cases of spine surgery for patients with spinal metastasis of prostate cancer, Ju *et al.* found that the prognosis of CRPC was clearly worse than that of HSPC, and that performance status and hormone sensitivity were important for determining the indication for surgery (22). In a retrospective study of 139 cases of spine surgery for prostate cancer, Chohan *et al.* reported median postoperative survival of about 6 months in 87% of patients with CRPC, and suggested that monitoring for spinal cord compression and spinal instability is important for these patients (23). Wänman *et al.* examined 84 patients with CRPC who underwent spine surgery based on SINS, and found no difference in OS between those with potentially unstable and unstable spines (24). These data were obtained from analyses of cases of spine surgery in

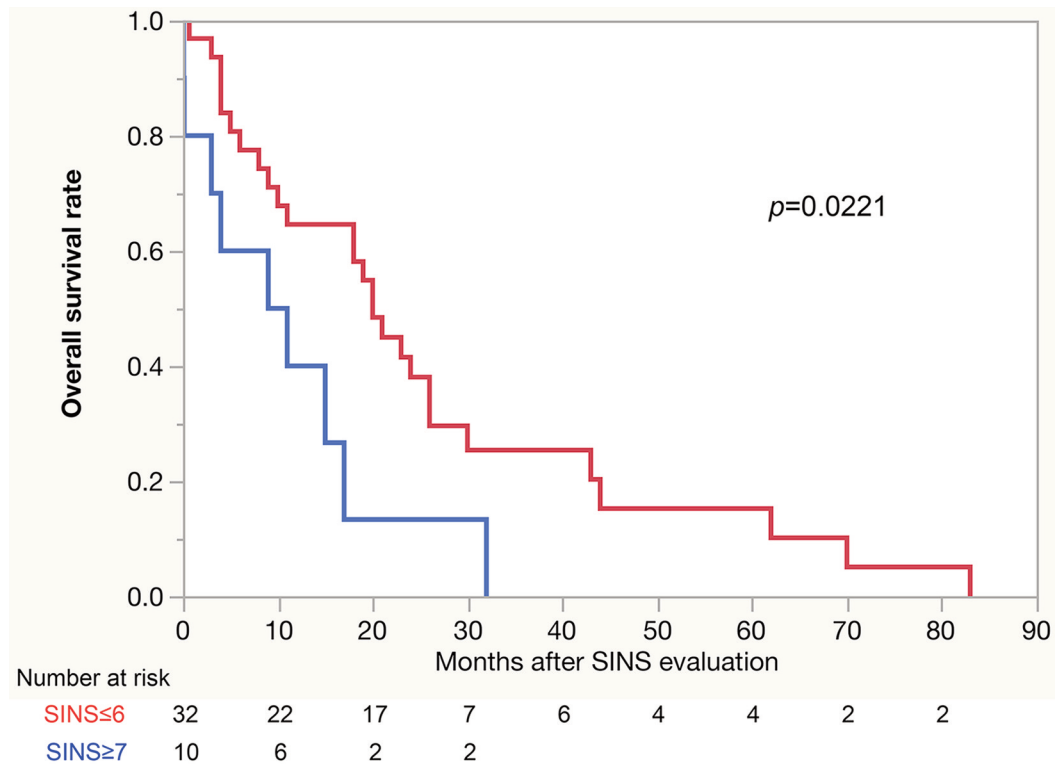


Figure 3. Kaplan-Meier curves showing probability of overall survival stratified by spinal instability.

neurosurgery and orthopedics departments, and not from analyses of all CRPC cases.

The major finding in this study was that spinal instability evaluated with SINS was an independent prognostic factor in patients with spinal metastasis of CRPC. EOD and BSI are conventionally used as indexes for quantitative measurement of tumor burden in the skeleton, whereas SINS reflects spinal instability caused by spinal metastasis, which is a different concept to that of EOD and BSI. In fact, no relationship between spinal instability and BSI was found in the current study (Figure 2, Table I). The number of subjects ($n=42$) was relatively small, but data were obtained from >42,000 whole body CT images collected at our hospital during a period of 32 months, and thus the bias is likely to be small. In addition, the findings were supported by multivariate analysis, which indicates the reliability of the results.

The study has several limitations, including its retrospective design, the long period from development of CRPC until SINS evaluation (median 20 months), and the wide variation in this period. Thus, the analysis included patients with highly advanced CRPC and those with newly developed CRPC. Next, SINS of the cohort was determined in a cross-sectional investigation. There was no difference in the periods from development of CRPC and diagnosis of bone metastasis to SINS evaluation for patients with and

without spinal stability, but the groups did not necessarily have the same background. Lastly, since the study was retrospective, treatment for CRPC was not selected based on strict criteria. During the study period, many new drugs, such as abiraterone acetate, enzalutamide, cabazitaxel and radium-223, were administered (7, 8, 25) and consistent treatment was not provided to all patients. The Liaison Treatment Team for Metastatic Spinal Tumors remains in place at our hospital, and this will facilitate a prospective study of the relationships among spinal instability and prognosis using SINS, spine treatment, and systemic treatment upon development of CRPC.

In conclusion, spinal instability was a prognostic factor in patients with spinal metastasis of CRPC, together with the PSA level and visceral metastasis. Spinal instability may be prevented by early intervention with radiotherapy with close observation and monitoring, and this may improve the prognosis. SINS is useful for clinical evaluation, planning of local and systemic treatments, and counseling of patients, and further studies of SINS are warranted.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Yoshiyuki Miyaji: Conceptualization; Formal analysis; Investigation; Visualization; Writing-original draft. Kazuo Nakanishi: Conceptualization; Investigation; Data curation; Methodology. Akira Yamamoto: Investigation; Data curation. Eisaku Yoden: Investigation. Ryuji Tokiya: Investigation. Makoto Okawaki: Investigation. Masayuki Inubushi: Investigation; Data curation. Kuniaki Katsui: Investigation; Supervision; Writing-review & editing.

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