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Prognostic comparison between osteoblastic and osteolytic metastases in prostate cancer

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Abstract: Over 80% of patients develop bone metastases in the advanced stages of prostate cancer, resulting in a poor prognosis. To date, no study has explored the relationship between the type of bone metastasis and patient outcomes. The objective of this study was to compare the clinical features and prognoses of patients with osteoblastic and osteolytic bone metastases. Among the 63 patients diagnosed with bone metastases from prostate cancer at our institution between May 2011 and September 2023, 51 were classified as having osteoblastic metastases and 12 as having osteolytic metastases based on imaging findings. Overall survival was analyzed using Kaplan–Meier survival curves, and differences between groups were assessed using the log-rank test. Clinical parameters were compared using the Mann–Whitney *U* test. Univariate and multivariate Cox proportional hazards analyses were conducted to identify the prognostic factors. No significant differences were observed between the osteoblastic and osteolytic groups in terms of clinical or laboratory parameters, except for a higher platelet count in the osteoblastic group ($p = 0.0181$). The five-year overall survival rate was significantly higher in the osteoblastic group than in the osteolytic group (49.5% *vs.* 30.0%, $p = 0.0437$), with median survival times of 59 months and 38.5 months, respectively. In both univariate and multivariate Cox analyses, the type of bone metastasis was the only factor significantly associated with increased hazard ratios. Patients with osteolytic bone metastases from prostate cancer have a markedly lower five-year overall survival than those with osteoblastic metastases.

***Keywords*:** bone metastases, osteoblastic, osteolytic, prostate cancer

1. Introduction

Prostate cancer (PCa) is the second most prevalent cancer among men, after lung cancer, and accounts for 3.8% of all cancer-related deaths, making it the fifth leading cause of cancer-related mortality worldwide. According to EUROCARE-5, the 5-year survival rate for patients with PCa diagnosed between 2003 and 2007 was 83% in Europe (*1*). In Japan, the five-year overall survival (OS) rate of patients treated with primary androgen deprivation therapy between 2001 and 2003 was 75.6% (*2*). Overall, these estimates indicate that the prognosis of PCa is relatively good.

However, the prognosis of patients with metastatic PCa remains poor. The adjusted 5-year OS rate for patients with metastatic castration-resistant PCa remained low at only 35% (95% confidence interval [CI]: 31–40%) between 2017 and 2020, showing only a modest increase from 26% (95% CI: 25–28%) between 2008 and 2012 (*3*). In advanced PCa, over 80% of patients develop metastases in the bone, reflecting the strong affinity of PCa for bone tissue (*4,5*). Notably, bone metastasis is recognized as an indicator of poor prognosis according to the Surveillance, Epidemiology, and End Results (SEER) database (*6*).

Depending on the roles of osteoblasts and osteoclasts in the formation of bone-metastatic lesions, bone metastases can be categorized into osteoblastic, osteolytic, or mixed types. Growth factors released by osteoclasts during bone resorption, including transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), bone morphogenetic protein (BMP), and platelet-derived growth factor (PDGF), promote osteoblast differentiation and induce bone formation. Tumor cells secrete osteoclast-activating factors, including macrophage colony-stimulating

factor (M-CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), and parathyroid hormone-related protein (PTHrP) to promote bone destruction. The balance of interactions between osteoclasts and osteoblasts determines the morphology of bone metastases (*7*).

While patients with a Gleason score (GS) ≥ 8 are reportedly more likely to develop osteolytic or mixed bone metastases compared with those with GS ≤ 7 (*8*), no previous research has explored the association between the bone metastasis types and the prognosis. Therefore, in this study, we classified patients with bone-metastatic PCa treated at our institution into osteoblastic, osteolytic, or mixed bone metastasis groups and compared their clinical features.

2. Patients and Methods

2.1. Patient selection and classification of bone metastases

We extracted patients from the medical records whose radiology reports contained the terms osteolytic metastasis or osteoblastic metastasis and seventy-four patients diagnosed with PCa with bone metastases at our hospital between May 2011 and September 2023 were included in this study. After excluding 11 patients with missing data, the clinical data of 63 patients were analyzed (Figure 1).

One of the excluded patients showed uptake on bone scintigraphy; however, bone metastasis from PCa was clinically ruled out. Another patient had been referred to our hospital for an unrelated condition, during which a CT scan incidentally revealed bone metastases from previously diagnosed and treated PCa at another institution. We did not treat PCa or metastasis ourselves, and no further clinical information was available. The third excluded patient was referred to our hospital for treatment but was lost to follow-up after the initial visit. Among the remaining eight cases, one was excluded from the analysis owing to the absence of PSA data at the time of bone metastasis diagnosis, two due to insufficient laboratory data aside from PSA, and the remaining five due to a lack of pathological findings.

Patients were categorized into one of the following groups based on bone scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) findings: osteoblastic, osteolytic, or mixed metastases. Of the 63 patients, 51 were classified as osteoblastic, 7 as osteolytic, and 5 as mixed-type.

Patients with mixed-type metastases were included in the osteolytic group to assess the impact of osteolytic metastasis on PCa. Consequently, 51 patients from the osteoblastic group and 12 patients from the osteolytic group were included in the analysis.

2.2. Ethical approval

Ethical approval for this study was obtained from the Institutional Review Board of NTT Medical Center Tokyo, which approved the researchs protocol (Approval No. 22-102). Informed consent was obtained from all participants through an opt-out method. All procedures were conducted in accordance with the principles of the Declaration of Helsinki (2013 revision).

2.3. Statistical analysis

OS was analyzed for 63 patients using Kaplan–Meier survival curves and the log-rank test. Clinical parameters, including age, prostate-specific antigen (PSA) levels, GS, and other laboratory test values, were compared between the osteoblastic and osteolytic groups using the Mann–Whitney *U* test.

To identify factors that influence the 5-year survival rate, both univariate and multivariate Cox proportional hazards analyses were performed. In the multivariate model, five clinically relevant variables were included: PSA level at the time of bone metastasis, International

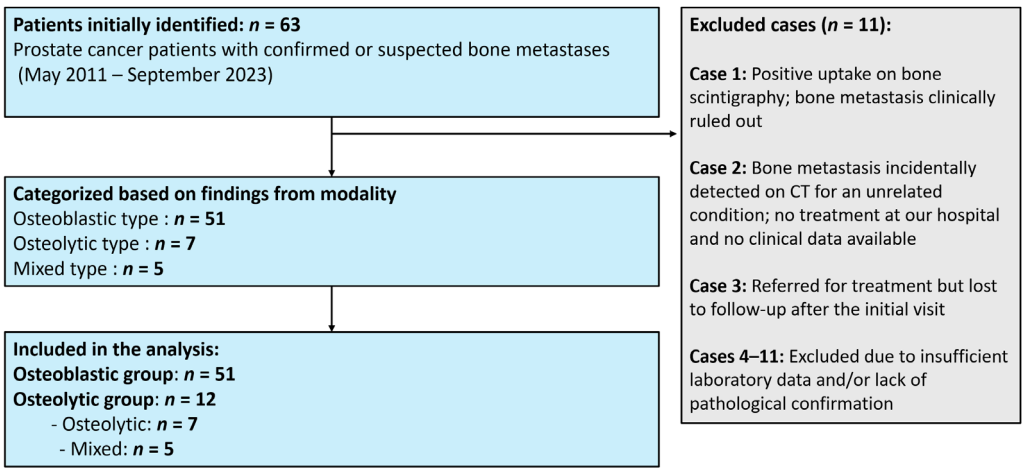


Figure 1. Inclusion and exclusion criteria of patient recruitment.

Society of Urological Pathology (ISUP) grade, extent of disease (EOD) score, age at bone metastasis, and bone metastasis type.

A total of 63 patients (51 with osteoblastic and 12 with osteolytic metastases) were analyzed, with 44 events observed. According to the commonly accepted event-per-variable (EPV) rule recommending at least 10 events per variable, the inclusion of four to five variables in the multivariate model was considered statistically appropriate and unlikely to result in model overfitting.

All the statistical analyses were performed using the EZR software. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical feature comparison

A total of 63 patients with bone-metastatic PCa were included in this study, with 51 (81.0%) classified as having osteoblastic lesions and 12 (19.0%) classified as having osteolytic or mixed lesions. There were no statistically significant differences in clinical parameters between the osteoblastic and osteolytic groups (Table 1).

In both groups, the median age at PCa diagnosis was 71 years. Likewise, there was no significant difference in the median age at bone metastasis between groups (71 and 73 years, respectively; $p = 0.269$). In both groups, a considerable number of patients had bone metastases at the time of PCa diagnosis. Furthermore, the interval between the diagnosis of PCa and bone metastasis did not differ significantly between the osteoblastic and osteolytic metastasis groups.

The median initial PSA level was 278 ng/mL in the osteoblastic group and 119.13 ng/mL in the osteolytic/mixed group ($p = 0.500$). PSA levels at bone metastasis were also similar between groups: 308 ng/mL in the osteoblastic group and 148.63 ng/mL in the osteolytic/mixed group ($p = 0.396$). The ISUP grade and clinical T stage distributions were similar between groups ($p = 0.672$ and 0.827, respectively).

Among laboratory parameters, platelet count was significantly lower in the osteolytic group than the osteoblastic group (median [interquartile range], 23.6 [19.65–30.15] *vs.* 18.75 [15.975–23.9] $\times 10^4/\mu L$, $p = 0.0181$).

3.2. Prognostic analysis

The five-year OS rate of patients with osteolytic metastases was notably lower than that of patients with osteoblastic metastases, at 30.0% (95% CI: 0.077–0.569) versus 49.5% (95% CI: 0.340–0.632), respectively ($p = 0.0437$). Furthermore, the median survival time was shorter in the osteolytic group, at 38.5 months (95% CI: 16–61 months), compared with 59 months (95% CI:

Table 1. Patient characteristics

Variables	Osteoblastic ($n = 51$)	Osteolytic ($n = 12$)	p-value
Age at diagnosis of PCa (years), median (IQR)	71 (66–74)	71 (67.5–76)	0.528
Age at bone metastases (years), median (IQR)	71 (67.5–75)	73 (69–78.25)	0.269
Initial PSA (ng/mL), median (IQR)	278 (32.4565–1240)	119.13 (55.175–381.75)	0.500
PSA at bone metastases (ng/mL), median (IQR)	308 (47.3065–1240)	148.63 (55.175–381.78)	0.396
ISUP Grade groups			0.672
Grade group 1–3, *n* (%)	5 (9.8%)	1 (8.3%)	
Grade group 4, *n* (%)	11 (21.6%)	2 (16.7%)	
Grade group 5, *n* (%)	35 (68.6%)	9 (75.0%)	
Clinical stage			
T stage			0.879
≤ cT2, *n* (%)	11 (21.6%)	3 (25.0%)	
T3, *n* (%)	27 (52.9%)	5 (41.7%)	
T4, *n* (%)	13 (25.4%)	4 (33.3%)	
N stage			0.769
N0, *n* (%)	23 (45.1%)	6 (50.0%)	
N1, *n* (%)	28 (54.9%)	6 (50.0%)	
EOD			0.0713
EOD1, *n* (%)	13 (25.5%)	2 (16.7%)	
EOD2, *n* (%)	13 (25.5%)	10 (83.3%)	
EOD3, *n* (%)	22 (43.1%)	0 (0%)	
EOD4, *n* (%)	3 (5.9%)	0 (0%)	
Laboratory findings at bone metastases			
LDH (IF) (IU/L), median (IQR)	202 (172.5–276)	196 (183.5–212)	0.436
ALP (IU/L), median (IQR)	459 (236.5–1100)	378.5 (270–574.5)	0.575
Ca (mg/dL), median (IQR)	9.2 (8.9–9.4)	9.4 (9.2–9.65)	0.0754
Alb (g/dL), median (IQR)	4.1 (3.7–4.3)	4.3 (4.075–4.425)	0.143
Hb (g/dL), median (IQR)	12.9 (11.75–14.5)	14.15 (12.575–15.9)	0.123
Plt ($\times 10^4/\mu L$), median(IQR)	23.6 (19.65–30.15)	18.75 (15.975–23.9)	0.0181

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; Hb, hemoglobin; EOD, extent of disease; ISUP, International Society of Urological Pathology; IQR, interquartile range; LDH, lactate dehydrogenase; PCa, prostate cancer; Plt, platelets; PSA, prostate-specific antigen.

41–115 months) in the osteoblastic group (Figure 2).

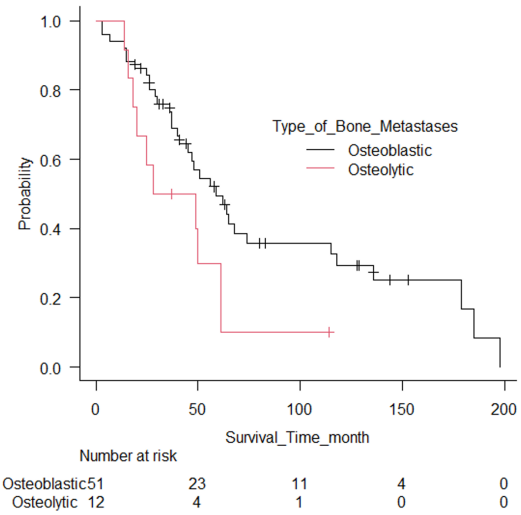
3.3. Results of Cox proportional hazards analyses

In the univariate Cox proportional hazards analysis, only bone metastasis type was significantly associated with OS (hazard ratio [HR] = 2.079; 95% CI: 1.002–4.317; p = 0.050) (Table 2).

A multivariate Cox proportional hazards analysis was performed, incorporating five clinically relevant factors: PSA level at the time of bone metastases, ISUP grade group, EOD, age at bone metastases, and bone metastases type. Consistent with the univariate analysis, only the bone metastasis type remained significantly associated with OS (HR = 2.334; 95% CI: 1.024–5.320; p = 0.044) (Table 2).

4. Discussion

Although osteoblastic lesions are typically observed in bone-metastatic PCa, bone formation (osteoblastic activity) and bone resorption (osteoclastic activity) coexist, with osteoclasts playing a critical role (*9*). Initially, bone metastases predominantly exhibit osteolytic activity, leading to bone destruction. The degradation process promotes tumor cell proliferation



Metastasis Type	*n*	5-YeaSurvival Rate	95% CI	Median Survival (months)	95% CI	*p* value
Osteoblastic	**51**	**0.495**	**0.340–0.632**	**59**	**41–115**	**0.0437**
Osteolytic	**12**	**0.3**	**0.077–0.569**	**38.5**	**16–61**	**–**

Figure 2. Kaplan–Meier curve for overall survival. The five-year overall survival rate was significantly higher in the osteoblastic group than in the osteolytic group.

Table 2. Univariate and multivariate analyses

Variable	Univariate HR (95% CI)	*p*-value	Multivariate HR (95% CI)	*p*-value
Age at diagnosis of PCa (years)	1.023 (0.974–1.073)	0.369	–	–
PSA at diagnosis of PCa (ng/mL)	1.000 (0.9997–1.000)	0.793	–	–
Age at bone metastases (years)	1.040 (0.990–1.093)	0.118	1.578 (0.795–3.13)	0.192
PSA at bone metastases (ng/mL)	1.000 (0.9998–1.000)	0.842	0.685 (0.345–1.363)	0.281
EOD score	1.042 (0.748–1.453)	0.807	1.644 (0.769–3.514)	0.2
ISUP Grade Group	1.189 (0.763–1.853)	0.444	1.051 (0.378–2.921)	0.925
T stage	0.843 (0.554–1.283)	0.426	–	–
N stage	0.767 (0.420–1.399)	0.387	–	–
Albumin at bone metastases (g/dL)	0.881 (0.549–1.414)	0.6	–	–
ALP at bone metastases (IU/L)	1.000 (1.000–1.001)	0.068	–	–
Hemoglobin at bone metastases (g/dL)	0.935 (0.803–1.088)	0.385	–	–
LDH at bone metastases (IU/L)	1.002 (0.9995–1.004)	0.133	–	–
Platelet count at bone metastases ($\times 10^4/\mu L$)	1.008 (0.973–1.045)	0.666	–	–
Corrected calcium at bone metastases (mg/dL)	1.008 (0.454–2.239)	0.984	–	–
Bone metastasis type (Osteolytic *vs.* Osteoblastic)	2.079 (1.002–4.317)	0.05	2.334 (1.024–5.32)	0.044

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; EOD, extent of disease; HR, hazard ratio; ISUP, International Society of Urological Pathology; LDH, lactate dehydrogenase; PCa, prostate cancer; Plt, platelets; PSA, prostate-specific antigen.

and stimulates osteoblast activation by releasing growth factors, such as TGF-β. This cascade initiates subsequent osteoblastic responses and new bone formation (*10*).

While RANKL-dependent signaling is predominant during the initial formation of bone metastases, subsequent progression may be driven by inflammatory signaling pathways involving factors such as interleukin (IL)-1β. For example, the expression of IL-1β is implicated in the progression of bone metastases (*11*) and promotes osteoclast differentiation and activation *via* RANKL-independent pathways (*12*). Osteoclasts co-cultured with PCa cells were shown to exhibit resistance to denosumab, accompanied by the activation of inflammatory signaling pathways (*13*). This mechanism aligns with clinical observations that denosumab prolongs the time to bone metastasis but does not improve OS (*14*). IL-1β–mediated activation of these pathways may lead to excessive osteoclast activity, thereby inhibiting the transition from bone resorption to bone formation, and clinically manifesting as an osteolytic metastatic phenotype.

In this cohort of patients with PCa and bone metastases, patients with osteolytic metastases exhibited a poorer prognosis than those with osteoblastic metastases. Although not statistically significant, patients with osteoblastic metastases tended to present with higher EOD scores at the time of diagnosis. Accordingly, osteolytic metastases may have a detrimental impact on survival, even when the extent of bone involvement is relatively limited.

A previous study reported that patients with osteolytic bone metastases more frequently presented with a GS of > 8 (*9*). In our cohort, we detected no statistically significant differences in GS between the two groups. Nevertheless, the association between osteolytic metastases and poor prognosis identified in this analysis was consistent with that reported in a previous study.

Notably, platelet counts were substantially lower in patients with osteoblastic metastasis. An increased platelet-to-lymphocyte ratio (PLR) may reflect systemic inflammation and cancer-related immunosuppression, both associated with poor prognosis (*15*). Interestingly, our results demonstrated the opposite trend in platelet counts, warranting further investigation.

The limitations of this study should be acknowledged. First, the relatively small sample size and the heterogeneity of treatment strategies among patients may have affected the robustness of the findings. To obtain more reliable and generalizable results, further studies with larger cohorts are warranted. Second, the diagnosis of bone metastases was evaluated qualitatively rather than quantitatively, and was not performed by a single radiologist; instead, different radiologists were involved, and the imaging modalities were not uniform, including bone scintigraphy, CT, and MRI examinations. Moreover, bone scintigraphy may have underestimated osteolytic metastases, and the potential impact of this limitation on the results cannot be excluded. Given that fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) reportedly has high sensitivity for detecting osteolytic metastases (*16*), a more accurate assessment may require PET-CT. Recent investigations have demonstrated favorable sensitivity and specificity of prostate-specific membrane antigen positron emission tomography/CT (PSMA-PET/CT) and MRI for detecting bone metastases (*17*). These modalities are expected to facilitate more comprehensive and accurate assessment.

Nonetheless, comparing survival outcomes based on the bone metastasis type in a real-world setting provides valuable insights.

In conclusion, our findings suggest that the presence of osteolytic metastases could serve as a prognostic factor for PCa. Given the relevance of IL-1β to resistance against docetaxel chemotherapy in patients with PCa (*18*), IL-1β overexpression, osteolytic bone metastases, and poor prognosis may be interrelated. Current risk stratification models, such as the high-risk/high-volume classification, do not account for the morphological characteristics of bone metastases. Incorporating the type of skeletal involvement may improve the accuracy of future risk classifications. This underscores the need for further research on the prognostic importance of the metastatic bone types in patients with PCa.

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