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ORIGINAL ARTICLE

Skeletal-related events and prognosis in urothelial cancer patients with bone metastasis

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Abstract
Background The aim of the present study was to elucidate the details of bone metastasis (BM) and the resulting skeletal-related events (SREs), and survival and prognostic factors, in urothelial cancer (UC) patients with BM.
Methods A total of 48 UC patients with BM who were treated at our institution between 1994 and 2013 were enrolled. Details of BM and SREs were investigated. The Kaplan–Meier method was used to estimate survival duration. Relationships between several clinical features and survival were analyzed using the log-rank test and the Cox hazard model.
Results Of the 48 patients, 39 (81.3%) were male, with a median age at diagnosis of BM of 68 years [interquartile range (IQR), 61–75 years]. Frequent metastatic sites included the pelvis (31 patients, 64.6%) and spine (28, 58.3%). SREs occurred in 31 patients (64.6%) at a median duration of 0.9 months (IQR, 0.3–5.4 months) after diagnosis of BM, including radiation therapy ($n = 23$; 74.2%), spinal cord compression ($n = 4$; 12.9%), pathological fracture ($n = 3$; 9.7%) and hypercalcemia ($n = 1$; 3.2%). Median overall survival periods after diagnosis of BM and SREs were 6.2 and 5.6 months, respectively. On multivariate analysis, factors significantly associated with survival after BM were performance status [hazard ratio (HR) for ≥2 vs. 0–1, 4.94; $P = 0.0003$], liver metastasis (HR, 4.08; $P = 0.0018$), chemotherapy after BM (HR, 0.31; $P = 0.0018$), and use of bone-modifying agents (HR, 0.36; $P = 0.0147$).
Conclusions We revealed clinicopathological factors that are predictive of prognosis of UC patients with BM. Although the prognosis is poor, chemotherapy and bone-modifying agents may confer survival benefits.

Keywords Skeletal-related event · Bone metastasis · Urothelial cancer

Introduction

Urothelial cancer (UC) arises from urothelium of the urinary bladder, renal pelvis, ureter, and urethra. Among these, UC of the bladder is the most common, with an estimated 429,793 new cases and 165,084 deaths worldwide in 2012 [1]. Metastatic UC is known to be intractable, and even after the introduction of cisplatin-based chemotherapy, the median survival still remains less than 15 months [2, 3].

Several studies have shown that bone metastasis (BM) is common in patients with UC [4, 5]. Patients with BM are at risk of skeletal-related events (SREs), including pathological fracture, spinal cord compression, surgery for BM, radiation therapy for BM, and hypercalcemia. SREs are significantly correlated with immobilization, loss of independence, poor quality of life, and reduced survival [6]. However, little is known about the demographics of BM and its sequelae in terms of SREs and prognosis in patients with UC. Increased understanding of SREs, survival period,

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Table 1 Patient characteristics

	Number	Percent (%)
Age at diagnosis of BM, years (median, IQR)	68	(61–75)
Sex		
Male	39	81.2
Female	9	18.8
Primary site		
Urinary bladder	31	64.6
Upper urinary tract	17	35.4
Histological grade		
2	8	16.7
3	36	75.0
Unknown	4	8.3
Surgery for primary site		
Radical cystectomy	27	56.2
Nephroureterectomy	12	25.0
None	9	18.8
Chemotherapy before BM		
Yes	26	54.2
No	22	45.8
BM was the initial metastasis		
Yes	25	52.1
No	23	47.9

BM bone metastasis, *IQR* interquartile range

Table 2 Details of bone metastasis and skeletal-related events

	Number	Percent (%)
Symptom on diagnosis of BM		
Pain	26	54.2
Paralysis	4	8.3
No	18	37.5
Location of BM		
Pelvis	31	64.6
Spine	28	58.3
Rib	10	20.8
Femur	6	12.5
Humerus	3	6.3
Clavicle	3	6.3
Tibia	2	4.2
Sternum	1	2.1
Scapula	1	2.1
Multiple bone metastases		
Yes	26	54.2
No	22	45.8
Character of BM		
Osteolytic	32	66.7
Osteoblastic	5	10.4
Mixed	8	16.7
Unknown	3	6.2
SREs		
Yes	31	64.6
No	17	35.4
Type of first SREs		
Radiation therapy	23	74.2
Spinal cord compression	4	12.9
Pathological fracture	3	9.7
Surgery	0	0.0
Hypercalcemia	1	3.2
Location of first SREs		
Pelvis	16	48.5
Spine	15	45.5
Femur	1	3.0
Tibia	1	3.0
Second SREs		
Yes	13	41.9
No	18	58.1

BM bone metastasis, *SREs* skeletal-related events

and prognostic factors in UC patients with BM would help physicians to decide on appropriate treatment options.

The aim of the present study was to elucidate the details of BM and SREs and to evaluate survival and prognostic factors in UC patients with BM.

Patients and methods

Study design

This is an institutional review board-approved (#3124) retrospective study. Medical records of UC patients who were treated at our institution between 1994 and 2013 were reviewed, and those who had radiologically proven BM during their disease course were identified. Clinicopathological data were collected via chart review. SREs were defined as follows: radiation therapy for BM, surgery for BM, spinal cord compression by BM, pathological fracture, or hypercalcemia. Relevant X-ray and/or computed tomography images were reviewed by two orthopedic surgeons (Y.T. and Y.S.), and BM lesions were classified as osteolytic, osteoblastic, or mixed metastasis.

Histological confirmation of BM was not mandated in our study, although previous studies by Shinagare et al. [7, 8] followed very precise methodology by only including the patients with biopsy-proven metastatic lesions.

Statistical analysis

The Kaplan–Meier method was used to estimate survival duration. Potential prognostic factors were identified by

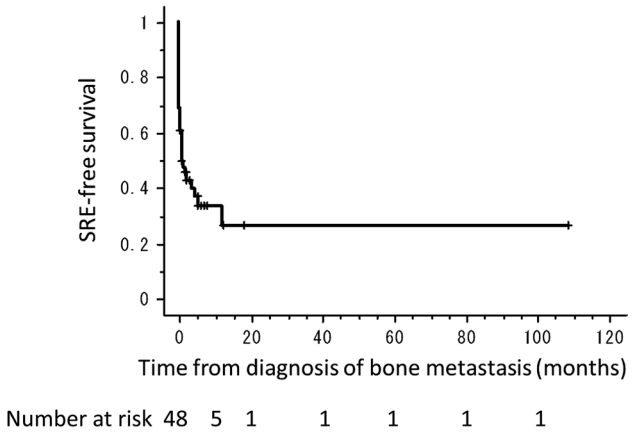

Fig. 1 Skeletal-related event (SRE)-free survival of urothelial cancer patients with bone metastasis

univariate analyses using the log-rank test. Variables with *P* values <0.05 in the univariate analyses were entered into a multivariate Cox proportional hazards model. The final model was performed using a stepwise backward selection method. All tests were two sided, and *P* values <0.05 were considered statistically significant. SPSS version 22.0 (IBM, Armonk, NY, USA) was used for all analyses.

Results

Patient demographics

Of the 141 metastatic UC patients who were treated at our institute, we identified 48 patients (34.0%) who had BM during their course of illness. Table 1 shows patient demographics. The median age of patients at diagnosis of BM was 68 years [interquartile range (IQR), 61–75 years], and 39 (81.2%) patients were male. Primary sites were urinary bladder in 31 (64.6%) and upper urinary tract in 17 (35.4%). A total of 39 patients underwent radical surgery (radical cystectomy or nephroureterectomy) and subsequently developed metastasis, and the remaining 9 patients had distant metastasis on initial diagnosis. Notably, 25 patients developed BM as an inaugural manifestation of metastasis, whereas BM was detected after the diagnosis of other metastasis in the remaining 23 patients.

Characteristics of BM and SREs

Symptom-triggered examinations revealed BM in 30 patients; in the remaining 18 patients, BM was detected incidentally via routine periodical imaging studies for post-surgical follow-up or during chemotherapy (Table 2). On initial diagnosis of BM, 22 patients (45.8%) had a solitary BM lesion and 26 (54.2%) exhibited multiple BM. The pelvis was the most frequent site of BM (31 cases; 64.6%), followed by the spine in 28 cases (58.3%) and ribs in 10 cases (20.8%). BM was predominantly osteolytic (32 cases; 66.7%), followed by osteoblastic (5 cases; 10.4%) and mixed (8 cases; 16.7%).

Of the 48 patients, SREs occurred in 31 (64.6%). The median time from BM diagnosis to the development of first SREs was 0.9 months (IQR, 0.3–5.4 months) (Fig. 1). Spinal cord compression, pathological fracture, and hypercalcemia triggered the detection of BM in 3, 1, and 1 patients, respectively. A total of 18 patients received radiation therapy for BM within 1 month of diagnosis.

The most common first SRE was radiation therapy for BM in 23 (74.2%) patients, followed by spinal cord compression in 4 (12.9%), pathological fracture in 3 (9.7%), and hypercalcemia in 1 (3.2%). Of the patients with spinal cord compression, 1 patient presented with motor and sensory dysfunction graded as Frankel C and 3 patients presented with Frankel D [9]. Pathological fractures occurred in the pelvis and thoracic spine; however, no patients underwent surgery for BM. A total of 13 patients (43.3%) developed second or further SREs during their clinical course; the rate of SREs in the UC patients with BM was 1.07/patient/year. A total of 10 patients

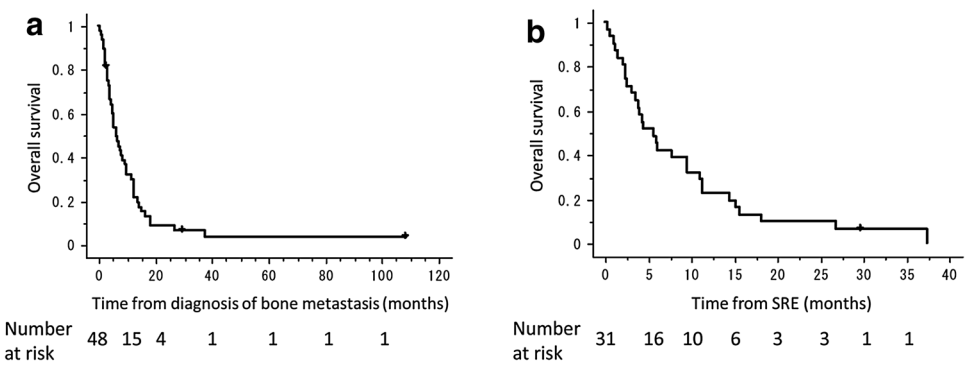

Fig. 2 Overall survival of urothelial cancer patients with bone metastasis after diagnosis of bone metastasis (**a**) and after development of skeletal-related events (**b**)

Table 3 Univariate analyses of risk factors for survival after bone metastasis

	Number	MST (months)	95% CI	*P* value
Sex				
Male	39	7.1	3.9–9.9	0.632
Female	9	5.3	1.9–14.5	
Age (years)				
<70	27	8.3	4.8–12.4	0.363
≥70	21	5.3	2.3–8.1	
PS				
<1	36	8.3	5.5–12.4	0.001
≥2	12	3.2	1.2–4.8	
Symptom				
Yes	30	5.4	3.9–9.9	0.8826
No	18	8.1	3.3–12.5	
Time to BM[a]				
≥1 year	23	8.1	4.1–12.7	0.177
<1 year	25	5.3	3.5–9.5	
Time to any metastasis				
≥1 year	14	11.3	4.1–18.4	0.042
<1 year	34	5.3	3.5–7.4	
Number of BM				
1	22	9.7	5.2–12.7	0.161
≥2	26	4.7	3.1–7.1	
Character of BM				
Osteoblastic	5	2.3	1.0–13.7	0.090
Osteolytic or mixed	40	7.1	4.8–9.9	
Visceral metastasis				
Yes	25	5.3	3.3–9.7	0.257
No	23	8.3	4.1–12.5	
Number of metastatic organs				
0–1	39	8.1	5.1–11.6	0.007
≥2	9	3.9	0.6–5.5	
Lung metastasis				
Yes	20	5.4	3.3–12.5	0.900
No	28	6.9	4.1–11.6	
Liver metastasis				
Yes	11	3.3	1.0–5.2	<0.0001
No	37	9.5	5.3–12.5	
SREs				
Yes	31	7.4	4.1–11.6	0.500
No	17	5.5	2.1–8.1	
Alkaline phosphatase				
<ULN	19	9.9	3.9–12.7	0.071
≥ULN	29	5.2	3.3–7.1	
C-reactive protein				
<2.5 mg/dl	35	9.5	5.5–12.5	<0.0001
≥2.5 mg/dl	13	3.3	1.2–4.8	
Hemoglobin				
<LLN[b]	34	5.9	3.5–9.7	0.234
≥LLN[b]	14	6.9	4.1–13.7	
Leukocyte counts				
<8000/μl	34	6.8	4.8–9.9	0.629
≥8000/μl	14	3.9	2.1–12.4	
eGFR				
<60 ml/min/1.73 m^2	29	8.1	3.9–9.9	0.532
≥60 ml/min/1.73 m^2	19	5.5	3.5–11.6	
Chemotherapy after BM				
Yes	26	11.6	6.1–15.2	<0.0001
No	22	3.7	2.1–6.2	
Bone-modifying agents				
Yes	10	15.8	4.5–26.9	0.003
No	38	5.2	3.5–7.4	

MST median survival time, *CI* confidence interval, *PS* performance status, *BM* bone metastasis, *SREs* skeletal-related events, *ULN* upper limit of normal, *LLN* lower limit of normal, *eGFR* estimated glomerular filtration rate

[a] Time to BM and time to any metastasis were calculated from the date of radical cystectomy or nephroureterectomy, or determined as 0 for the cases with metastasis on initial presentation

[b] 13 g/dl for males and 11 g/dl for females

(20.8%) received bone-modifying agents, 7 patients received zoledronic acid, and 3 patients received denosumab.

Survival and prognostic factors

Of the 48 patients, 45 died during follow-up. The median survival time (MST) was 6.2 months (IQR, 4.5–9.5) after diagnosis of BM, and 5.6 months (IQR, 3.1–9.6) after SREs, respectively (Fig. 2a, b). In the univariate analyses, factors significantly associated with shorter overall survival (OS) after diagnosis of BM included poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) (PS ≥2; $P = 0.001$), time from radical surgery to any remote metastasis (<1 year; $P = 0.042$), two or more metastatic organs in addition to BM ($P = 0.007$), liver metastasis ($P < 0.0001$), high serum C-reactive protein level (≥2.5 mg/dl; $P < 0.0001$), no chemotherapy after diagnosis of BM ($P < 0.0001$), and no bone-modifying agents ($P = 0.003$) (Table 3). Distribution of chemotherapy regimens is shown in the Supplementary table. Presence or absence of symptoms and the location of BM were not associated with OS. On multivariate analysis, independent predictors of OS included PS ≥2 [hazard ratio (HR), 4.94; $P = 0.0003$], liver metastasis (HR 4.08; $P = 0.0018$), chemotherapy after diagnosis of BM (HR 0.31; $P = 0.0018$), and bone-modifying agents (HR 0.36; $P = 0.0147$) (Table 4). Figure 3 presents Kaplan–Meier estimates of the survival of patients with or without bone-modifying agents.

Table 4 Multivariate analysis of risk factors for survival after bone metastasis

	Hazard ratio (95% CI)	*P* value
PS		0.0003
≤1	Referent	
≥2	4.94 (2.13–11.22)	
Liver metastasis		0.0018
No	Referent	
Yes	4.08 (1.72–9.52)	
Chemotherapy after BM		0.0018
No	Referent	
Yes	0.31 (0.15–0.65)	
Bone-modifying agents		0.0147
No	Referent	
Yes	0.36 (0.14–0.82)	

CI confidence interval, *PS* performance status, *BM* bone metastasis

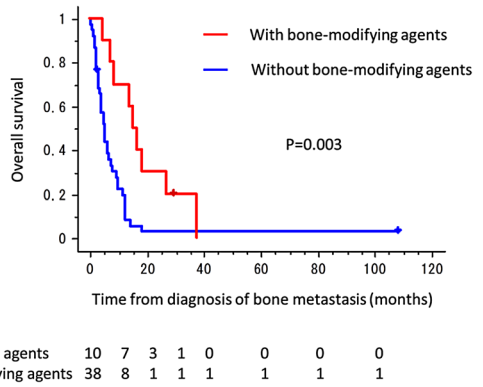

Fig. 3 Overall survival of urothelial cancer (UC) patients with bone metastasis who did or did not receive bone-modifying agents

Discussion

The details of SREs and survival/prognostic factors in UC patients with BM are yet to be fully elucidated, although previous studies have reported a 20–47% incidence of BM in metastatic UC patients [3–5, 7, 8]. The present study showed that the frequent sites of BM were the pelvis and spine, and that the lesions were predominantly osteolytic (66.7%), followed by osteoblastic (10.4%) and mixed (16.7%). Notably, the majority of BM from renal cell carcinoma and prostate cancer is osteolytic [10] and osteoblastic [11], respectively. Not consistent with these other urological cancers, our data demonstrated that BM from UC had varying characteristics.

The rate of SREs in our study was 64.6%, and the most frequent SREs were radiation therapy for BM. Yokomizo et al. reported that the rates of SREs in bladder, renal pelvic, and ureteral cancer were 39–68% and that radiation therapy was the most frequent cause [12]. The high prevalence and distribution of SREs shown in previous studies and our data indicate the need for careful observation for BM in UC patients, particularly in the pelvis and spine. Furthermore, the median time from diagnosis of BM to the development of the first SRE was only 0.9 months. These data suggest that the diagnosis of BM in UC patients should warrant immediate attention and close follow-up.

Estimation of survival is critical when orthopedic oncologists are deciding on treatment options for BM, such as radiation therapy or more invasive surgery. However, the OS of UC patients with BM has not been reported previously. We showed that the MST of UC patients with BM was as poor as 6.2 months.

Number, characteristics, and location of BM were not associated with survival in the present study. On the other hand, we identified poor PS, liver metastasis, no chemotherapy after BM, and no bone-modifying agents as independent predictors of poor prognosis. PS has been reported as an important prognostic factor in patients with BM from various types of cancer [13, 14]. Liver metastasis was reported as the most powerful prognostic factor in metastatic UC [15]. On the other hand, chemotherapy after diagnosis of BM or bone-modifying agents may extend survival duration. In fact, zoledronic acid was shown to prevent second SREs and extend survival in bladder cancer patients with BM [16]. Emerging evidence has suggested that zoledronic acid or denosumab, a fully human anti-RANKL monoclonal antibody, may not only impede the development of SREs but may thereby prolong OS in cases of several solid tumors and multiple myeloma [17, 18]. The mechanism responsible for this additional clinical benefit of zoledronic acid has been assessed in cell cultures and animal models of human cancer, and direct and indirect anticancer activity has been demonstrated [19, 20]. Further study is required to evaluate the effect of these drugs on the duration of survival.

What is the role of orthopedic physicians in the management of metastatic UC patients? There is limited scope for surgical management of BM. Therefore, what about the early diagnosis of BM? In the present study, 22 of 48 patients did not undergo systemic chemotherapy after the diagnosis of BM. Systemic chemotherapy is the standard treatment for metastatic UC, and was seen to confer a survival advantage in our cohort. Although the reason why these patients did not undergo chemotherapy was not always known in our retrospective chart review, 13 of 22 patients without chemotherapy had symptomatic BM,

and its prompt diagnosis and proper treatment may have improved the general condition of the affected patients and increased their chance of receiving chemotherapy. Treatment of patients with metastatic solid cancers involves a multidisciplinary approach. Orthopedic physicians may have an active role in the management of metastatic UC not only by treating BM but also by assisting in its early diagnosis and prompt care.

The present study has several limitations. First, this is a retrospective study with a small sample size. Second, asymptomatic bone metastases may not be detected during the clinical course, and the incidence of BM may be underestimated. Diagnostic modality varied, and whole-body bone scintigraphy was not consistently used. Imaging modalities would be used less often after terminating standard chemotherapy. Third, pathological confirmation of BM was lacking, with the exception of the two patients who underwent autopsy.

In conclusion, our study clarified the details of BM and SREs and the survival and prognostic factors in UC with BM. We believe that these data may help physicians to better evaluate and treat UC patients with BM.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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