Original Article

Oncologic emergency in patients with skeletal metastasis of unknown primary

Tomoaki Torigoe,[1] Jungo Imanishi,[1] Yasuo Yazawa,[1] Tadaaki Koyama,[2] Yuho Kadono,[3] Hiromi Oda,[3] and Kazuo Saita[4]

[1]Department of Orthopedic Oncology and Surgery, Saitama Medical University International Medical Center, Hidaka, [2]Division of Orthopedic Oncology, Shizuoka Cancer Center Hospital, Nagaizumi, [3]Department of Orthopedic Surgery, Saitama Medical University, Moroyama, and [4]Department of Orthopedic Surgery, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Aim: Patients with skeletal metastasis from prediagnosed primary malignancy sometimes have concurrent oncologic emergency (OE) during the first visit. This study aims to investigate the types of OEs and treatment outcome in such patients.

Methods: We have experienced 359 patients with skeletal metastasis from unknown primary malignancy. Among them, 130 patients required immediate admission for OE treatment (OE group), 229 patients had no OE and did not required immediate admission (non-OE group).

Results: The recognized types of OE were spinal cord compression in 60 patients, cancer pain in 30, hypercalcemia in 19, delirium in 16, deep vein thrombosis in 13, acute renal failure in 6, respiratory failure in 3, gastrointestinal hemorrhage in 3, and disseminated intravascular coagulation in 1. The overall 5-year survival rates were 28% and 37% in the OE and non-OE groups, respectively ($P < 0.001$). The multivariate analysis revealed that delirium (hazard ratio 4.2; 95% confidence interval, 1.6–12.5; $P < 0.005$) and respiratory failure (hazard ratio 22.6; 95% confidence interval, 4.5–92.8; $P < 0.001$) were significant prognostic factors in patients with OEs, whereas other OEs did not confer a significant risk for patient outcomes.

Conclusion: In this study, OE was observed in as many as 36% of patients with skeletal metastasis from unknown primary malignancy. Delirium and respiratory failure were only two significant prognostic risk factors, which suggest that many of the OEs in untreated advanced cancer patients have probable chance to resolve. Early detection followed by appropriate treatment of such OEs is recommended.

Key words: Oncologic emergency, prognosis, skeletal metastasis, unknown primary malignancy

INTRODUCTION

ONCOLOGIC EMERGENCY (OE), which is related to cancer or cancer-related treatment,[1] are pathological conditions that can cause irreversible dysfunction within several hours to days after onset and lead to early death. The causes of OE are diverse and can be classified into the following nine categories based on the 2016 edition of the European Society for Medical Oncology (ESMO) Handbook of Oncology Emergencies: cardiovascular, neurological, urological, metabolic, respiratory, gastrointestinal, immunohematological, psychological, and cancer pain.[2] Bone is a common site of cancer metastasis, and metastatic bone tumors develop much more frequently than primary malignant tumors, especially in middle-aged and elderly patients.[3] Bone metastasis is the first manifestation of cancer in 25%–30% of patients with cancer of unknown primary malignancy; these patients are already in the advanced stage of cancer during their first medical consultation and there is a possibility of complication with OE.[4] In the present study, we investigated the types and incidence rates of OE, treatment outcome, and their prognostic impact on patients with skeletal metastasis of unknown primary malignancy.

Corresponding: Tomoaki Torigoe, MD, PhD, Department of Orthopedic Oncology and Surgery, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka City, Saitama 350-1298, Japan. E-mail: ttorigoe@saitama-med.ac.jp

Received 5 Aug, 2020; accepted 16 Oct, 2020

Funding information

No funding information provided.

METHODS

FOR THIS RETROSPECTIVE study, data were extracted from the medical records of 1,003 patients

with skeletal metastasis as the initial diagnosis who visited our department between July 2008 and July 2017. Bone biopsy and histopathological examination revealed eight cases of primary bone sarcoma (three angiosarcomas, two osteosarcomas, two undifferentiated pleomorphic sarcoma, and one leiomyosarcoma), which were excluded from this study. Among 995 patients with metastatic bone tumors, 359 patients who had no history of cancer or existing cancer were referred to our hospital; all 359 patients were provisionally diagnosed with skeletal metastasis of unknown primary malignancy during their first visit to our institution. The remaining 636 patients who had a history of cancer or had existing cancer during the first visit were excluded.

Oncologic emergency was diagnosed on the basis of the ESMO classification. Each OE in this study was defined as follows. Spinal cord compression was defined as progressive paralysis due to spinal metastasis with spinal cord compression detected by computed tomography (CT) and/or magnetic resonance imaging.[5] Cancer pain was defined as pain in patients with cancer that required hospitalization for pain control.[6] Hypercalcemia was defined as elevated serum calcium levels of ≥10.6 mg/dL and was corrected in case of hypoalbuminemia. Delirium, a consciousness disorder, was diagnosed according to all four criterions of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) as follows: (i) disturbance of consciousness with reduced ability to focus, sustain, or shift attention, (ii) change in cognition or development of a perceptual disturbance that is not accounted for by a preexisting, established, or evolving dementia, (iii) disturbance that develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day, (iv) evidence from history, physical examination, or laboratory findings that the disturbance is due to direct physiological consequences of a general medical condition.[7] Deep venous thrombosis (DVT) was defined as a thrombosis in the vein deeper than the fascia and diagnosed by venous ultrasonography or contrast-enhanced CT. Acute renal failure was defined according to the Risk Injury Failure Loss ESRD (RIFLE) criteria; ≥50% increase in serum creatinine or ≥25% decrease in estimated glomerular filtration rate from the normal levels.[8] Respiratory failure was defined as <60 Torr PaO_2.[9] Disseminated intravascular coagulation (DIC) was diagnosed according to the criteria of the Japanese Ministry of Health and Welfare[10] (Fig. 1).

Approval for the study was obtained from the ethics committee of the Saitama Medical University International Medical Center before study initiation.

In this cohort, 130 patients presented with OE and required emergency hospitalization for immediate OE treatment (OE group), whereas 229 patients without OE were examined at the outpatient clinic and systematically hospitalized for primary cancer treatment and skeletal metastasis (non-OE group). The OE group was comprised of 81 men and 49 women, with a mean age of 67.5 ± 11.2 (range, 35–93) years, and the mean follow-up period was 12 ± 17.3 (range, 1–86) months. The non-OE group was comprised of 144 men and 85 women, with a mean age of 67.5 ± 11.0 (range, 22–93) years, and the mean follow-up period was 17 ± 19.3 (range, 1–89) months.

Primary malignancy was detected by whole body CT scans, positron emission tomography scans, blood examination, including tumor markers, serum and urine immune electrophoresis, and gastric and colon fiberscopy. In case the primary cancer could not be detected by these examinations, bone biopsy from metastatic bone tumor and histopathological examination was carried out.

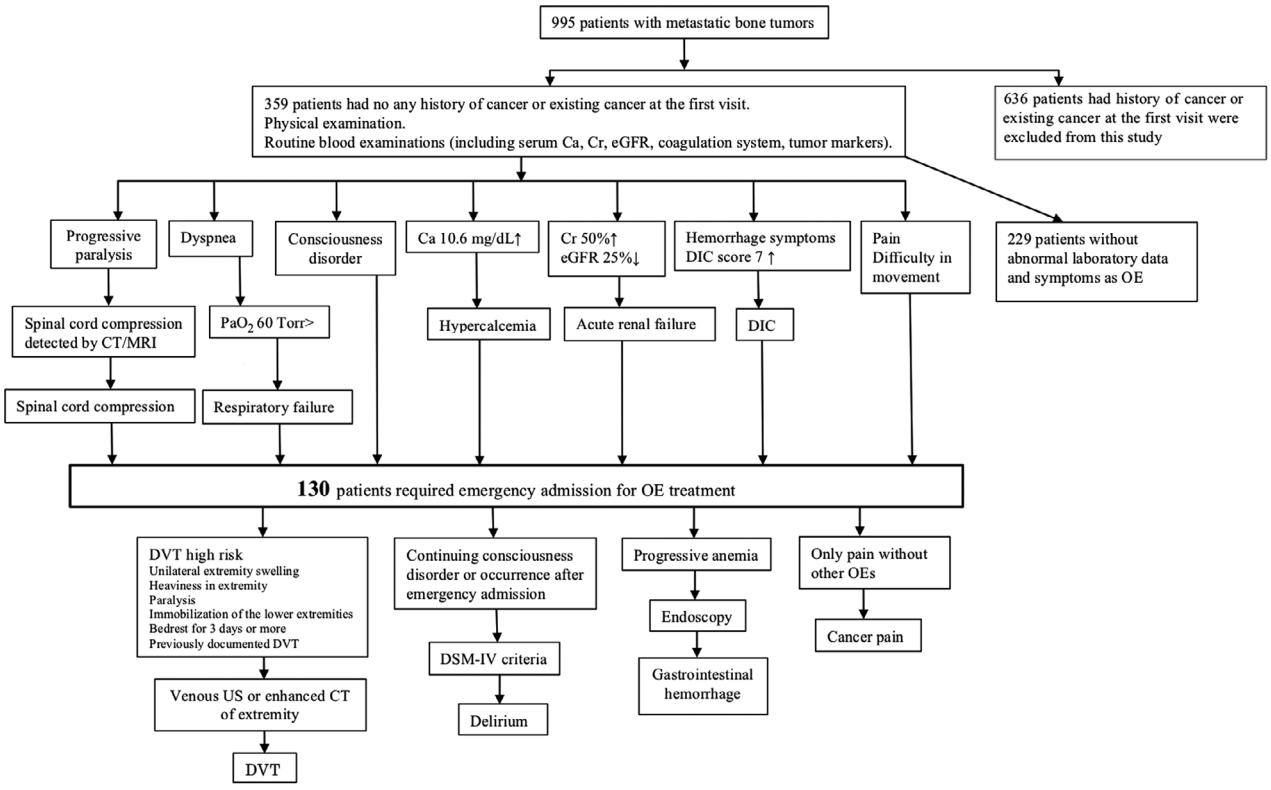
Statistical analyses were undertaken using JMP software (version 13.0 for Macintosh; SAS Institute, Cary, NC, USA), and P-values < 0.05 were considered statistically significant. Survival rates were estimated using the Kaplan–Meier method and compared using the log–rank test. Multivariate analysis was carried out using the Cox regression model to further assess prognostic factors.

RESULTS

THE RECOGNIZED DIAGNOSES of OE were spinal cord compressions in 60 patients, followed by cancer pain in 30, hypercalcemia in 19, delirium in 16, DVT in the lower extremities in 13, acute renal failure in 6, respiratory failure in 3, gastrointestinal hemorrhage in 3, and DIC in 1. Two or more OEs were observed in 15 patients.

The primary cancer diagnoses of the OE group were lung cancer in 28 patients, prostate cancer in 16, lymphoma in 16, multiple myeloma in 13, gastric cancer in 10, breast cancer in 8, hepatocellular carcinoma in 3, pancreatic cancer in 3, and others in 22; the remaining 11 patients were conclusively diagnosed with unknown primary malignancy. There was no primary malignancy that had statistically significant association with particular OEs. The primary cancer diagnoses of the non-OE group were lung cancer in 43, multiple myeloma in 32, breast cancer in 24, prostate cancer in 22, lymphoma in 20, hepatocellular carcinoma in 12, gastric cancer in 8, pancreas cancer in 4, and others in 50; 14 patients were conclusively diagnosed with unknown primary cancer. There were no significant differences in the rates of primary malignancies between the OE and non-OE groups (Table 1).

The treatments and treatment outcomes of OEs were as follows. Among 60 patients with spinal cord compression, surgery with/without radiotherapy was applied in 7 patients,



OE, oncologic emergency; Ca, calcium; Cr, creatinine; eGFR, estimated glomerular filtration rate; DVT, deep venous thrombosis; DIC, disseminated intravascular coagulation; Pa02, partial pressure of arterial oxygen; DSM-IV, diagnostic and statistical manual of mental disorders 4th edition.

Fig. 1. Flowchart for oncologic emergency (OE) diagnosis of skeletal metastasis of unknown primary malignancy. We selected cases with and without history of cancer by collecting patient history. Physical and routine blood examinations were then carried out to determine the presence of OE. Ca, calcium; Cr, serum creatinine; CT, computed tomography; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; US, ultrasound.

whereas radiotherapy and only best supportive care were undertaken in 42 and 11 patients, respectively. Cancer pain was calculated to have a mean value of 6.6 ± 2.2 (3–10) as evaluated by the numerical rating scale on emergency admission, and it was due to skeletal metastasis in all cases. Surgical treatment was undertaken in 10 patients with pathological fractures. The remaining 20 patients were treated with analgesics and 13 of these patients were also treated with radiotherapy. Cancer pain improved to numerical rating scale 1.8 ± 1.7 (0–5) after treatment. Serum calcium level was examined at first visit in all cases and its mean value in patients with hypercalcemia was 13.1 ± 2.1 mg/dL (10.7–16 mg/dL; normal range, 8.5–10.5 mg/dL). Patients with hypercalcemia were treated with i.v. hydration using physiological saline, calcitonin agents, and bone-modifying agents. The serum calcium levels were normalized after treatment in all patients, and there were no severe functional disorders or fatalities due to hypercalcemia. Among 16 cases of delirium, the etiologies were as follows: medication-induced in 7 (opioid, anticholinergic agent, and benzodiazepine), hypercalcemia in 6, vitamin B1 deficiency (Wernicke encephalopathy) in 4, and hyperammonemia in 1; multiple causes were observed in 2 patients. All cases of delirium were investigated by brain CT and/or magnetic resonance imaging, and there were no cases of cerebral lesions, such as metastatic brain tumors, in the study. The mean value of serum vitamin B1 levels in patients with vitamin B1 deficiency was 17.8 ± 3.5 ng/mL (13–22 ng/mL; normal range, 24–66 ng/mL) (Table 2). Vitamin B1 deficiency was diagnosed when the levels were below the lower limit of normal, other causes of delirium were ruled out, and improved consciousness was observed following vitamin administration. The specific treatments were based on the status of each case and included discontinuation of the causative medication, correction of hypercalcemia, and treatment with multivitamin preparations, branched-chain amino acid replacement, and synthetic disaccharide lactose. Observed delirium tended to improve after those treatments

Table 1. Characteristics of 130 patients with oncologic emergency (OE) and 229 patients without OE

Factor	Patients with OE Number	Patients without OE Number
Age, years (mean)	35–93 (67.5 ± 11.2)	22–93 (67.5 ± 11.0)
Sex		
Male	81	144
Female	49	85
OE		
Spinal cord compression	60	
Cancer pain	30	
Hypercalcemia	19	
Delirium	16	
Deep vein thrombosis	13	
Acute renal failure	6	
Respiratory failure	3	
Gastrointestinal hemorrhage	3	
Disseminated intravascular coagulation	1	
Primary malignancy		
Lung	28	43
Prostate	16	22
Lymphoma	16	20
Multiple myeloma	13	32
Gastric	10	8
Breast	8	24
Liver	3	12
Pancreas	3	4
Others	22	50
Unknown	11	14

Table 2. Characteristics of 16 patients with oncologic emergency and delirium

Factor	Number
Age, years (mean)	51–87 (73.4 ± 9.1)
Sex	
Male	11
Female	5
Etiology (multiple etiologies were observed in 2 patients)	
Medication-induced (opioid 7, anticholinergic agent 2, and benzodiazepine 1)	7
Hypercalcemia	6
Vitamin B1 deficiency (13–22 ng/mL, mean 17.8 ± 3.5; normal range 24–66)	4
Hyperammonemia	1
Primary malignancy	
Lung	4
Lymphoma	4
Prostate	2
Breast	1
Multiple myeloma	1
Kidney	1
Skin	1
Unknown	2

in all cases, although the level of improvement varied among patients. For DVT evaluation, imaging studies (venous ultrasonography, contrast-enhanced CT) were carried out in 35 patients who were estimated to be at high risk for DVT. There were 13 DVT cases (10% of all OEs) in this series. The treatment of DVT usually included initiation treatment with unfractionated heparin and maintenance treatment with direct oral anticoagulants after the completion of biopsy and surgery and there were no fatalities due to venous thromboembolism. Patients with acute renal failure were treated with venous hydration using extracellular fluid and administration of diuretics. All patients improved with treatment, and emergency dialysis was not necessary in any of the cases. Respiratory failure in 3 patients was caused by carcinomatous lymphangitis. However, treatment with oxygen and corticosteroids did not lead to an improvement in respiratory status. Only palliative treatment with morphine hydrochloride was given for respiratory failure, and all 3 patients died within 1 month after the initial admission. In cases with gastrointestinal hemorrhage, endoscopic hemostasis treatment was carried out and all cases improved consequently. Finally, one patient with DIC was treated with anticoagulant agents and blood transfusion, which led to resolution of DIC.

The overall 5-year survival rates were 28% in the OE group and 37% in the non-OE group. The survival rate of the OE group was significantly lower than that of the non-OE group ($P < 0.001$; Fig. 2).

The overall survival rates of each type of OE with statistically significant differences compared with the non-OE group were as follows. The overall 5-year survival rate was 37% in spinal cord compression ($P < 0.003$), the overall 2-year survival rate was 16% in DVT ($P < 0.001$), the overall 1-year survival rate was 33% in acute renal failure ($P < 0.007$), the overall 1-year survival rate was 18% in delirium ($P < 0.001$), and the overall 1-year survival rate

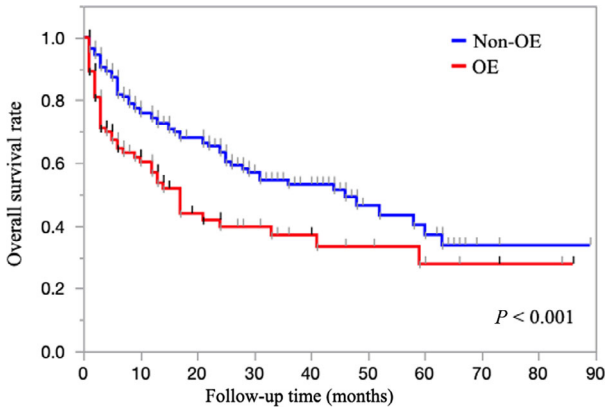


Fig. 2. Kaplan–Meier survival curve of the oncologic emergency (OE) and non-OE groups of patients with skeletal metastasis of unknown primary malignancy. The overall 1-year, 2-year, and 5-year survival rates were 54%, 40%, and 28% in the OE group, and 73%, 60%, and 37% in the non-OE group, respectively. There was a statistically significant difference ($P < 0.001$).

was 0% in respiratory failure ($P < 0.001$; Fig. 3A). The overall survival rates of each OE without statistically significant differences compared with the non-OE group were as follows: the overall 5-year survival rate was 59% in cancer pain ($P = 0.813$), the overall 5-year survival rate was 100% in gastrointestinal hemorrhage ($P = 0.305$), the overall 5-year survival rate was 18% in hypercalcemia ($P = 0.115$), and the overall 1-year survival rate was 0% in DIC ($P = 0.193$; Fig. 3B), respectively.

In the multivariate analysis of the prognostic risk of each OE among the OE group, a statistically significant difference was observed in terms of respiratory failure (hazard ratio [HR] 22.6; 95% confidence interval [CI], 4.5–92.8; $P < 0.001$), and delirium (HR 4.2; 95% CI, 1.6 – 12.5; $P < 0.005$). No statistically significant difference was observed in terms of spinal cord compression (HR 2.2; 95% CI, 1.0 – 5.9; $P = 0.061$), DVT (HR 2.8; 95% CI, 0.9 – 8.8; $P = 0.066$), renal failure (HR 3.5; 95% CI, 0.9 – 12.4; $P = 0.068$), and hypercalcemia (HR 2.4; 95% CI, 0.8–6.9; $P = 0.091$; Table 3).

DISCUSSION

THE FREQUENCY OF each OE depends on the characteristics of each health-care department. In the emergency department, respiratory, gastrointestinal, neurological OEs, and cancer pain were reported to be more frequent, which varied from the findings of this study.[11,12] This difference in the tendency of OEs could be attributed to the fact that ours is an orthopedic surgery department at a local university hospital, and 81% of the referrals of OE cases were from nearby orthopedic clinics and hospitals. As there has been no previous report of the incidence of OE in patients with skeletal metastasis of initially unknown origin, our study of 36% incidence highlighted important information. We consider OE to be probably a common complication of patients with skeletal metastasis of unknown primary.

Some previous reports have already shown that OE is a poor prognostic factor in patients with cancer.[13,14] However, the results of this study did not indicate that the prognosis for all OEs in patients with skeletal metastasis of unknown malignancy was always equally worse. Spinal cord compression, cancer pain, hypercalcemia, DVT, acute renal failure, gastrointestinal hemorrhage, and DIC were not statistically significantly poor prognostic factors in this study. For example, previous studies have reported that the mean survival times for patients with spinal cord compression were 3–7 months and spinal cord compression was considered to be a poor prognostic factor.[15] However, a recent study reported a mean survival time of 23 months in patients with spinal cord compression as an initial onset of malignancy, without adjuvant cancer treatment, which was significantly longer than that of 15.5 months in patients with spinal cord compression occurring after adjuvant cancer treatment.[16] This difference suggests that cancer treatment might be more effective in cases with no previous treatment than in cases previously treated because the cancer remains treatment-naive.

The OEs that were correlated with a significantly worse prognosis in this study were delirium and respiratory failure. Delirium is defined as an acute and variable disorder of consciousness caused by factors such as medical condition and medications.[17] Delirium in patients with malignancy was already reported as a poor prognostic factor, and the reported median survival times of cancer patients with delirium were 1.23 months.[18] In this study, medication was the most frequent cause of delirium, followed by hypercalcemia and vitamin B1 deficiency (Wernicke encephalopathy). We would like to emphasize this vitamin B1 deficiency in cancer patients. Vitamin B1 deficiency was considered to be frequent complication among alcohol abusers, but it was reported that vitamin B1 deficiency was also frequent in patients with malignancies because of eating disorders, gastrointestinal tract absorption disorders, and increase in vitamin B1 consumption due to the malignancy itself.[19,20] Vitamin B1 deficiency might not have much recognition as a cause of delirium in patients with cancer; however, up to 25% of delirium patients showed vitamin B1 deficiency in this study. Therefore, vitamin B1 deficiency should also be considered one of the major reasons of delirium in patients

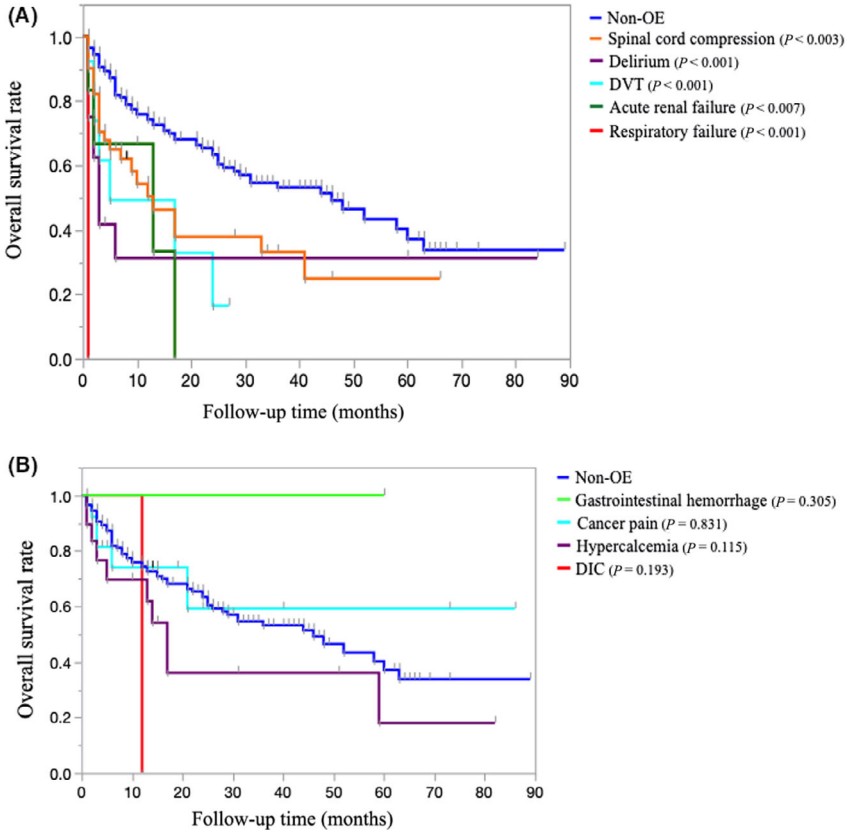


Fig. 3. A, Kaplan–Meier survival curves of spinal cord compression, delirium, deep venous thrombosis (DVT), acute renal failure, and respiratory failure among patients with skeletal metastasis of unknown primary malignancy. There was a statistically significant between each oncologic emergency (OE) and the non-OE group. B, Kaplan–Meier survival curves of gastrointestinal hemorrhage, cancer pain, hypercalcemia, and disseminated intravascular coagulation (DIC). There was no statistical significance between each OE and the non-OE group.

Table 3. Multivariate analysis of disease-specific survival in oncologic emergencies (OEs)

OE	Hazard ratio	95% CI	*P*-value
Respiratory failure	22.6	4.5–92.8	<0.001
Delirium	4.2	1.6–12.5	<0.005
Spinal cord compression	2.2	1.0–5.9	0.061
DVT	2.8	0.9–8.8	0.066
Renal failure	3.5	0.9–12.4	0.068
Hypercalcemia	2.4	0.8–6.9	0.091

CI, confidence interval; DVT, deep vein thrombosis.

with skeletal metastasis. As vitamin B1 deficiency often brings irreversible encephalopathy even in a short period, serum vitamin B1 level measurement and treatment with vitamin preparations should be taken immediately if it is suspected.[21] Delirium improved after treatment in all of our cases, but the prognosis was still poor. We considered that an improvement of delirium did not necessarily correlate with improvement of survival. The pathology of delirium probably simply indicates a more advanced oncological status than other OE patients.

Respiratory failure is defined as less than 60 Torr Pa02 and was reported in 70% of patients with end-stage malignancy.[9,22] Respiratory failure was reported as an independent poor prognostic factor with a variety of pathology, including pleural effusion, pulmonary embolism, and carcinomatous lymphangitis. The reported median survival time of patients with pulmonary carcinomatous lymphangitis was 3 months,[23] and our study also confirmed similar prognostic outcomes. Effective chemotherapy was reported for carcinomatous lymphangitis,[24,25] but prompt chemotherapy was considered to be indemonstrable in patients with skeletal metastasis if the primary malignancy is not known. In this

study, treatment for patients with respiratory failure was consequently only palliative treatment, which might not have improved their prognosis.

LIMITATIONS

THE PRESENT STUDY had several limitations. First, as this was a retrospective study, selection biases were inherent. Second, the prognosis might have been overestimated by a short follow-up because some patients were transferred to another hospital early after treatment and no further follow-up was accomplished. Finally, depending on the type of OE, the numbers of each classified case were too small.

CONCLUSIONS

WE DISCUSSED OES in patients with skeletal metastasis of initially unknown primary malignancy. Oncologic emergency was observed in 36% of those patients, and was considered to be a common complication in this cohort. The OE group had worse prognosis compared to the non-OE group. Respiratory failure and delirium were statistically significant prognostic risk factors. However, spinal cord compression, hypercalcemia, DVT, renal failure, DIC, and cancer pain did not show statistical significance, and those OEs were considered to be reversible conditions. The results suggested that early detection and appropriate treatment of OEs in patients with skeletal metastasis of initially unknown primary malignancy is important.

DISCLOSURE

Approval of the research protocol: This prospective study protocol was approved by the review board of Saitama Medical University International Medical Center (approval number: 18–133).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

REFERENCES

1 Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: Pathophysiology, presentation, diagnosis, and treatment. CA. Cancer J. Clin. 2011; 61: 287–314.
2 Provencio-Pulla M. ESMO handbook of Oncology Emergencies, 2nd edn. Hertfordshire: ESMO Press, 2016.
3 Simon MA, Bartucci EJ. The search for the primary tumor in patients with skeletal metastases of unknown origin. Cancer 1986; 58: 1088–95.
4 Piccioli A, Maccauro G, Spinelli MS, Biagini R, Rossi B. Bone metastases of unknown origin: epidemiology and principles of management. Orthop. Traumatol. 2015; 16: 81–6.
5 Macdonald AG, Lynch D, Garbett I, Nazeer N. Malignant spinal cord compression. J. R. Coll. Physicians Edinb. 2019; 49: 151–6.
6 Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. J. Pain Res. 2016; 22: 515–34.
7 Meagher DJ, Morandi A, Inouye SK, *et al*. Concordance between DSM-IV and DSM-5 criteria for delirium diagnosis in a pooled database of 768 prospectively evaluated patients using the delirium rating scale-revised-98. BMC Med. 2014; 12: 164.
8 Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin. J. Am. Soc. Nephrol. 2014; 9: 12–20.
9 Ishigaki Y. Home respiratory management: from COPD to neurological diseases. Japan Med. Assoc. J. 2015; 58: 36–9.
10 Wada H, Gabazza EC, Asakura H, *et al*. Comparison of diagnostic criteria for disseminated intravascular coagulation (DIC): diagnostic criteria of the International Society of Thrombosis and Hemostasis and of the Japanese Ministry of Health and Welfare for overt DIC. Am. J. Hematol. 2003; 74: 17–22.
11 Leak A, Mayer DK, Wyss A, Travers D, Waller A. Why do cancer patients die in the emergency department?: an analysis of 283 deaths in NC EDs. Am. J. Hosp. Palliat. Care. 2013; 30: 178–82.
12 van der Meer DM, Weiland TJ, Philip J, *et al*. Presentation patterns and outcomes of patients with cancer accessing care in emergency departments in Victoria. AustraliaSupport Care Cancer 2016; 24: 1251–60.
13 Thandra K, Salah Z, Chawla S. Oncologic Emergencies-The Old, the New, and the Deadly. J. Intensive Care Med. 2020; 35: 3–13.
14 Samphao S, Eremin JM, Eremin O. Oncological emergencies: clinical importance and principles of management. Eur. J. Cancer Care. 2010; 19: 707–13.
15 Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala NB, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. Health Technol. Assess. 2013; 17: 1–274.
16 Park JS, Park SJ, Lee CS. Incidence and prognosis of patients with spinal metastasis as the initial manifestation of malignancy: analysis of 338 patients undergoing surgical treatment. Bone Joint J. 2019; 101(B): 1379–84.

17 Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097–101.
18 Elsayem AF, Bruera E, Valentine A, *et al*. Advance directives, hospitalization, and survival among advanced cancer patients with delirium presenting to the emergency department: a prospective study. Oncologist 2017; 22: 1368–73.
19 Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007; 6: 442–55.
20 Isenberg-Grzeda E, Rahane S, DeRosa AP, Ellis J, Nicolson SE. Wernicke-Korsakoff syndrome in patients with cancer: a systematic review. Lancet Oncol. 2016; 17: 142–8.
21 Onishi H, Kawanishi C, Onose M, *et al*. Successful treatment of Wernicke encephalopathy in terminally ill cancer patients: report of 3 cases and review of the literature. Support Care Cancer. 2004; 12: 604–8.
22 Escalante CP, Martin CG, Elting LS, *et al*. Dyspnea in cancer patients. Etiology, resource utilization, and survival-implications in a managed care world. Cancer 1996; 78: 1314–9.
23 Hominal S, Falchero L, Perol M, Guérin JC. Carcinomatous lymphangitis. Presse. Med. 1999; 28: 979–84.
24 Takeuchi N, Koike K, Yoshida S, Fujiwara M. Efficacy of regorafenib in acute pulmonary carcinomatous lymphangitis as a manifestation of rectal cancer: A case report. Oncol. Lett. 2019; 18: 6469–74.
25 Funakoshi T, Yasui H, Boku N, *et al*. Clinicopathological features and outcomes of gastric cancer patients with pulmonary lymphangitis carcinomatosa. Jpn. J. Clin. Oncol. 2014; 44: 792–8.