Clinical features and prognostic factors in patients with esophageal cancer with bone metastasis

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Abstract. There have been few reports on bone metastases (BMs) from esophageal cancer (EC). The aim of the present study was to investigate the clinicopathological features and prognostic factors in patients with EC with BMs. The present study retrospectively collected data from 58 patients with BMs from EC who were treated at our institution between 2007 and 2016. Patient, tumor and BM-associated characteristics were analyzed. Kaplan-Meier survival curves were constructed and analyzed using the univariate log-rank test. Multivariate analyses were conducted using the Cox proportional hazards model. The median patient age was 67 years (range, 39-84 years). Multiple BMs were detected in 38 patients (65.5%) and 52 patients (89.7%) exhibited osteolytic BMs. Skeletal-related events (SREs) occurred in 53 patients (91.4%). The one-year overall survival (OS) was 25.3%, and the median OS was 5 months (range, 0-54). Univariate analyses revealed that performance status, visceral or brain metastasis, serum carcinoembryonic antigen (CEA), C-reactive protein, albumin level, and receipt of chemotherapy following BM diagnosis were significantly associated with OS. Multivariate analyses of these factors demonstrated that higher serum CEA levels and no chemotherapy were significant risk factors for poor OS. Multiple osteolytic BMs are frequently observed in patients with EC with BMs, and SREs commonly occur. The prognoses of patients with EC with BMs are poor, but chemotherapy administration following the BM diagnosis should confer a survival benefit.

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Introduction

Esophageal cancer (EC) is the ninth most common cancer worldwide and the sixth leading cause of death due to cancer (1,2). The main pathological subtypes include squamous cell carcinoma (SCC) and adenocarcinoma (AC) (1-4). In contrast to Western countries, where esophageal adenocarcinoma (EAC) is predominant, esophageal squamous cell carcinoma (ESCC) is predominant in some Asian countries, including Japan and China (2-4). EC remains a highly lethal malignant tumor, with poor prognosis, despite advances in diagnosis and treatment in recent decades. Approximately half of patients with EC have distant metastases at the time of initial diagnosis and more than one-third develop distant metastases following surgery or radiotherapy (3,5). Although chemotherapy is standard treatment for patients with EC with distant organ metastases, the prognosis is dismal, with a five-year overall survival (OS) of less than 5% (6,7). Most distant metastases of EC involve the distant lymph nodes, liver, and lungs (8-10).

Bone is a frequent site of metastasis from breast, prostate, and lung cancers (11-13), and bone metastasis (BM) typically indicates a poor prognosis. BM's incidence and prevalence has been increasing since a large portion of the population is elderly. Patients with BMs should be treated with a multidisciplinary approach, using modalities such as radiotherapy, surgery and various medical treatments that include chemotherapy, hormone therapy, and bone-modifying agents (BMAs) (11). BMs frequently cause skeletal-related events (SREs), such as pathological fracture, spinal cord compression, and hypercalcemia, which may require radiotherapy or surgery, and reduce physical function and quality of life (14). EC generally metastasizes to the skeletal system late in the course of the disease, so patients with EC with BMs are relatively uncommon. Several studies have reported BM incidence rates ranging from 5.2-7.7% in all-stage patients with EC and 15.3-23.6% in patients with metastases (8-10,15). However, there is little information regarding the clinicopathological features and prognostic factors of patients with EC with BMs. Therefore, we aimed to investigate these features and factors retrospectively in patients with EC with BMs who were treated at our institution.

Materials and methods

Study design and patients. We retrospectively and anonymously reviewed the medical records of 58 patients with EC, including five patients with esophagogastric junction (EGJ) cancers, who were diagnosed with BMs and treated at the Osaka International Cancer Institute between January 2007 and December 2016. The inclusion criteria were: 1) histological diagnosis of SCC or AC with the esophagus or EGJ recognized as the primary tumor; 2) BM diagnosis based on clinical signs and symptoms as well as radiographic imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT. The exclusion criteria was: 1) patients with other synchronous malignancies. The Institutional Review Board of the Osaka International Cancer Institute approved the study.

Data collection. Patient data, including age, sex, and Eastern Cooperative Oncology Group performance status (ECOG PS), was collected. Tumor characteristics, including location, histology, differentiation, resection of primary site, visceral or brain metastasis, and serum levels of SCC antigen (SCC-Ag), carcinoembryonic antigen (CEA), C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin, and alkaline phosphatase (ALP), were also noted. BM characteristics, including presence at initial diagnosis, number, type (osteolytic, osteoblastic, mixed, and intertrabecular), SRE, pathological fracture, spinal cord compression, hypercalcemia, and treatment received (chemotherapy before and after the BM diagnosis, BMA, radiotherapy, and surgery), as well as follow-up period and outcome at last follow-up were determined.

Statistical analysis. OS, defined as the time from the date of BM diagnosis to the date of death from any cause or last follow-up visit, was calculated using the Kaplan-Meier method. The impact of prognostic factors on OS was first assessed using the log-rank test in univariate analysis, and then multivariate analysis was performed using the Cox proportional hazard model with variables chosen using a forward conditional stepwise approach. Statistical significance was defined as $P<0.05$. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and tumor-related characteristics. Fifty-eight patients diagnosed with BMs from EC were enrolled in this study. The median follow-up period for all patients was three months (range, 0-54). Patient and tumor characteristics are shown in Table I. Fifty-three patients (91.4%) were male and five (8.6%) were female. The median age was 67 years (range, 39-84). ECOG PS was 0-2 in 35 patients (60.3%) and 3-4 in 23 patients (39.7%). Tumor location was esophagus in 53 patients (91.4%) and EGJ in five patients (8.6%). Tumor histology of the primary lesion was SCC in 54 patients (93.1%) and AC in four patients (6.9%). Among the 32 patients whose tumor differentiation was evaluated, 12 (37.5%) had poorly differentiated tumors and 20 (62.5%) had well to moderately differentiated tumors. Twenty-four patients (41.4%) underwent surgery for their primary tumor. Visceral or brain metastasis was observed at the time of BM diagnosis in 38 patients (65.5%). Elevated levels of serum SCC-Ag (>1.5 ng/ml), CEA (>5 ng/ml), CRP (>0.3 mg/dl), LDH (>250 U/l), and ALP (>350 U/l) at the time of BM diagnosis were observed in 68.8, 27.5, 75.4, 27.8, and 30.9% of patients, respectively. Decreased serum albumin level (≤3.7 g/dl) was detected in 65.5% of the patients.

Bone metastasis-related characteristics. The median interval from the diagnosis of EC to BM detection was seven months (range, 0-80). BM characteristics are shown in Table II. Fourteen patients (24.1%) had BMs at initial presentation. A solitary BM was found in 20 patients (34.5%) and multiple BMs were detected in 38 patients (65.5%). Frequent metastatic sites included the thoracic vertebrae (31 patients, 53.4%), lumbar vertebrae (18 patients, 31.0%) and pelvic bones (16 patients, 27.6%). The bone metastatic lesions were osteolytic in 52 patients (89.7%), mixed in two (3.4%), and intertrabecular in four (6.9%). No patient showed an osteoblastic type of BM. Chemotherapy was administered before the diagnosis of BM in 38 patients (65.5%), and 32 patients (55.2%) received palliative chemotherapy after the BM diagnosis. BMAs, such as zoledronic acid and denosumab, were administered to 19 patients (32.8%).

Skeletal-related events. SREs occurred in 53 patients (91.4%), including radiation therapy (48 patients, 82.8%), surgery (four patients, 6.9%), pathological fracture (13 patients, 22.4%), spinal cord compression (six patients, 10.3%), and hypercalcemia (15 patients, 30.0%). SREs occurred at the time of the BM diagnosis in 44 patients. In the remaining nine patients, the median time from identification of BM to SRE was two months (range, 1-13). The association between type of BMs and interval from BM diagnosis to SREs was shown in Table III.

Predictive factors of OS. The six-month, one-year, and two-year OS rates after BM diagnosis were 48.7, 25.3, and 6.1%, respectively (Fig. 1). The median OS following BM diagnosis was five months (range, 0-54). In univariate analyzes, ECOG PS ($P<0.001$), visceral or brain metastasis ($P=0.018$), serum levels of CEA ($P=0.012$), CRP ($P=0.011$), albumin ($P=0.018$), and receipt of chemotherapy following BM diagnosis ($P<0.001$) were significant prognostic factors (Tables I, II, Fig. 2A-F). The prognosis of EGJ cancer was not significantly different from other types of EC ($P=0.373$). Tumor histology was also not a significant impact on OS ($P=0.272$). Multivariate analyzes showed that elevated serum CEA level (hazard ratio (HR) 2.400; 95% confidence interval (CI) 1.020-5.649; $P=0.045$) and no chemotherapy following the diagnosis of BM (HR 2.621; 95% CI 1.015-6.769; $P=0.046$) were significant independent prognostic factors for poor OS (Table IV).

Smokers tend to have higher CEA levels and the majority of patients with EC must have been heavy smokers (data not shown). However, the cutoff line of 5.0 ng/ml was chosen in accordance with previous studies (16,17). There were 10 patients who had SCC histologically but elevated serum CEA levels ranging from 5.2 to 55 ng/ml. The prognosis of those patients was also significantly worse than that of

Table I. Patient and tumor-related characteristics and univariate analysis of prognostic factors for OS.

Factors	Number (%)	1-year OS, %	P-value
Age, years			0.701
<65	22 (37.9)	21.9	
≥65	36 (62.1)	28.3	
Sex			0.719
Male	53 (91.4)	25.2	
Female	5 (8.6)	25.0	
ECOG PS			<0.001
0-2	35 (60.3)	34.7	
3-4	23 (39.7)	7.6	
Location			0.373
Esophagus	53 (91.4)	28.6	
EGJ	5 (8.6)	0	
Histology			0.272
SCC	54 (93.1)	27.9	
AC	4 (6.9)	0	
Differentiation			0.536
Poorly	12 (37.5)	41.9	
Moderately/Well	20 (62.5)	23.8	
Resection of primary site			0.224
Yes	24 (41.4)	37.3	
No	34 (58.6)	16.1	
Visceral or brain metastasis			0.018
Present	38 (65.5)	17.2	
Absent	20 (34.5)	41.9	
SCC-Ag, ng/ml			0.389
≤1.5	15 (31.3)	39.6	
>1.5	33 (68.8)	25.5	
CEA, ng/ml			0.012
≤5	29 (72.5)	37.2	
>5	11 (27.5)	18.2	
CRP, mg/dl			0.011
≤0.3	14 (24.6)	42.3	
>0.3	43 (75.4)	20.5	
LDH, U/l			0.213
≤250	39 (72.2)	28.5	
>250	15 (27.8)	9.3	
Albumin, g/dl			0.018
≤3.7	36 (65.5)	15.2	
>3.7	19 (34.5)	43.8	
ALP, U/l			0.878
≤350	38 (69.1)	24.7	
>350	17 (30.9)	25.9	

OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, esophagogastric junction; SCC, squamous cell carcinoma; SCC-Ag, SCC antigen; AC, adenocarcinoma; CEA, carcinoembryonic antigen; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Table II. BM-related characteristics and univariate analysis of prognostic factors for OS.

Factors	Number (%)	1-year OS, %	P-value
BM at initial diagnosis			
Yes	14 (24.1)	30.8	0.270
No	44 (75.9)	23.5	
Number of BM			
Solitary	20 (34.5)	21.6	0.932
Multiple	38 (65.5)	27.2	
Type of BM			
Osteolytic	52 (89.7)	25.5	0.745
Mixed/intertrabecular	6 (10.3)	22.2	
Chemotherapy before BM			
Yes	38 (65.5)	22.0	0.240
No	20 (34.5)	30.6	
Chemotherapy after BM			
Yes	32 (55.2)	37.7	<0.001
No	26 (44.8)	6.5	
Use of BMA			
Yes	19 (32.8)	38.3	0.147
No	39 (67.2)	18.8	
SRE			
Present	53 (91.4)	25.1	0.836
Absent	5 (8.6)	30 (6-month)	
Radiotherapy for BM			
Yes	48 (82.8)	23.6	0.978
No	10 (17.2)	40.0	
Orthopedic surgery for BM			
Yes	4 (6.9)	25.0	0.956
No	54 (93.1)	25.7	
Pathological fracture			
Present	13 (22.4)	30.8	0.559
Absent	45 (77.6)	22.5	
Spinal cord compression			
Present	6 (10.3)	31.2	0.429
Absent	52 (89.7)	24.8	
Hypercalcemia			
Present	15 (30.0)	10.0	0.086
Absent	35 (70.0)	28.9	

Since the one-year OS in patients in whom SRE did not occur could not be calculated, the 6-month OS is shown. BM, bone metastasis; OS, overall survival; BMA, bone-modifying agent; SRE, skeletal-related event.

the patients with SCC who had no elevation of CEA level (26 patients, P=0.014).

Among 35 patients with EC with BMs whose ECOG PS was 0-2 at BM diagnosis, 26 patients (74.3%) received chemotherapy after BM diagnosis. On the other hand, among 23 patients with ECOG PS of 3-4, only six patients (26.1%)

Table III. Association between type of BMs and interval from BM diagnosis to SREs.

Type of BM	Incidence rate of SRE, n (%)	Timing of SRE occurrence		Median interval from BM to SRE, months
		At BM diagnosis, n (%)	After BM diagnosis, n (%)	
Osteolytic	49/52 (94.2)	41/49 (83.7)	8/49 (16.3)	4 (range, 1-13)
Mixed	1/2 (50)	1/1 (100)	0/1 (0)	-
Intertrabecular	3/4 (75)	2/3 (66.7)	1/3 (33.3)	1
Total	53/58 (91.4)	44/53 (83)	9/53 (17)	2 (range, 1-13)

BM, bone metastasis; SRE, skeletal-related event.

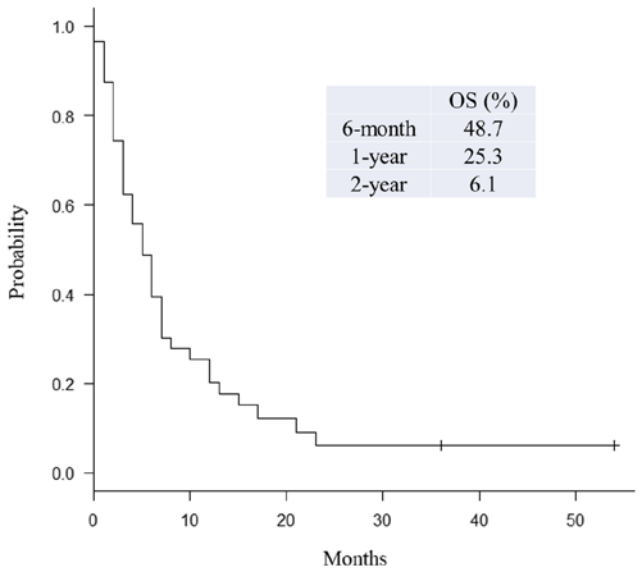

Figure 1. Kaplan-Meier survival curve for OS in all 58 patients with EC with bone metastases. OS, overall survival; EC, esophageal cancer.

received chemotherapy after BM diagnosis. The patients with ECOG PS of 0-2 who underwent chemotherapy after BM diagnosis tended to show better prognosis than those who did not. However, there was no statistically significant difference between the two groups (P=0.183).

Discussion

BMs are generally categorized, based on morphology, as osteolytic, osteoblastic, mixed, or intertrabecular. In osteolytic lesions, factors secreted by tumor cells induce osteoclast recruitment and activation, leading to increased osteolysis (12). This frequently decreases bone integrity and causes severe bone pain, an increased risk of fracture, and the release of minerals from the bone matrix, which results in hypercalcemia (14). For these reasons, osteolytic BMs are associated with a higher probability of SREs, which frequently cause morbidity and deterioration of PS. In turn, poor PS may prevent a patient from receiving further available treatment. Metastases from lung, kidney, and thyroid cancers are predominantly osteolytic. In this study of patients with EC with BMs, multiple osteolytic BMs commonly occurred in the axial skeleton, and SREs occurred in nearly all (91.4%) patients. Therefore, physicians caring for patients with EC should consider BM in the differential diagnosis when a patient complains of spontaneous somatic axial pain. Additionally, when routine follow-up CT reveals osteolytic changes in a vertebral body, BM should be suspected. Serum ALP, LDH, and tumor markers, including SCC-Ag and CEA, are not always elevated when BMs are present. Since MRI and FDG-PET/CT are able to easily detect BMs from EC (18,19), using these modalities can allow early and accurate diagnosis to prevent SREs and preserve PS.

Currently, palliative radiotherapy for painful BM is a well-established treatment. However, some patients with fracture, spinal cord compression, or spinal instability due to BM require surgery, if their life expectancy is not too short. Conversely, patients with a short life expectancy should receive radiotherapy and/or supportive care. Therefore, accurate survival data regarding patients with BMs is necessary so appropriate treatment recommendations can be made. In breast cancer, patients with BMs have significantly better survival than those who have metastases to other sites (20). On the other hand, OS is significantly worse in patients with EC with BMs compared to those with metastases to other sites (9,21). In the current study, the median OS from the time of BM diagnosis in patients with EC was five months, which is consistent with previous reports of 2-4 months (9,22). These results suggest that the prognosis of patients with EC with BMs is usually poor and that palliative radiotherapy is a standard treatment for those patients. However, for example, surgical treatment is widely considered more effective for pathologic proximal femur fractures than radiotherapy because they are mainly treated with surgery to stabilize the fractured bones to improve quality of life via pain relief and restoration of function and mobility. Operative methods are divided into internal fixation and prosthesis replacement. Only palliative surgery such as internal fixation may be appropriate for patients with EC with BMs. On the other hand, despite relatively common perioperative complications, salvage using endoprostheses is associated with fewer failures for the treatment of pathologic proximal fractures compared with internal fixation (23-25). Araki *et al* (26) reported that with regard to bone destruction, the involvement of the head, neck, calcar, and intertrochanteric region, transverse destruction >1/2, and soft-tissue tumor

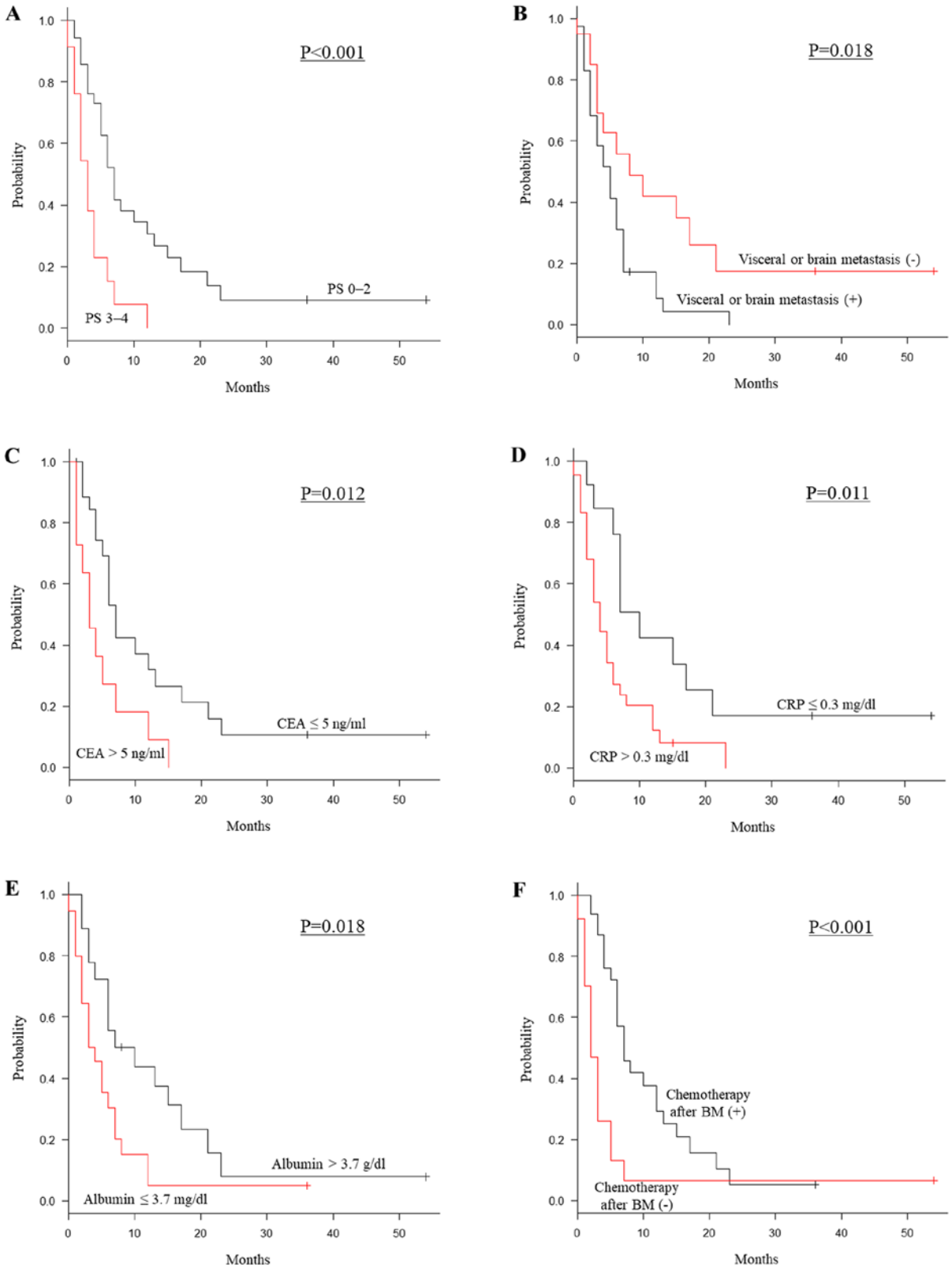

Figure 2. Kaplan-Meier survival curve for OS and univariate survival analyses for significant prognostic factors. (A) ECOG PS; (B) visceral or brain metastasis; (C) serum CEA; (D) serum CRP; (E) serum albumin; (F) chemotherapy following the diagnosis of BM. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CRP, C-reactive protein; BM, bone metastasis.

extension, were the factors that led to the choice of prosthesis treatment.

Katagiri *et al* (22) identified six significant prognostic factors for survival in patients with BMs: the primary lesion, visceral or cerebral metastases, abnormal laboratory data, poor PS, previous chemotherapy and multiple skeletal metastases. The study included patients with BMs from various cancers. Wu *et al* (9) demonstrated the relationship between

Table IV. Multivariate analysis of prognostic factors for OS.

	Univariate analysis		Multivariate analysis	
Factors	P-value	HR	95% CI	P-value
ECOG PS				
0-2	<0.001	1		
3-4		2.034	0.698-5.922	0.193
Visceral or brain metastasis				
Present	0.018	1.444	0.529-3.938	0.473
Absent		1		
CEA, ng/ml				
≤5	0.012	1		
>5		2.400	1.020-5.649	0.045
CRP, mg/dl				
≤0.3	0.011	1		
>0.3		2.230	0.692-7.183	0.179
Albumin, g/dl				
≤3.7	0.018	1.052	0.386-2.868	0.921
>3.7		1		
Chemotherapy after BM				
Yes	<0.001	1		
No		2.621	1.015-6.769	0.046

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CRP, C-reactive protein; BM, bone metastasis.

the patterns of distant metastasis and prognosis in metastatic EC. The most common site of distant metastasis was the liver, followed by distant lymph nodes, lungs, bone and brain. Site and number of distant metastases were independent prognostic factors for OS. OS was worst for BMs and greatest for distant lymph node metastases. However, clinicopathological features and prognostic factors of patients with EC with BMs remain unknown. To the best of our knowledge, the present study is the first to report clinicopathological features and prognostic factors in patients with EC with BMs. Although univariate analysis showed that visceral or brain metastasis, abnormal serum CRP and albumin levels, and PS were significant prognostic factors, multivariate analysis found that these factors were not significantly associated with OS. Only elevated serum CEA level and no chemotherapy following BM diagnosis were shown to be significant independent poor prognostic factors.

Serum tumor markers play an important role in cancer diagnosis and prognosis. CEA is relevant in several malignancies, such as colorectal, lung, and breast cancers. In general, CEA is a useful marker for EAC; however, it has been reported that CEA was positive in only 11.4 to 39% of patients with ESCC (27,28). In the present study, tumor histology was SCC in most patients (93.1%), and SCC-Ag showed a higher positivity rate (68.8%) than CEA (27.5%) at the time of BM diagnosis. Some studies have noted that SCC-Ag was a better OS predictor in patients with EC (29-31), while other studies have demonstrated CEA's efficacy as a diagnostic and prognostic marker in patients with EC (17,32,33). Until now, there has been no agreement on which biomarker is the best predictor for prognosis in patients with EC with BMs. In the current study, tumor histology was not associated with patients with OS with EC. Multivariate analysis showed that serum CEA level was an independent prognostic factor, but serum SCC-Ag level was not. CEA is associated with adhesion of malignant tumors, which might explain the correlation between CEA level and hematogenic metastasis such as BM.

Chemotherapy improves survival compared to supportive care alone in patients with metastatic EC, but the improvement is modest and must be weighed against the side effects of chemotherapy (34). First-line chemotherapy usually includes platinum-based agents, such as cisplatin and oxaliplatin, and a fluoropyrimidine, such as fluorouracil and capecitabine (34-36). The addition of a third drug, such as epirubicin or docetaxel, might be considered for patients who are generally in good health (35,36). Second-line chemotherapy with docetaxel, paclitaxel, or irinotecan might be considered for patients with stable PS (37-39). In the present study, the patients with good PS who received chemotherapy after BM diagnosis tended to show better prognosis than those who did not, but there was no significant difference between the two groups. One reason may be that a patient with good PS who did not undergo chemotherapy after BM diagnosis had been alive for 54 months. This patient had a solitary rib BM and no visceral or brain metastasis. The BM was treated with radiotherapy and no other metastatic lesion had occurred. ECOG PS and

chemotherapy after BM diagnosis ware significant prognostic factors for OS in univariate analyses. However, only receipt of chemotherapy but not good PS was associated with better OS in multivariate analyses. The prognosis of patients with EC with BMs who did not receive chemotherapy due to poor PS, advanced age, comorbidity, or patient refusal was dismal. Our results indicate that chemotherapy should be considered, whenever possible, at the time of BM diagnosis in patients with EC.

In conclusion, the prognosis of BM from EC was extremely poor, with a median OS of five months following BM diagnosis. Multiple osteolytic BMs occurred predominantly in the axial skeleton with a high incidence of SREs. Univariate analysis showed that PS, visceral or brain metastasis, receipt of chemotherapy following the diagnosis of BM, and serum CEA, CRP, and albumin levels were significant prognostic factors for OS. Multivariate analysis demonstrated that no chemotherapy following the diagnosis of BM and elevated CEA level were independent prognostic factors for poor OS. In patients with EC with BMs, early diagnosis and appropriate treatment could prevent SREs and maintain quality of life and PS, allowing continuation of chemotherapy.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YI, SY, KS, HM, RI, and MY organized the study. YI, TW, TT, HT and NN collected and analyzed the data. YI wrote the manuscript. SY, KS, HM, RI and MY treated the patients presented in this manuscript. SY, TW, TT, HT, KS, HM, RI, MY and NN revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Osaka International Cancer Institute (Osaka, Japan).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
2. Lagergren J, Smyth E, Cunningham D and Lagergren P: Oesophageal cancer. Lancet 390: 2383-2396, 2017.
3. Rustgi AK and El-Serag HB: Esophageal carcinoma. N Engl J Med 371: 2499-2509, 2014.
4. Arnold M, Soerjomataram I, Ferlay J and Forman D: Global incidence of oesophageal cancer by histological subtype in 2012. Gut 64: 381-387, 2015.
5. Enzinger PC and Mayer RJ: Esophageal cancer. N Engl J Med 349: 2241-2252, 2003.
6. Tanaka T, Fujita H, Matono S, Nagano T, Nishimura K, Murata K, Shirouzu K, Suzuki G, Hayabuchi N and Yamana H: Outcomes of multimodality therapy for stage IVB esophageal cancer with distant organ metastasis (M1-Org). Dis Esophagus 23: 646-651, 2010.
7. Wu SG, Xie WH, Zhang ZQ, Sun JY, Li FY, Lin HX, Yong Bao and He ZY: Surgery combined with radiotherapy improved survival in metastatic esophageal cancer in a surveillance epidemiology and end results population-based study. Sci Rep 6: 28280, 2016.
8. Ai D, Zhu H, Ren W, Chen Y, Liu Q, Deng J, Ye J, Fan J and Zhao K: Patterns of distant organ metastases in esophageal cancer: A population-based study. J Thorac Dis 9: 3023-3030, 2017.
9. Wu SG, Zhang WW, He ZY, Sun JY, Chen YX and Guo L: Sites of metastasis and overall survival in esophageal cancer: A population-based study. Cancer Manag Res 9: 781-788, 2017.
10. Wu SG, Zhang WW, Sun JY, Li FY, Lin Q and He ZY: Patterns of distant metastasis between histological types in esophageal cancer. Front Oncol 8: 302, 2018.
11. Nielsen OS, Munro AJ and Tannock IF: Bone metastases: Pathophysiology and management policy. J Clin Oncol 9: 509-524, 1991.
12. Mundy GR: Metastasis to bone: Causes, consequences and therapeutic opportunities. Nat Rev Cancer 2: 584-593, 2002.
13. Coleman RE: Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 12: 6243s-6249s, 2006.
14. Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, Dreicer R, Kuross SA, Lipton A and Seaman JJ: Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 91: 1191-1200, 2001.
15. Goodner JT and Turnbull AD: Bone metastases in cancer of the esophagus. Am J Roentgenol Radium Ther Nucl Med 111: 365-367, 1971.
16. Ma Z, Wu X, Xu B, Jiang H, Tang P, Yue J, Ma M, Chen C, Zhang H and Yu Z: Development of a novel biomarker model for predicting preoperative lymph node metastatic extent in esophageal squamous cell carcinoma[1]. Oncotarget 8: 105790-105799, 2017.
17. Yang Y, Huang X, Zhou L, Deng T, Ning T, Liu R, Zhang L, Bai M, Zhang H, Li H and Ba Y: Clinical use of tumor biomarkers in prediction for prognosis and chemotherapeutic effect in esophageal squamous cell carcinoma. BMC Cancer 19: 526, 2019.
18. Rybak LD and Rosenthal DI: Radiological imaging for the diagnosis of bone metastases. Q J Nucl Med 45: 53-64, 2001.
19. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, Sohda M, Fukai Y, Masuda N, Fukuchi M, *et al*: Comparison between whole-body positron emission tomography and bone scintigraphy in evaluating bony metastases of esophageal carcinomas. Anticancer Res 25: 4439-4444, 2005.
20. Wu SG, Li H, Tang LY, Sun JY, Zhang WW, Li FY, Chen YX and He ZY: The effect of distant metastases sites on survival in de novo stage-IV breast cancer: A SEER database analysis. Tumour Biol 39: 1010428317705082, 2017.
21. Liu M, Wang C, Gao L, Lv C and Cai X: A nomogram to predict long-time survival for patients with M1 diseases of esophageal cancer. J Cancer 9: 3986-3990, 2018.
22. Katagiri H, Okada R, Takagi T, Takahashi M, Murata H, Harada H, Nishimura T, Asakura H and Ogawa H: New prognostic factors and scoring system for patients with skeletal metastasis. Cancer Med 3: 1359-1367, 2014.
23. Wedin R and Bauer HC: Surgical treatment of skeletal metastatic lesions of the proximal femur: Endoprosthesis or reconstruction nail? J Bone Joint Surg Br 87: 1653-1657, 2005.

24. Forsberg JA, Wedin R and Bauer H: Which implant is best after failed treatment for pathologic femur fractures? Clin Orthop Relat Res 471: 735-740, 2013.
25. Steensma M, Boland PJ, Morris CD, Athanasian E and Healey JH: Endoprosthetic treatment is more durable for pathologic proximal femur fractures. Clin Orthop Relat Res 470: 920-926, 2012.
26. Araki N, Chuman H, Matsunobu T, Tanaka K, Katagiri H, Kunisada T, Hiruma T, Hiraga H, Morioka H, Hatano H, *et al*: Factors associated with the decision of operative procedure for proximal femoral bone metastasis: Questionnaire survey to institutions participating the Bone and Soft Tissue Tumor Study Group of the Japan Clinical Oncology Group. J Orthop Sci 22: 938-945, 2017.
27. Shimada H, Takeda A, Arima M, Okazumi S, Matsubara H, Nabeya Y, Funami Y, Hayashi H, Gunji Y, Suzuki T, *et al*: Serum p53 antibody is a useful tumor marker in superficial esophageal squamous cell carcinoma. Cancer 89: 1677-1683, 2000.
28. Munck-Wikland E, Kuylenstierna R, Wahren B, Lindholm J and Haglund S: Tumor markers carcinoembryonic antigen, CA 50, and CA 19-9 and squamous cell carcinoma of the esophagus. Pretreatment screening. Cancer 62: 2281-2286, 1988.
29. Cao X, Zhang L, Feng GR, Yang J, Wang RY, Li J, Zheng XM and Han YJ: Preoperative Cyfra21-1 and SCC-Ag serum titers predict survival in patients with stage II esophageal squamous cell carcinoma. J Transl Med 10: 197, 2012.
30. Shimada H, Nabeya Y, Okazumi S, Matsubara H, Shiratori T, Gunji Y, Kobayashi S, Hayashi H and Ochiai T: Prediction of survival with squamous cell carcinoma antigen in patients with resectable esophageal squamous cell carcinoma. Surgery 133: 486-494, 2003.
31. Kosugi S, Nishimaki T, Kanda T, Nakagawa S, Ohashi M and Hatakeyama K: Clinical significance of serum carcinoembryonic antigen, carbohydrate antigen 19-9, and squamous cell carcinoma antigen levels in esophageal cancer patients. World J Surg 28: 680-685, 2004.
32. Zhang HQ, Wang RB, Yan HJ, Zhao W, Zhu KL, Jiang SM, Hu XG and Yu JM: Prognostic significance of CYFRA21-1, CEA and hemoglobin in patients with esophageal squamous cancer undergoing concurrent chemoradiotherapy. Asian Pac J Cancer Prev 13: 199-203, 2012.
33. Yi Y, Li B, Wang Z, Sun H, Gong H and Zhang Z: CYFRA21-1 and CEA are useful markers for predicting the sensitivity to chemoradiotherapy of esophageal squamous cell carcinoma. Biomarkers 14: 480-485, 2009.
34. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J and Fleig WE: Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev: CD004064, 2010.
35. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, *et al*: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: A report of the V325 Study Group. J Clin Oncol 24: 4991-4997, 2006.
36. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, *et al*: Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: A study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26: 1435-1442, 2008.
37. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, *et al*: Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. Lancet Oncol 15: 78-86, 2014.
38. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, *et al*: Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 30: 1513-1518, 2012.
39. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, Sugimoto N, Shimodaira H, Tokunaga S, Moriwaki T, *et al*: Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31: 4438-4444, 2013.