

Clinical Features and Prognostic Factors of Bone Metastasis in Esophageal Squamous Cell Carcinoma: a retrospective cohort study

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Abstract

Background

This study aimed to characterize the clinical features and identify prognostic factors of bone metastasis in patients with esophageal squamous cell carcinoma.

Methods

We retrospectively analyzed 334 consecutive patients with histologically confirmed esophageal squamous cell carcinoma and bone metastasis treated at the Second Affiliated Hospital of Anhui Medical University between January 2010 and September 2025. Clinical characteristics, treatments, and outcomes were collected. Factors associated with progression-free survival (PFS) and overall survival (OS) were analyzed using two multivariate models based on the number of extrabony metastatic sites and on specific metastatic sites.

Results

Bone metastases most frequently involved the spine (65.6%), ribs (32.6%), and pelvis (22.5%); pulmonary and hepatic metastases were present in 24.9% and 18.6% of patients, respectively. The median PFS, cancer-specific survival (CSS), and OS were 5, 13, and 11 months, respectively. Multivariate analysis identified an Eastern Cooperative Oncology Group performance status of 2 or higher (PFS: HR = 1.701; OS: HR = 2.331) and ≥ 2 extrabony metastatic sites (PFS: HR = 1.654; OS: HR = 2.383) as independent adverse prognostic factors, whereas local therapy for bone metastasis was an independent protective factor (PFS: HR = 0.592; OS: HR = 0.592). When extrabony metastatic sites were replaced by pulmonary and hepatic metastases, hepatic metastasis remained an independent adverse prognostic factor for PFS (HR = 1.817) and OS (HR = 2.068), whereas pulmonary metastasis was not significant.

Conclusions

Performance status, the number of extrabony metastases, hepatic metastasis, and local therapy for bone metastasis are independent prognostic factors for progression-free survival and overall survival in patients with esophageal squamous cell carcinoma and bone metastasis. Patients with concurrent hepatic metastasis represent a subgroup with a poorer prognosis who may require more intensive systemic therapy and closer surveillance.

Introduction

Esophageal cancer is a malignant tumor originating from the esophageal mucosal epithelium and is one of the most prevalent gastrointestinal malignancies in China. According to GLOBOCAN statistics,

esophageal cancer ranks 11th in cancer incidence and 7th in cancer mortality worldwide¹. China bears one of the heaviest burdens of esophageal cancer, with approximately 224,000 new diagnoses and 188,000 deaths in 2022, ranking as the fifth leading cause of cancer death in China and accounting for nearly half of global cases². Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype in China, accounting for more than 85% of cases^{3,4}. Unlike Western countries, where esophageal adenocarcinoma predominates, ESCC in China exhibits distinct epidemiological and demographic characteristics^{3,4}. Moreover, ESCC and esophageal adenocarcinoma differ significantly in terms of recurrence patterns, survival outcomes, and prognostic factors⁵. ESCC histology has been reported to be associated with an unfavorable prognosis in metastatic esophageal cancer⁶. Although advances in surgery, chemoradiotherapy, and immunotherapy have improved the overall prognosis of patients with esophageal cancer—the 5-year overall survival (OS) rate for ESCC in China now reaches approximately 36.9%⁷—the prognosis of metastatic esophageal cancer remains poor.

Bone is one of the most common sites of distant metastasis in esophageal cancer, with a reported incidence of approximately 6.8%–8%^{8,9}. Bone metastasis can cause a series of skeletal-related events (SREs), including intractable bone pain, pathological fractures, spinal cord compression, and neurological deficits, which severely impair patients' quality of life and adversely affect overall prognosis. Although immune checkpoint inhibitors (ICIs) have demonstrated durable clinical efficacy in patients with cancer, their effectiveness is diminished in those with bone metastasis¹⁰. In contrast to breast cancer, prostate cancer, and lung cancer, in which bone metastasis has been extensively studied, large-scale prognostic studies focusing specifically on esophageal cancer with bone metastasis remain relatively limited. Systematic evaluation of the clinical characteristics, prognostic factors, and the value of local therapy in this setting is still lacking. Available data are predominantly derived from studies with small sample sizes or from studies of mixed histological types in which esophageal adenocarcinoma predominates. Large-scale, systematic analyses of prognostic factors in patients with ESCC and bone metastasis therefore remain scarce.

Therefore, the present study aimed to systematically describe the clinical characteristics of patients with ESCC and bone metastasis and to identify independent prognostic factors on the basis of large-scale, real-world, single-center data, thereby providing an evidence base for individualized treatment and prognostic assessment in this population.

Methods

Study Population

This study was a single-center retrospective cohort study that consecutively enrolled 334 patients with histologically confirmed ESCC and bone metastasis who were admitted to the Second Affiliated Hospital of Anhui Medical University between January 2010 and September 2025. The inclusion criteria were as follows: (1) a histological diagnosis of ESCC; (2) bone metastasis confirmed by imaging, including

computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), or bone scintigraphy, or by pathological examination of a bone biopsy specimen; and (3) complete clinical and follow-up data. The exclusion criteria were: (1) a history of other primary malignancies and (2) insufficient evidence of bone metastasis. The study was approved by the Institutional Review Board of the Second Affiliated Hospital of Anhui Medical University, and the requirement for informed consent was waived because of the retrospective nature of the study.

Data Collection and Variable Definition

Clinical data were retrospectively collected through the hospital electronic medical record system, including demographic characteristics (age and sex), Karnofsky Performance Status (KPS) score, Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor characteristics (location, pathological type, and degree of differentiation), bone metastasis characteristics (time of bone metastasis diagnosis, symptoms, number of metastatic lesions, metastatic sites, imaging features, peripheral soft tissue invasion, presence of extrabony metastases, and presence of pathological fractures or spinal cord compression), the interval from primary tumor diagnosis to bone metastasis, treatment modalities for the primary tumor and bone metastases (including surgery, radiotherapy, systemic therapy, and their combinations, as well as bone-modifying agents), and survival follow-up information. Follow-up was conducted through outpatient visits, inpatient medical records, and telephone interviews.

The primary endpoint was OS, defined as the time from the diagnosis of bone metastasis to death from any cause; patients who were alive at the last follow-up were censored. The secondary endpoints were progression-free survival (PFS), cancer-specific survival (CSS), and recurrence patterns. PFS was defined as the time from the diagnosis of bone metastasis to the first radiographic or clinical evidence of disease progression or recurrence, or to death from any cause. CSS was defined as the time from the diagnosis of bone metastasis to death attributable to esophageal cancer. The timing of bone metastasis was classified as synchronous or metachronous: bone metastasis detected at the initial diagnosis of the primary tumor or within 6 months thereafter was defined as synchronous, whereas metastasis occurring later than 6 months was defined as metachronous.

Statistical Analysis

Statistical analysis was performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were expressed as the mean $\pm$ standard deviation, and non-normally distributed continuous variables as the median (range). Categorical variables were presented as numbers (percentages). Survival was analyzed using the Kaplan–Meier method. Univariate P-values in Table 1 were calculated by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) in Table 1 were estimated by univariate Cox proportional hazards regression analysis, with the reference category denoted as Ref, to assess the association of each clinical variable with PFS and OS. Because pulmonary and hepatic metastases represent specific sites of extrabony metastasis, their simultaneous

inclusion with the variable “number of extrabony metastases” would introduce multicollinearity and compromise model stability. Therefore, two separate multivariate models were constructed: Model 1 incorporated the composite indicator “number of extrabony metastases (0–1 vs. ≥ 2)”, which represents the overall metastatic burden, whereas Model 2 replaced the number of extrabony metastases with pulmonary and hepatic metastases to evaluate the independent prognostic value of different metastatic sites. Variables with $P < 0.1$ in the univariate analysis were entered into the multivariate Cox proportional hazards regression model to adjust for confounding factors; P-values in Tables 2 and 3 were obtained from the Wald test within the multivariate model. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Table 1

Clinical characteristics and univariate survival analysis of ESCC patients with bone metastasis

Clinical Characteristics	No. (n = 334)	PFS		OS	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age		0.817 (0.607–1.099)	0.154	0.788 (0.541–1.147)	0.201
≤ 60 years	130				
> 60 years	204				
Sex		0.849 (0.575–1.253)	0.381	0.752 (0.457–1.237)	0.249
Male	284				
Female	50				
Primary Tumor Location			< 0.001†		0.001†
Cervical	1	103.487 (9.196–1164.557)	< 0.001†	22.524 (1.977–256.673)	0.012†
Upper thoracic	28	0.661 (0.237–1.845)	0.429	0.682 (0.140–3.309)	0.635
Middle thoracic	193	0.914 (0.371–2.253)	0.845	1.196 (0.291–4.912)	0.804
Lower thoracic	100	1.036 (0.415–2.587)	0.940	1.222 (0.293–5.101)	0.783
Multifocal	12	1 (Ref.)	-	1 (Ref.)	-
Pathological Differentiation			0.361		0.552
Poor	173	1 (Ref.)	-	1 (Ref.)	-
Moderate	99	1.177 (0.841–1.646)	0.342	1.209 (0.790–1.850)	0.383
Well	10	1.904 (0.769–4.713)	0.164	1.965 (0.708–5.449)	0.195
Undifferentiated	10	0.720 (0.348–1.488)	0.375	0.773 (0.308–1.939)	0.584
Unknown	42	1.014 (0.647–1.588)	0.953	0.992 (0.578–1.705)	0.978
Note:					

Clinical Characteristics	No. (n = 334)	PFS		OS	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Symptoms of BM			< 0.001*		< 0.001*
Pain	240	1.306 (0.941–1.811)	0.110	1.728 (1.106–2.700)	0.016*
SC compression/ paraplegia	6	5.482 (2.147–13.996)	< 0.001*	12.031 (4.485–32.270)	< 0.001*
Asymptomatic	88	1 (Ref.)	-	1 (Ref.)	-
Pathological Fracture		0.805 (0.458–1.416)	0.424	0.836 (0.423–1.653)	0.598
Yes	31				
No	303				
KPS Score			0.016*		< 0.001*
≤ 70	77	1 (Ref.)	-	1 (Ref.)	-
80	96	0.607 (0.396–0.930)	0.022*	0.558 (0.344–0.906)	0.018*
≥ 90	161	0.611 (0.417–0.895)	0.011*	0.387 (0.245–0.612)	< 0.001*
ECOG PS		1.636 (1.134–2.361)	0.005*	2.344 (1.541–3.564)	< 0.001*
0–1	257				
≥ 2	77				
Timing of BM		1.172 (0.865–1.588)	0.275	1.306 (0.881–1.935)	0.172
Synchronous	122				
Metachronous	212				
Number of BM		1.118 (0.833–1.501)	0.428	1.256 (0.864–1.825)	0.220
Single	126				
Multiple	208				
Note:					

Clinical Characteristics	No. (n = 334)	PFS		OS	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Peripheral Soft Tissue Invasion		1.491 (1.103–2.016)	0.005*	1.497 (1.026–2.185)	0.030*
Yes	107				
No	227				
Nature of BM			0.221		0.330
Osteolytic	298	1 (Ref.)	-	1 (Ref.)	-
Osteoblastic	14	1.251 (0.660–2.373)	0.493	0.990 (0.434–2.260)	0.982
Mixed	22	0.670 (0.386–1.162)	0.154	0.589 (0.286–1.214)	0.151
Extrabony Metastasis			< 0.001*		< 0.001*
No	144	1 (Ref.)	-	1 (Ref.)	-
Single metastatic site	39	0.855 (0.520–1.407)	0.538	0.674 (0.314–1.444)	0.310
Multiple metastatic sites	151	1.834 (1.338–2.514)	< 0.001*	2.522 (1.689–3.765)	< 0.001*
Pulmonary Metastasis		1.576 (1.144–2.171)	0.003*	1.723 (1.161–2.556)	0.005*
Yes	83				
No	251				
Hepatic Metastasis		1.896 (1.332–2.700)	< 0.001*	2.074 (1.351–3.184)	< 0.001*
Yes	62				
No	272				
History of Primary Tumor Surgery		1.112 (0.833–1.486)	0.442	1.041 (0.724–1.497)	0.824
Yes	170				
No	164				
Local Therapy for BM			0.010*		0.192
Note:					

Clinical Characteristics	No. (n = 334)	PFS		OS	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Radiotherapy	122	0.674 (0.495–0.916)	0.012*	0.695 (0.470–1.028)	0.069
PVP	10	0.382 (0.155–0.941)	0.037*	0.573 (0.208–1.575)	0.280
Surgery	5	1.100 (0.448–2.700)	0.836	1.211 (0.440–3.332)	0.711
No	197	1 (Ref.)	-	1 (Ref.)	-
Bone-Modifying Agents		0.878 (0.658–1.173)	0.349	0.838 (0.582–1.207)	0.330
Yes	154				
No	180				
Systemic Therapy		1.055 (0.754–1.475)	0.742	1.033 (0.677–1.577)	0.877
Yes	224				
No	110				
Interval from Primary Tumor to BM		0.883 (0.657–1.187)	0.380	0.902 (0.623–1.307)	0.577
≤ 1 year	199				
> 1 year	135				
Note:					

Table 2
Multivariate analysis of PFS and OS by extrabony metastatic burden

Clinical Characteristics	PFS	OS		
	HR (95% CI)	P-value	HR (95% CI)	P-value
ECOG PS				
0–1 vs ≥ 2	1.701 (1.156–2.504)	0.007*	2.331 (1.487–3.654)	< 0.001*
SREs				
Yes vs No	1.209 (0.845–1.730)	0.298	1.508 (0.932–2.439)	0.094
Peripheral Soft Tissue Invasion				
Yes vs No	1.480 (1.080–2.027)	0.015*	1.405 (0.948–2.083)	0.091
Number of Extrabony Metastases				
0–1 vs ≥ 2	1.654 (1.220–2.243)	0.001*	2.383 (1.617–3.512)	< 0.001*
Local Therapy for Bone Metastasis				
Yes vs No	0.592 (0.434–0.808)	0.001*	0.592 (0.400–0.876)	0.009*

Table 3
Multivariate analysis of PFS and OS by pulmonary and hepatic metastases

Clinical Characteristics	PFS	OS		
	HR (95% CI)	P-value	HR (95% CI)	P-value
ECOG PS				
0–1 vs ≥ 2	1.690 (1.143–2.500)	0.009*	2.457 (1.549–3.896)	< 0.001*
SREs				
Yes vs No	1.258 (0.879–1.801)	0.210	1.567 (0.966–2.541)	0.069
Peripheral Soft Tissue Invasion				
Yes vs No	1.476 (1.074–2.030)	0.016*	1.464 (0.983–2.181)	0.061
Pulmonary Metastasis				
Yes vs No	1.357 (0.970–1.897)	0.075	1.414 (0.936–2.135)	0.100
Hepatic Metastasis				
Yes vs No	1.817 (1.271–2.597)	0.001*	2.068 (1.336–3.200)	0.001*
Local Therapy for Bone Metastasis				
Yes vs No	0.591 (0.432–0.807)	0.001*	0.590 (0.397–0.878)	0.009*

Results

Patient Baseline Characteristics

A total of 334 patients with ESCC and bone metastasis were enrolled, and their baseline clinical characteristics are summarized in Table 1. The median age was 64 years (range, 38–90 years). Of these patients, 284 (85.0%) were male and 50 (15.0%) were female. Most patients presented with bone pain as the initial clinical manifestation (n = 240, 71.9%), whereas 88 patients (26.3%) were asymptomatic. KPS scores were 50 in 2 patients, 60 in 11, 70 in 64, 80 in 96, 90 in 151, and 100 in 10. Nearly half of the patients (n = 145, 43.4%) had visceral metastases beyond bone, including pulmonary metastasis in 83 patients (24.9%), hepatic metastasis in 62 (18.6%), and brain metastasis in 6 (1.8%). Approximately one-third of the patients (n = 122) had synchronous bone metastasis. The median interval from primary tumor diagnosis to bone metastasis was 10 months (range, 0–147.5 months), from pulmonary

metastasis diagnosis to bone metastasis 0 months (range, 0–81 months), and from hepatic metastasis diagnosis to bone metastasis 0.5 months (range, 0–9 months). Bone metastasis occurred within the first year after primary tumor diagnosis in 59.6% of patients, within 2 years in 75.7%, and within 3 years in 85.6%. The most common sites of bone metastasis were the spine (n = 219, 65.6%; including 42 cervical, 143 thoracic, 79 lumbar, 17 sacral, and 1 coccygeal vertebra), ribs (n = 109, 32.6%), pelvis (n = 75, 22.5%), limb bones (n = 46, 13.8%), scapula (n = 25, 7.5%), sternum (n = 24, 7.2%), skull (n = 18, 5.4%), and clavicle (n = 7, 2.1%) (Fig. 1).

Treatment of Bone Metastasis in ESCC

Among the ESCC patients with bone metastasis, 137 received local therapy directed at bone metastatic lesions. Most of these patients (n = 122, 89.1%) received radiotherapy for bone metastases, 10 underwent percutaneous vertebroplasty (PVP), and 5 underwent surgical resection of bone metastatic lesions (of whom 2 received surgical resection followed by postoperative tumor bed radiotherapy). Compared with patients who did not receive local therapy for bone metastases, those who received radiotherapy or PVP demonstrated superior PFS, although no significant difference was observed in OS. Only 5 patients underwent surgical resection of bone metastatic lesions; their PFS (HR = 1.100, 95% CI 0.448–2.700, P = 0.836) and OS (HR = 1.211, 95% CI 0.440–3.332, P = 0.711) did not differ significantly from those of patients who did not receive local therapy for bone metastatic lesions, which may be attributable to the small sample size.

Nearly half of the patients (n = 154, 46.1%) received bone-modifying agents, of whom 130 (84.4%) received bisphosphonates and 24 received denosumab. Univariate analysis showed that patients receiving bisphosphonates had superior PFS and OS compared with those receiving denosumab (PFS: P = 0.039; OS: P = 0.040). However, after adjustment for ECOG PS, extrabony metastatic burden, and local therapy for bone metastasis, multivariate analysis revealed no statistically significant difference between the two groups in either PFS (P = 0.144) or OS (P = 0.069). In addition, 224 patients received systemic therapy, of whom half (n = 112, 50.0%) received chemotherapy, 61 received ICIs combined with chemotherapy, 16 received ICI monotherapy, 18 received targeted therapy monotherapy, 6 received ICIs combined with targeted therapy, 7 received chemotherapy combined with targeted therapy, and 4 received ICIs plus targeted therapy plus chemotherapy. Whether systemic therapy was administered after the diagnosis of bone metastasis was not significantly associated with PFS or OS. Compared with chemotherapy alone, no statistically significant differences in PFS or OS were observed in patients receiving ICIs plus chemotherapy with or without targeted therapy or in those receiving ICI alone. Subgroup analysis showed that, among patients receiving ICIs, PFS and OS did not differ significantly between those with and those without concurrent bone-modifying agent therapy.

Survival Analysis

Survival Outcomes

The median follow-up time was 5 months (range, 0.5–116 months). At the last follow-up, 185 patients had experienced disease progression, including visceral progression (n = 88, 47.6%), bone progression (n = 74, 40.0%), lymph node progression (n = 54, 29.2%), and primary tumor or anastomotic recurrence (n = 19, 10.3%). A total of 117 patients died: 109 of tumor-related causes, 6 of other diseases (pancreatitis, pulmonary infection, myocardial infarction, pulmonary embolism, and chronic obstructive pulmonary disease), 1 of immune-related pneumonitis, and 1 of drug-induced liver injury. Among the 334 ESCC patients with bone metastasis, the median PFS was 5 months, the median CSS was 13 months, and the median OS was 11 months (Fig. 2). The 1-, 2-, and 3-year PFS rates were 22.4%, 11.8%, and 9.5%, respectively; the 1-, 3-, and 5-year CSS rates were 51.1%, 31.1%, and 21.4%, respectively; and the corresponding OS rates were 49.4%, 30.1%, and 20.7% (Fig. 2).

Univariate Survival Analysis

Univariate analysis showed that age, sex, pathological differentiation (poor, moderate, well, undifferentiated, or unknown), presence of pathological fracture, timing of bone metastasis (synchronous vs. metachronous), number of bone metastases (single vs. multiple), nature of bone metastasis (osteolytic, osteoblastic, or mixed), interval from primary tumor diagnosis to bone metastasis (≤ 1 year vs. > 1 year), primary tumor surgery, systemic therapy after bone metastasis, and bone-modifying agent therapy were not significantly associated with PFS or OS in ESCC patients with bone metastasis ($P > 0.05$) (Table 1). In contrast, primary tumor location, KPS score, ECOG PS, peripheral soft tissue invasion, presence of multiple extrabony metastatic sites, presence of pulmonary or hepatic metastasis, and local therapy for bone metastasis were significantly associated with both PFS and OS (Table 1). Patients with SREs had a poorer prognosis, and those with spinal cord compression or paraplegia had the worst prognosis. Patients with bone pain showed a trend toward a difference in PFS compared with asymptomatic patients, although this difference did not reach statistical significance, whereas a statistically significant difference was observed for OS. Primary tumor location was significantly associated with both PFS ($P < 0.001$) and OS ($P = 0.001$). However, this finding should be interpreted with caution, because the cervical esophageal cancer subgroup comprised only one patient (n = 1), and the corresponding hazard ratios were therefore derived from a single observation (PFS: HR = 103.487, 95% CI 9.196–1164.557; OS: HR = 22.524, 95% CI 1.977–256.673); the extremely wide CIs indicate that these estimates are highly unstable. In a sensitivity analysis excluding this single patient, primary tumor location was no longer significantly associated with either PFS ($P = 0.433$) or OS ($P = 0.502$), indicating that the apparent association was largely driven by this one case. Accordingly, the prognostic value of primary tumor location in this cohort should be regarded as exploratory.

Multivariate Cox Regression Analysis (Extrabony Metastatic Burden)

Multivariate analysis (Table 2) demonstrated that ECOG PS ≥ 2 and ≥ 2 extrabony metastatic sites were independent adverse prognostic factors in ESCC patients with bone metastasis, with a stronger impact on OS (HR = 2.331 and 2.383, respectively) than on PFS (HR = 1.701 and 1.654, respectively). SREs did

not reach statistical significance for either PFS or OS. Peripheral soft tissue invasion was an independent adverse prognostic factor for PFS but did not reach statistical significance for OS. Local therapy for bone metastasis exerted an independent protective effect on both PFS and OS.

Multivariate Cox Regression Analysis (Pulmonary and Hepatic Metastases)

When the number of extrabony metastases was replaced by pulmonary and hepatic metastases in the multivariate model, the results are shown in Table 3. Hepatic metastasis (PFS: HR = 1.817, 95% CI 1.271–2.597, $P = 0.001$; OS: HR = 2.068, 95% CI 1.336–3.200, $P = 0.001$) was an independent adverse prognostic factor for both PFS and OS in ESCC patients with bone metastasis, whereas pulmonary metastasis did not reach statistical significance (PFS: HR = 1.357, 95% CI 0.970–1.897, $P = 0.075$; OS: HR = 1.414, 95% CI 0.936–2.135, $P = 0.100$) (Fig. 3). ECOG PS remained an independent adverse prognostic factor, and local therapy for bone metastasis exerted an independent protective effect, in both models. SREs did not reach statistical significance for either PFS or OS. Peripheral soft tissue invasion reached statistical significance for PFS ($P = 0.016$) and showed a borderline trend for OS (HR = 1.464, 95% CI 0.983–2.181, $P = 0.061$).

Discussion

ESCC is the predominant histological subtype of esophageal cancer in China, and bone is one of the most common sites of distant metastasis. Previous studies of esophageal cancer with bone metastasis have been limited by small sample sizes, heterogeneous histological types (predominantly adenocarcinoma), or reliance on the Surveillance, Epidemiology, and End Results (SEER) database^{8,9,11}. Based on large-scale, single-center data from a Chinese population with ESCC and bone metastasis, this study systematically analyzed the clinical characteristics, treatment strategies, and prognostic factors of 334 patients, thereby providing a useful reference for stratified clinical management and, in particular, offering important insights to guide local treatment decisions for bone metastases and the management of patients with hepatic metastases.

In the present study, most ESCC patients with bone metastasis were male (85.0%), consistent with the epidemiological characteristics of ESCC itself¹². Bone metastasis predominantly involved the spine (65.6%; particularly the thoracic vertebrae, followed by the lumbar vertebrae), ribs (32.6%), and pelvis (22.5%), consistent with the previously reported predilection for axial skeletal involvement¹¹. This pattern may be closely related to the anatomical features of the Batson venous plexus, a valveless venous system with slow blood flow that communicates with the esophageal venous plexus and thereby facilitates the retrograde seeding of tumor cells to the vertebral column, which may explain the high frequency of spinal metastasis.

In the present study, visceral progression (47.6%) and bone progression (40.0%) were the most common patterns of disease progression, which reflects the systemic nature of disease progression in ESCC

patients with bone metastasis. This finding is consistent with the results of the multivariate analysis, in which hepatic metastasis was identified as an independent adverse prognostic factor. Furthermore, the median OS of 11 months in the present study was substantially longer than the 4–5 months reported previously^{8,9,11,13}, suggesting that recent advances in immunotherapy-based systemic therapy and aggressive local therapy for bone metastases may have prolonged survival in this patient population.

Both multivariate Cox regression models in the present study indicated that ECOG PS is an independent adverse prognostic factor for both PFS and OS. In these models, patients with ECOG PS ≥ 2 had significantly higher risks of progression and death, consistent with prognostic studies of other tumors with bone metastasis^{14,15}. ECOG PS reflects a patient's overall health status and organ functional reserve. Patients with poor PS have reduced treatment tolerance, more aggressive tumor biology, and impaired immune function, and consequently have a poorer prognosis. Therefore, comprehensive assessment of PS before treatment is of considerable value for prognostic evaluation and treatment decision-making.

The present study demonstrated that the extrabony metastatic burden is closely associated with prognosis. The presence of ≥ 2 extrabony metastatic sites was an independent adverse prognostic factor for PFS and OS, suggesting that multi-organ extrabony metastasis reflects a higher systemic tumor burden, a greater susceptibility to visceral progression, and a poorer prognosis. Models constructed by replacing the number of extrabony metastases with pulmonary and hepatic metastases further revealed differences in the independent prognostic value of different metastatic sites: hepatic metastasis was an independent adverse prognostic factor for PFS (HR = 1.817, P = 0.001) and OS (HR = 2.068, P = 0.001), whereas pulmonary metastasis did not reach statistical significance for either endpoint. Previous studies based on the SEER database identified hepatic and pulmonary metastases as independent adverse prognostic factors in esophageal cancer patients with bone metastasis⁹, and hepatic metastasis has likewise been reported as an independent adverse prognostic factor in ESCC patients with bone metastasis, whereas pulmonary metastasis showed no significant association¹⁶, consistent with our findings. Several mechanisms may account for these observations. (1) Hepatic metastasis often reflects more extensive systemic dissemination and a higher tumor burden, indicating a more advanced disease stage. (2) Hepatic metastatic lesions progressively replace the hepatic parenchyma, leading to progressive hepatic insufficiency (jaundice, hypoalbuminemia, coagulopathy, and others) that directly compromises patient survival, whereas pulmonary metastasis has a relatively limited effect on respiratory function at an early stage. Moreover, deterioration of hepatic function restricts subsequent systemic therapies such as chemotherapy and immunotherapy, creating a vicious cycle of metastatic burden, treatment restriction, and accelerated progression. (3) Esophageal venous drainage enters the liver through the portal venous system, and esophageal cancer cells readily lodge in the hepatic sinusoids via the portal circulation, resulting in early-onset, high-burden hepatic metastases; the abundant blood supply and high blood flow of the liver further promote the rapid growth of metastatic lesions. (4) Pulmonary metastases are more readily detected at an early stage by routine chest CT and exert a limited effect on early progression, whereas hepatic metastasis is often already

extensive at diagnosis. In addition, pulmonary metastasis, particularly oligometastatic disease, may occasionally benefit from local therapy such as stereotactic body radiotherapy (SBRT), whereas extensive hepatic metastasis usually precludes curative local treatment and responds poorly to systemic therapy, further widening the prognostic difference. Therefore, ESCC patients with bone metastasis who also have hepatic metastasis should be recognized as a subgroup with a poorer prognosis who require more intensive systemic therapy and closer surveillance.

Univariate analysis in the present study showed that local therapy for bone metastasis was significantly associated only with PFS ($P = 0.010$) but not with OS ($P = 0.192$), with a trend toward benefit in the radiotherapy subgroup ($HR = 0.695$, $P = 0.069$). However, after adjustment for ECOG PS, extrabony metastatic burden, and other confounding factors, both multivariate models demonstrated that local therapy for bone metastasis was an independent protective factor for prognosis. This discrepancy suggests that the univariate result may have been confounded by indication bias, whereas multivariate analysis more accurately reflects the true prognostic value of local therapy. Radiotherapy, as the most commonly used local therapy for bone metastasis, effectively alleviates bone pain, prevents pathological fractures and spinal cord compression, and improves quality of life. PVP provides rapid pain relief and restores spinal stability by injecting bone cement or artificial bone into the affected vertebrae and is particularly beneficial for spinal metastasis. These results indicate that, for symptomatic bone metastatic lesions or those at risk of complications, aggressive local palliative therapy can improve prognosis and should be an integral component of comprehensive bone metastasis management. Notably, only 5 patients in the present study underwent surgical resection of bone metastatic lesions, and neither PFS nor OS showed a statistically significant benefit; all 5 patients experienced disease progression due to extrabony metastases. This result may be influenced by several factors: (1) the extremely small sample size ($n = 5$) provided insufficient statistical power to detect a potential clinical benefit; (2) patients who underwent surgery generally had more aggressive clinical presentations requiring decompression and fixation because of spinal instability, spinal cord compression, or pathological fractures, and therefore had a poorer baseline prognosis than those treated with radiotherapy or PVP alone, so that selection bias cannot be fully adjusted for; and (3) perioperative trauma may adversely affect the overall condition and subsequent treatment tolerance of patients with advanced esophageal cancer. Therefore, verification in larger prospective studies is warranted.

This study demonstrated that whether systemic therapy was administered after the diagnosis of bone metastasis was not significantly associated with PFS or OS, which is inconsistent with previous studies reporting chemotherapy as an independent prognostic factor in esophageal cancer patients with bone metastasis^{16,17}. Several possible reasons should be considered. First, this was a real-world retrospective study, and decisions regarding systemic therapy were influenced by multiple factors, including performance status, organ function, financial status, and treatment preference; patients with a heavier tumor burden were more likely to receive systemic therapy, resulting in substantial indication bias. In addition, "whether systemic therapy was administered" was included as a binary variable without adjustment for the timing of treatment, which may have introduced time-related bias. Second, the systemic therapy regimens used in this study were highly heterogeneous and included chemotherapy,

immunotherapy combined with chemotherapy, immunotherapy alone, and targeted therapy (predominantly chemotherapy, 112 cases, 50%), and the substantial variation in efficacy among these regimens may have diluted the overall effect when they were analyzed together. Third, the relatively short median follow-up (5 months) and the high censoring rate may have compromised the assessment of any true benefit of systemic therapy. Therefore, this negative result should not be interpreted as evidence that systemic therapy is ineffective. Previous studies have reported that, compared with patients without bone metastasis, those with bone metastasis have poorer survival after ICI therapy^{10,18}. In the present study, survival analysis showed no statistically significant differences in PFS or OS between patients receiving ICIs plus chemotherapy with or without targeted therapy or ICI monotherapy and those receiving chemotherapy alone. The reasons may be as follows: (1) bone metastatic lesions harbor a unique immunosuppressive microenvironment, in which bone marrow stromal cells, osteoblasts, and osteoclasts secrete immunosuppressive factors such as TGF- β and IL-10, and the enrichment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) may attenuate the antitumor efficacy of ICIs¹⁹; (2) the prognosis of ESCC patients with bone metastasis is extremely poor (median OS and PFS of only 11 and 5 months, respectively), and differences between treatment groups may be masked by the aggressive nature of the disease itself; (3) patients receiving combination immunotherapy may have had poorer baseline characteristics, and selection bias may have offset the potential benefit of immunotherapy; (4) recent studies have shown that ICIs exert negative effects on skeletal structure, as activated T cells can secrete RANKL to promote osteoclast differentiation and bone resorption, and skeletal muscle toxicity among immune-related adverse events can lead to osteoporosis and pathological fractures¹⁰, so that the increased fracture risk may partially offset the survival benefit of immunotherapy; (5) bone metastatic lesions may exhibit specific resistance to immunotherapy, and factors such as low PD-L1 expression levels, growth factors released from the bone matrix that promote immune escape, and a hypoxic microenvironment that inhibits T-cell function may all contribute to the limited efficacy of ICIs in patients with bone metastasis^{10,20}; and (6) this study was retrospective and spanned a long period (2010–2025), during which treatment concepts and drug availability changed substantially; some patients may have received immunotherapy only after progression on chemotherapy, which may also have affected the comparability of the treatment groups. Subgroup analysis in this study further showed that, among patients receiving immunotherapy, PFS and OS did not differ significantly between those who did and did not receive concurrent bone-modifying agent therapy. The reasons are as follows. First, the primary mechanism of bone-modifying agents is inhibition of osteoclast activity and reduction of the incidence of SREs rather than a direct antitumor effect²¹, and their impact on PFS and OS may therefore be limited. Second, patients receiving bone-modifying agents in this study may have had a heavier bone metastatic burden and a poorer baseline prognosis, and selection bias may have offset any potential survival benefit. Third, patients varied considerably in the timing, duration, and compliance of bone-modifying agent therapy, and some may have received non-standard treatment or an insufficient duration, which would limit the full realization of therapeutic efficacy. Fourth, bone-modifying agents may indirectly influence the efficacy of immunotherapy by improving the bone microenvironment¹⁰, but this effect may require longer follow-up to become apparent. In summary, the

immunosuppressive characteristics of the bone metastatic microenvironment, immunotherapy-related skeletal adverse events, the indirect antitumor mechanisms of bone-modifying agents, sample size limitations, and selection bias collectively contributed to the absence of statistically significant differences in PFS and OS among the three treatment groups and among the bone-modifying agent subgroups. Previous randomized controlled trials demonstrated that, in patients with bone metastasis from solid tumors (excluding breast and prostate cancer), denosumab was non-inferior to zoledronic acid in delaying the first SRE, with similar OS and time to disease progression between the two groups²¹. In the present study, 46.1% of patients received bone-modifying agents, predominantly bisphosphonates (130 cases, 84.4%). Univariate analysis showed statistically significant differences in PFS and OS between the bisphosphonate and denosumab groups, whereas multivariate analysis revealed no statistically significant difference between the two groups. This may be related to the following factors: the small sample size of the denosumab group (n = 24) resulted in insufficient statistical power, and denosumab was predominantly used in patients with poorer baseline characteristics, such as renal insufficiency or prior bisphosphonate resistance, resulting in indication bias. Therefore, whether the two types of bone-modifying agents differ in survival benefit in ESCC patients with bone metastasis remains undetermined and awaits verification in larger randomized studies.

This study has several limitations. First, as a single-center retrospective study, it is inherently subject to selection bias and unmeasured confounding. Second, the follow-up duration was relatively short (median, 5 months), and only a small proportion of patients achieved long-term survival, which may have reduced the precision of the OS estimates. Third, the sample size was relatively limited, particularly in the surgery and denosumab subgroups, resulting in insufficient statistical power for some subgroup analyses. Fourth, molecular markers, such as circulating tumor DNA (ctDNA) and PD-L1 expression, were not included. Nevertheless, the strengths of this study include the use of large-scale, real-world data from an ESCC-predominant Chinese population; the systematic integration of clinical characteristics, treatment, and prognostic analyses of bone metastasis; and the differentiation of the prognostic value of different metastatic sites using sensitivity models, which together provide evidence to support individualized treatment of patients with ESCC and bone metastasis.

In summary, this study demonstrated that ECOG PS, local therapy for bone metastasis, extrabony metastatic burden, and hepatic metastasis are independent prognostic factors for PFS and OS in patients with ESCC and bone metastasis. Improving performance status, appropriately applying local therapy, and paying particular attention to patients with hepatic metastasis may help improve prognosis.

Abbreviations

BMs: bone metastases

CI: confidence interval

CSS: cancer-specific survival

CT: computed tomography

ECOG PS: Eastern Cooperative Oncology Group performance status

ESCC: esophageal squamous cell carcinoma

GLOBOCAN: Global Cancer Observatory

HR: hazard ratio

ICIs: immune checkpoint inhibitors

KPS: Karnofsky Performance Status

MRI: magnetic resonance imaging

OS: overall survival

PET/CT: positron emission tomography/computed tomography

PFS: progression-free survival

PVP: percutaneous vertebroplasty

SBRT: stereotactic body radiotherapy

SEER: Surveillance, Epidemiology, and End Results

SREs: skeletal-related events

Declarations

Ethics approval and consent to participate:

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Second Affiliated Hospital of Anhui Medical University and with the 1964 Declaration of Helsinki (as revised in Edinburgh in 2000). The requirement for individual informed consent was waived because of the retrospective nature of the analysis.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

YY conceived and designed the study. RX and XT collected and assembled the data. YY and RX performed the statistical analysis and interpreted the data. YY drafted the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because of patient privacy and institutional restrictions, but are available from the corresponding author on reasonable request.

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Figures

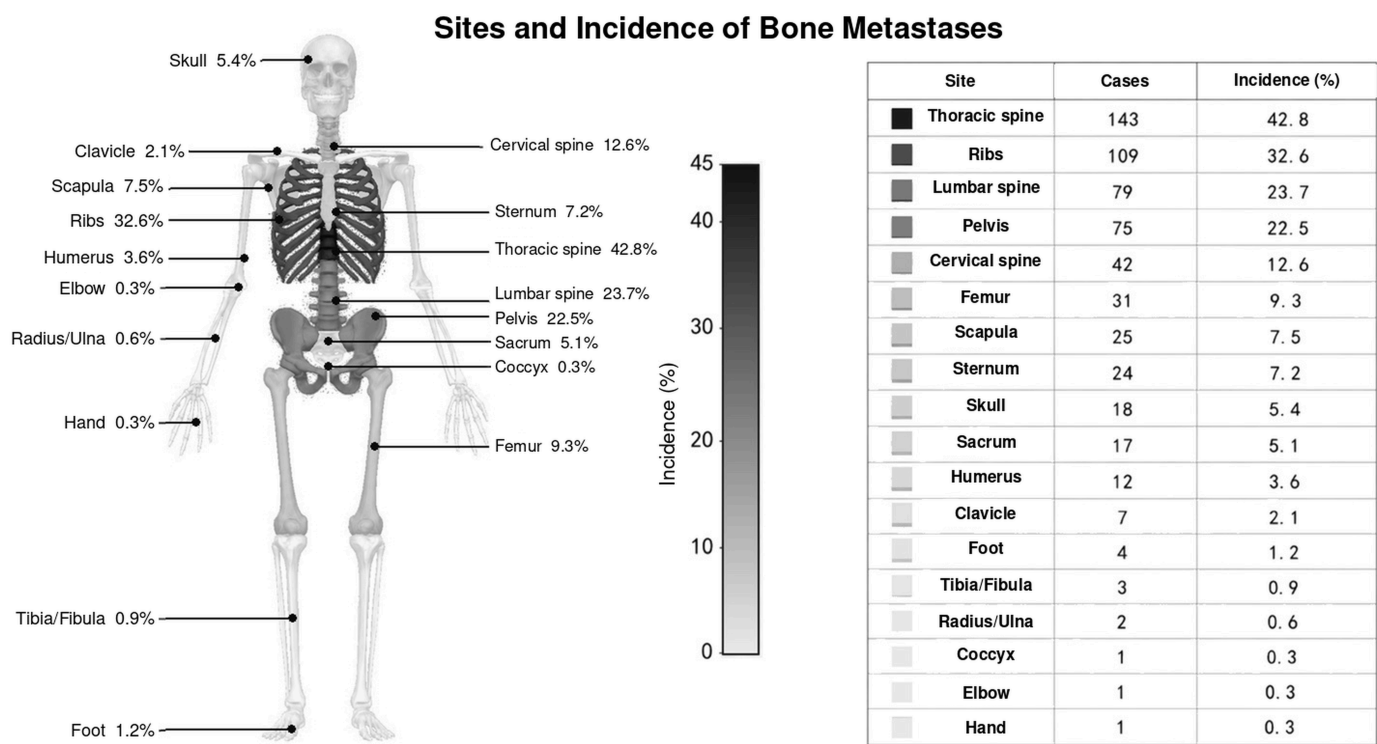


Figure 1

Sites and incidence of bone metastases in patients with esophageal squamous cell carcinoma (ESCC).

Figure 1. Schematic illustration of the human skeleton (left) and the corresponding table (right) showing the sites and incidence of bone metastases. The incidence at each skeletal site is expressed as a percentage of the 334 patients; shading in both panels encodes incidence, with darker shading indicating a higher incidence. The thoracic spine (42.8%), ribs (32.6%), lumbar spine (23.7%), and pelvis (22.5%) were the most frequently involved sites.

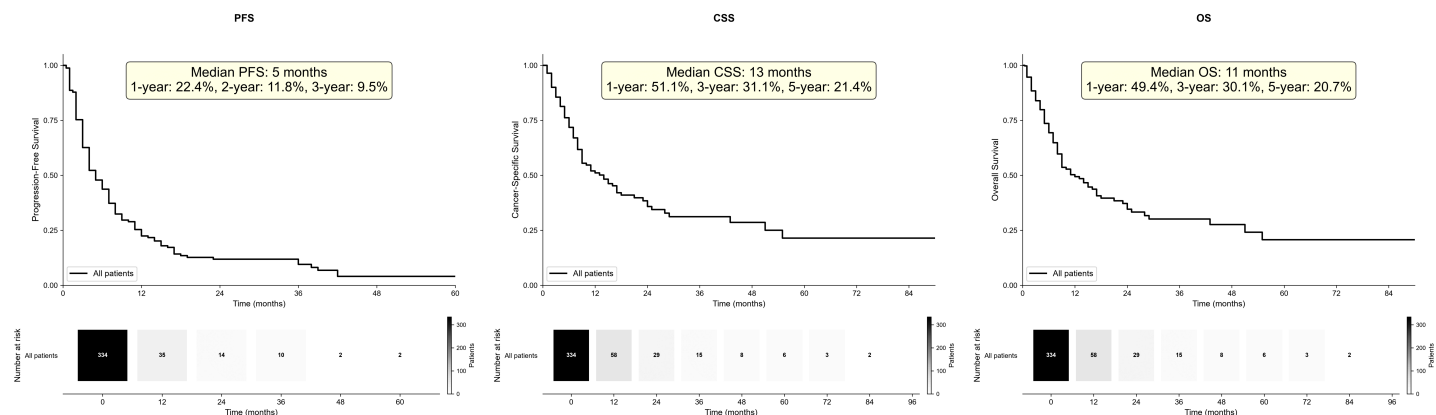


Figure 2

Progression-free, cancer-specific, and overall survival of patients with ESCC and bone metastasis.

Figure 2. Kaplan-Meier curves for progression-free survival (PFS; left), cancer-specific survival (CSS; middle), and overall survival (OS; right) in all 334 patients. Median survival and 1-, 2-, 3-, or 5-year survival rates are shown in the inset boxes: median PFS 5 months (1-, 2-, and 3-year rates 22.4%, 11.8%, and 9.5%); median CSS 13 months (1-, 3-, and 5-year rates 51.1%, 31.1%, and 21.4%); and median OS 11 months (1-, 3-, and 5-year rates 49.4%, 30.1%, and 20.7%). The number of patients at risk is shown beneath each panel.

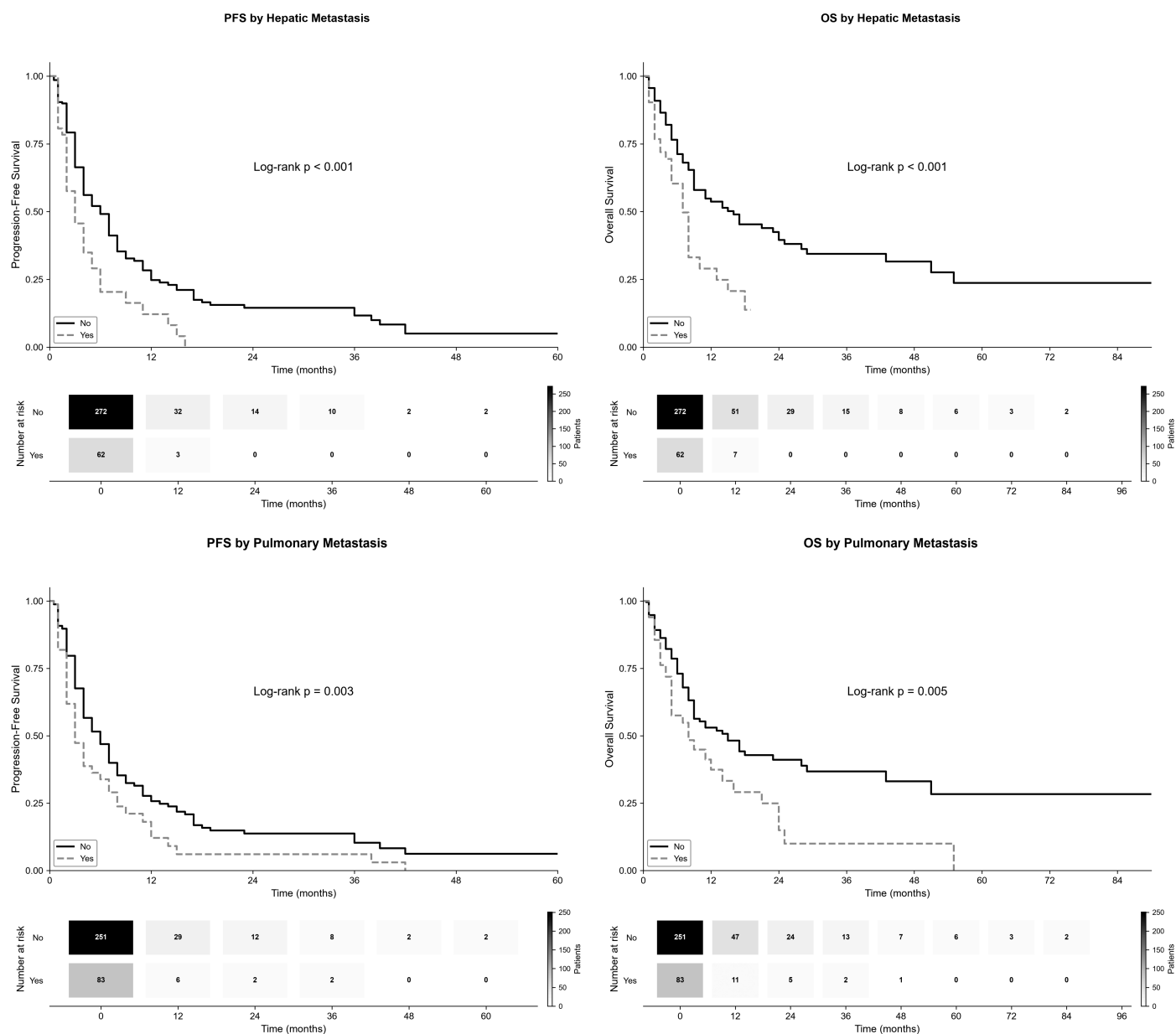


Figure 3

Survival of patients with ESCC and bone metastasis by hepatic and pulmonary metastasis.

Figure 3. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) according to the presence (dashed line) or absence (solid line) of hepatic metastasis (top) or pulmonary metastasis (bottom). Patients with hepatic metastasis had significantly shorter PFS (log-rank $P < 0.001$) and OS ($P < 0.001$) than those without; pulmonary metastasis was also associated with significantly shorter PFS ($P = 0.003$) and OS ($P = 0.005$). The number of patients at risk at each time point is shown beneath each panel.