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Brain metastasis from esophageal squamous cell carcinoma: a clinical review of 30 cases

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This study aimed to retrospectively evaluate the treatment strategies and possible prognostic factors in patients with brain metastases (BMs) from esophageal squamous cell carcinoma (ESCC). We retrospectively reviewed 30 patients with BMs from ESCC who were treated at our center between November 2011 and January 2022. Clinicopathological characteristics and clinical outcomes were analyzed. The median follow-up time was 2 (range, 0.5–33) months. The median survival time after diagnosis of BMs was 2 months. The 1-year overall survival (OS) rate was 13.6%. The OS was better in patients with intracranial benefit. Multivariate analysis showed that local treatment of BMs influenced OS. The median survival with or without local treatment of BMs was 4 and 1 month, respectively. The median time interval between the diagnosis of the primary tumor and BMs was 11 (range, 1–156) months. Among these BMs, 55.6% of the BM occurred within the first year after diagnosis of the primary tumor, 66.7% in the first 2 years, and 85.2% in the first 3 years. The median time interval from lung metastasis to BMs was 3 months, from liver metastasis to BMs 3.5 months, and from bone metastasis to BMs 0.5 months. Local treatment of BMs was an independent prognostic factor for patients with BMs from ESCC. Earlier detection followed by an aggressive local therapeutic approach for BMs had a great influence on treatment outcomes as well as the long-term prognosis and quality of life for appropriately selected patients.

Key words: esophageal squamous cell carcinoma; brain metastasis; prognosis

Esophageal carcinoma (EC) is the seventh most common cancer worldwide and the sixth most common cause of cancer-related death [1]. The common pathological subtypes include adenocarcinoma (AC) and squamous cell carcinoma (SCC). In contrast to Western countries, where esophageal adenocarcinoma (EAC) is predominant, esophageal squamous cell carcinoma (ESCC) is predominant in some eastern and southeast Asian countries, including Japan and China [2]. EC is a tumor that is prone to distant metastases. The most common sites of distant metastases are the liver, lungs, and bone, but rarely disseminate to the brain, muscle, and soft tissue [3–5]. The incidence of brain metastasis (BM) accounts for 0.3–5% in EC [3, 4, 6–13]. Compared to other metastatic sites such as the liver, lungs, and bone, BM has worse overall survival (OS) in EC [8, 14]. Compared to patients with EAC, patients with ESCC are less likely to present with BMs [4, 12, 14]. The incidence of BM accounts for 0.3–1.4% in ESCC [11–13] and 4.2–16% in EAC [12, 13, 15]. Few articles systematically analyze BM in EC, especially ESCC, so it requires a deeper analysis. The present study reviewed our single institution experience and aimed to investigate the clinicopathological characteristics, prognostic factors, and treatment modalities in this group of patients.

Patients and methods

We retrospectively analyzed data from 37 consecutive patients with BMs from EC who were treated at The Second Affiliated Hospital of Anhui Medical University (Hefei, China) between November 2011 and January 2022. All procedures performed in studies 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 the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Individual consent for this retrospective analysis was waived. In all cases, the EC was pathologically confirmed, and the BM was diagnosed by computed tomography or magnetic resonance imaging

(MRI). Among the 37 patients with BMs from EC, five cases of neuroendocrine carcinoma, one case of EAC, and one case of adenosquamous carcinoma were excluded, while the remaining 30 cases of ESCC were included in the present study. Clinicopathological characteristics, including age at BM diagnosis, gender, histological subtype, neurological symptoms, primary tumor location, Karnofsky Performance Status (KPS), Eastern Cooperative Oncology Group performance status (ECOG PS), number of BMs, extracranial metastases at BM, date of initial diagnosis of EC, date of diagnosis of metastatic disease, date of diagnosis of BM, treatment modalities, clinical outcomes, and causes of death were reviewed.

A previous large cohort, recursive partitioning analysis (RPA)-based classification model was used to split all patients with BMs into 3 groups [16]: Class I included all patients with KPS ≥70 and age <65 years who had a controlled primary tumor and no extracranial metastases; Class III included all patients with KPS <70, and Class II included all remaining patients.

The primary endpoints of this study were OS and intracranial progression-free survival (iPFS). OS was defined as the time interval from the date of diagnosis of BMs until death. iPFS was defined as the time interval from the date of diagnosis of BMs until intracranial progression or last follow-up or death. The intracranial response was assessed two months after the diagnosis of BMs based on adapted criteria as proposed by the Response Assessment in Neuro-Oncology Brain Metastases working group (RANO-BM) [17]. Intracranial progression was defined as a new enhancing lesion or an increase of at least 20% in the maximum diameter of the target lesion. Intracranial tumor control rate was defined as the proportion of patients with the best intracranial response of complete response (CR), partial response (PR), or stable disease (SD). Survival curves were plotted using the Kaplan-Meier method and compared by the log-rank test. The significant variables in univariate analyses ($p<0.05$) were included in a multivariate analysis, and multivariate analysis was then performed using the Cox proportional hazard model. Statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 25.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided and a $p<0.05$ was considered to be statistically significant.

Results

Patients' clinicopathological characteristics. In total, 30 ESCC patients with BMs were included in the present study. A summary of the patients' clinicopathological characteristics is listed in Table 1. The median age at diagnosis of BMs was 63.5 (range, 39–77) years, including 27 men and 3 women. There was an obvious male preponderance (n=27; 90%), with a male-to-female ratio of 9:1. Most patients with BMs were accompanied by neurological symptoms, including motor disturbance (40%), headache (40%), dizziness (36.7%), nausea/emesis (13.3%), speech difficulty (10%), visual disturbance (3.3%), emotional change (3.3%), memory deterioration (3.3%), and hypersomnia (3.3%). Among these, motor disturbance and headache were the most common symptoms, followed by dizziness. No patients had combined meningeal metastases. One patient was accompanied by cerebral infarction, and three patients presented with an intertumoral hemorrhage. The location of the primary tumor was the upper thoracic esophagus in 3 cases, the middle thoracic esophagus in 17 cases, and the lower thoracic esophagus in 9 cases. In addition, one patient presented with multifocal lesions. A total of 3 patients (10%) had synchronous BMs, while the remaining 27 patients (90%) had metachronous BMs. All 3 patients with synchronous BMs had more than one extracranial metastasis. At diagnosis of BMs, 5 patients had metastasis confined to the brain, and the remaining 25 patients had combined extracranial metastasis, including 16 with lung metastasis (64%, among them 2 [8%] with lung-only metastasis), 12 with cervical lymph node metastasis (48%), 10 with liver metastasis (40%), 8 with bone metastasis (32%, among them 1 [4%] with bone-only metastasis), 8 with adrenal gland metastasis (32%), 4 with pleural metastasis (16%), 4 with retroperitoneal lymph node metastasis (16%), and 3 with other metastases (12%). According to the RPA classification, 3 patients were in Class I, 21 in Class II, and 6 in Class III.

Timing of BM occurrence. Of the patients with metachronous BMs, the median time interval between the diagnosis of the primary tumor and BMs was 11 (range, 1–156) months. Among these BMs, 55.6% of the BM occurred within the first year after diagnosis of the primary tumor, 66.7% in the first 2 years, and 85.2% in the first 3 years. The extracranial organ most frequently affected was the lung, followed by the liver and the bone. The time interval between extracranial metastasis and BMs was also analyzed: the median time interval from lung metastasis to BMs was 3 (range, 0–31) months, from liver metastasis to BMs 3.5 (range, 0–22) months, and from bone metastasis to BMs 0.5 (range, 0–19) months (Table 2).

Treatments. Among the 30 patients in our study, more than half of patients (n=17; 56.7%) underwent surgical resections of primary tumors before. Local treatment of BMs included stereotactic radiosurgery (SRS) in 3 cases and whole brain radiotherapy (WBRT) in 17 cases. In addition, 10 patients received no local treatment of BMs (Figure 1). The radiation dose of WBRT was 40 Gy in 20 fractions or 30 Gy in 10 fractions. Among these, 2 patients received WBRT with the simultaneous in-field boost of 50Gy. Most patients had no adverse effects, but one patient, who received WBRT, experienced a transient worsening of headache that resolved with mannitol. The intracranial lesions that received SRS shrank obviously, but two of the patients who underwent SRS developed new BMs within 3 months. The median survival time for patients who underwent WBRT and no local treatment was 4 and 1 month, respectively ($p<0.001$).

Table 1. Univariate analysis of intracranial progression-free survival (iPFS) and overall survival (OS) in esophageal squamous cell carcinoma patients (n=30) with brain metastases.

Clinicopathological characteristics	Patients (n=30)	iPFS		OS	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diagnosis, n (%)		0.962 (0.419–2.208)	0.916	1.344 (0.570–3.167)	0.458
Median (range)	63.5 (39–77)				
<65 years	16 (53.3)				
≥65 years	14 (46.7)				
Sex, n (%)		0.626 (0.144–2.719)	0.456	0.555 (0.127–2.418)	0.380
Male	27 (90)				
Female	3 (10)				
Primary tumor location, n (%)		0.949 (0.518–1.738)	0.979	1.003 (0.560–1.798)	0.999
Upper	3 (10)				
Middle	17 (56.7)				
Lower	9 (30)				
Multifocal	1 (3.3)				
ECOG PS, n (%)		1.617 (0.892–2.932)	0.001*	1.868 (0.988–3.535)	< 0.001*
0	0 (0)				
1	8 (26.7)				
2	16 (53.3)				
3	5 (16.7)				
4	1 (3.3)				
Intertumoral hemorrhage, n (%)		0.885 (0.205–3.817)	0.847	0.900 (0.208–3.894)	0.876
Yes	3 (10)				
No	27 (90)				
Cerebral infarction, n (%)		1.254 (0.165–9.551)	0.792	1.809 (0.234–13.978)	0.510
Yes	1 (3.3)				
No	29 (96.7)				
Number of BMs, n (%)		1.430 (0.857–2.387)	0.248	1.579 (0.940–2.652)	0.141
1–3	22 (73.3)				
4–9	3 (10)				
≥10	5 (16.7)				
Time of BMs, n (%)		1.922 (0.434–8.513)	0.319	1.965 (0.442–8.726)	0.328
Synchronous	3 (10)				
Metachronous	27 (90)				
Interval from diagnosis of primary ESCC to BMs, n (%)		1.155 (0.469–2.847)	0.717	1.141 (0.467–2.785)	0.751
<12 months	17 (56.7)				
≥12 months	13 (43.3)				
Extracranial metastases, n (%)		1.564 (0.845–2.897)	0.090	2.056 (0.982–4.305)	0.024*
Yes	25 (83.3)				
No	5 (16.7)				
Primary tumor resection, n (%)		0.530 (0.232–1.213)	0.076	0.459 (0.193–1.090)	0.047*
Yes	17 (56.7)				
No	13 (43.3)				
Local treatment of BMs, n (%)		0.500 (0.301–0.831)	< 0.001*	0.465 (0.280–0.772)	< 0.001*
SRS	3 (10)				
WBRT	17 (56.7)				
No	10 (33.3)				
Systemic treatment, n (%)		0.693 (0.305–1.578)	0.308	0.820 (0.353–1.902)	0.611
Yes	15 (50)				
No	15 (50)				
RPA, n (%)		1.505 (0.746–3.036)	0.355	2.098 (0.997–4.413)	0.086
I	3 (10)				
II	21 (70)				
III	6 (20)				

Notes: *p<0.05; Abbreviations: iPFS-intracranial progression-free survival; OS-overall survival; HR-hazard ratio; CI-confidence interval; ECOG-Eastern Cooperative Oncology Group; PS-performance status; BMs-brain metastases; ESCC-esophageal squamous cell carcinoma; SRS-stereotactic radiosurgery; WBRT-whole brain radiotherapy; RPA-recursive partitioning analysis

Half of the patients (n=15) received systemic treatment after BM diagnosis and 15 patients received palliative care. For the systemic therapy, 8 patients received chemotherapy (fluorouracil, S-1, platinum, paclitaxel, docetaxel, etc.), 4 patients received PD-1 inhibitors, and 3 patients received PD-1 inhibitors with chemotherapy (Figure 1).

Survival analyses. The median follow-up time was 2 (range, 0.5–33) months. At the time of the last follow-up, 22 patients (73.3%) died of cancer. The median survival time after diagnosis of BMs was 2 (95% confidence interval [CI]: 1.86–4.15) months. The 1-year OS rate was 13.6%.

Five patients achieved PR, 20 patients had progressive disease (PD), and 5 patients remained stable in terms of intracranial responses 2 months after the diagnosis of BMs. The intracranial tumor control rate in our series was achieved at 33.3%. The OS was better in patients with intracranial benefit: the median OS was 16 months in patients with PR and 2 months in patients with PD. The median OS was not obtained in patients with SD due to missing follow-up data.

In the univariate analysis, the age, gender, number of BMs, synchronous BMs, the interval time from diagnosis of the primary tumor to BMs, intertumoral hemorrhage, cerebral infarction, primary tumor location, RPA classification, and systemic treatment showed no significant effects on iPFS and OS (Table 1). The absence of extracranial metastases and primary tumor resection were significantly associated with better OS but not iPFS, while ECOG PS and local treatment

Table 2. Time interval from the occurrence of extracranial metastasis to the development of BM.

Time	No. of patients	Median time interval months (range)
Time interval from the occurrence of lung metastasis to the development of BM	16	3 (0–31)
Time interval from the occurrence of liver metastasis to the development of BM	10	3.5 (0–22)
Time interval from the occurrence of bone metastasis to the development of BM	8	0.5 (0–19)

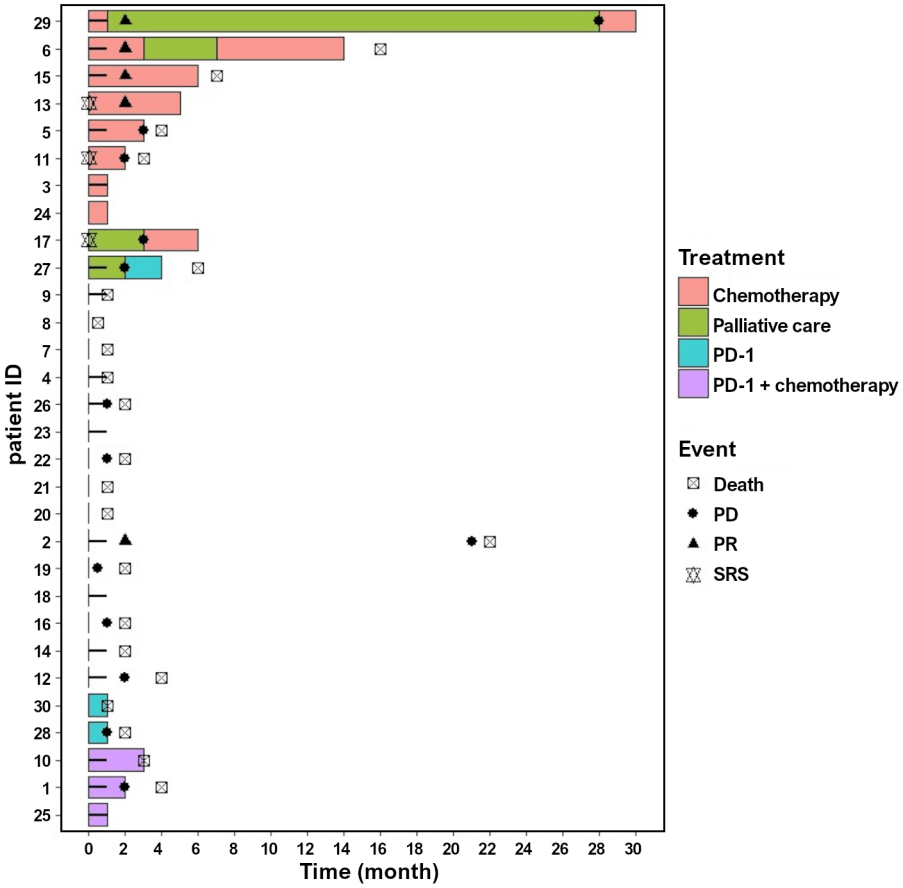

Figure 1. Outcomes of 30 patients with brain metastases from esophageal squamous cell carcinoma.

of BMs were significantly associated with better iPFS and OS (Table 1). Multivariate analysis showed that local treatment of BMs influenced the iPFS and OS (Table 3).

The median survival with or without local treatment of BMs was 4 and 1 month, respectively. Patients with local treatment of BMs had better iPFS (p<0.001) and OS (p<0.001) (Figure 2A). In addition, the median survival with or without extracranial metastases was 2 and 6 months, respectively. Patients with extracranial metastasis had a worse prognosis (p=0.024, Figure 2B). Similarly, the median survival with or without esophagectomy was 4 and 2 months, respectively. Patients with esophagectomy had a better prognosis (p=0.047, Figure 2C).

Discussion

BMs from EC, especially ESCC, are extremely rare. BMs in EC are diagnosed only when symptoms arise and, thus, often at a late stage. It will not only fail to get timely and effective treatment but will also lead to a poor quality of life caused by late detection. The poor median OS of 3.9–11.1 months after the diagnosis of BMs is consistent with this [3, 10, 12, 13, 18, 19]. The median OS after BM diagnosis was 2 months in our study. The 1-year OS rate was 13.6%, similar to 14% of those reported by Ogawa et al. [18] and 18% by Welch et al. [13]. One of the reasons for the lower OS than previously reported was considered to be that one-third of the patients did not

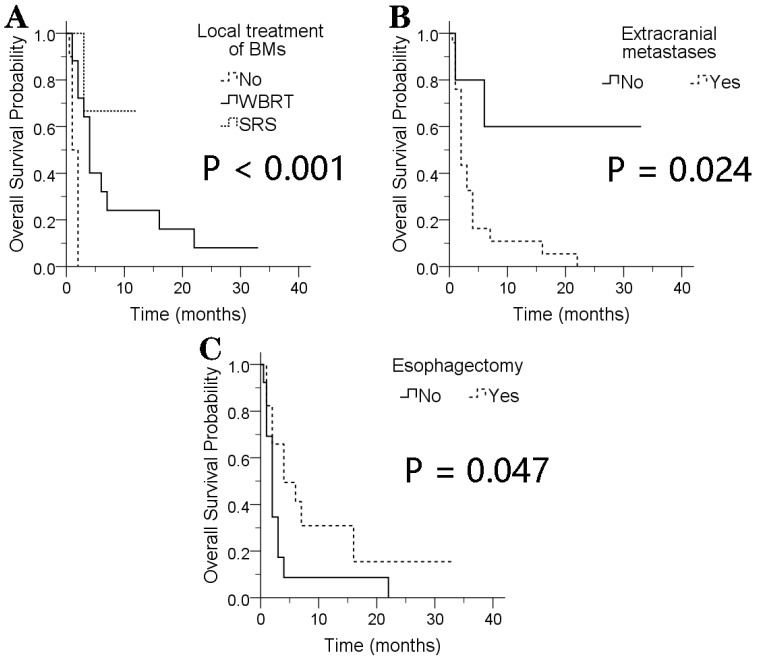

Figure 2. The overall survival curves of esophageal squamous cell carcinoma with brain metastases (BMs) according to local treatment of BMs (A), extracranial metastases (B), and esophagectomy (C).

Table 3. Multivariate analysis of prognostic factors associated with intracranial progression-free survival (iPFS) and overall survival (OS) in 30 esophageal squamous cell carcinoma patients with brain metastases.

Parameter	iPFS	p-value	OS	p-value
	HR (95% CI)		HR (95% CI)	
ECOG PS 0–1 vs. ≥2	2.104 (0.708–6.251)	0.180	1.013 (0.279–3.681)	0.985
Extracranial metastases Yes vs. No	–	–	1.748 (0.739–4.131)	0.204
Local treatment of BMs Yes vs. No	0.143 (0.039–0.529)	0.004*	0.195 (0.059–0.642)	0.007*
Primary tumor resection Yes vs. No	–	–	0.756 (0.289–1.981)	0.570

Notes: *p<0.05; Abbreviations: iPFS-intracranial progression-free survival; OS-overall survival; HR-hazard ratio; CI-confidence interval; ECOG-Eastern Cooperative Oncology Group; PS-performance status; BMs-brain metastases

receive any local treatment of BMs. No patients underwent surgical resection of BMs and only 3 cases were treated with SRS. The majority of the patients who received local treatment of BMs opted for palliative treatment with WBRT. Secondly, half of the patients did not undergo systemic therapy leading to systemic disease progression. Thirdly, several previous reports have pointed out a low incidence of lung metastasis (25.8–30.6%) at the time BM appeared in EC patients [3, 18]. However, the current study indicated that 16 of 25 patients (64%) had lung metastases at the time BMs appeared, indicating that the patients were at a late stage of the disease.

Previous studies have shown that prognostic factors for BMs from EC include KPS [12, 18], RPA classification [12, 20], number of BMs [12, 20], extracranial metastasis [21], and treatment of BMs [12, 18]. However, conclusions were varied among different studies, possibly due to the small sample size and selection bias. In our study, we confirmed that the independent prognostic factor was the local treatment of BMs. The RPA-based classification model was suggested to be an independent prognostic factor for patients with BMs in a variety of malignant tumors [22]. High RPA class was often associated with poor prognosis [12, 22, 23]. However, in contrast, we found no correlation between RPA classification and survival in ESCC patients with BMs, which was consistent with the previous reports [3, 19].

The standard treatment scheme for ESCC patients with BMs was not yet evidence-based and therefore remained controversial. Previous studies revealed that aggressive treatments of BMs can improve the prognosis [3, 19, 22]. The median survival after surgical resection of BM with or without WBRT was 6–31.5 months in the EC patients [11, 12, 18, 19]. Li et al. revealed that ESCC patients who underwent surgical resection of BM followed by WBRT achieved better OS than those who underwent WBRT [11]. Vanstraelen et al. reported that EC patients with BMs who underwent surgery or SRS had a significantly better median OS compared to those without (16 vs. 3.7 months; $p<0.001$) [7]. Similarly, Song et al. reported that the median survival was 7 months for patients who received surgical resection of BM, 4 months for those who received radiotherapy, and 1.8 months for those who received chemotherapy [12]. Multivariate analysis showed that local treatment of BMs influenced the iPFS and OS in our study. The median survival time for patients who underwent WBRT and no local treatment was 4 and 1 month, respectively. Unfortunately, in the present study, no patients underwent surgical resection of BMs, and two of three patients who underwent SRS developed new BMs within 3 months and died quickly. We inferred that active treatment, such as surgery, SRS, or WBRT, could improve survival for ESCC patients with BMs. In addition, our study demonstrated that the OS was better in ESCC patients with intracranial benefit, suggesting that patients can benefit from aggressive treatment of BMs. Therefore, aggressive treatments of BMs may be recommended for EC patients, especially those with controlled systemic diseases as well as a relatively good general condition. However, since cranial monitoring is not a routine examination, BMs from EC are often detected at a late stage with uncontrolled extracranial metastases, resulting in the loss of opportunities for aggressive treatments such as surgery. Hence, it is important to detect BMs in EC patients as early as possible.

With the prolonged survival of EC patients and the advance in imaging techniques aiding increased detection, the incidence of BMs from EC was increasing. However, the actual incidence of EC patients with BMs may be underestimated given that it was diagnosed only based on neurological symptoms and sub-clinical cases may have been missed in the absence of routine cranial examination. Due to the low incidence of BMs, following up on all EC patients was deemed cost-ineffective. Therefore, it was important to know who needed cranial monitoring and when to do it for EC patients. In the current study, BMs occurred 11 months after the diagnosis of the primary tumor in ESCC, which was within the reported range (6.7–16 months) [3, 11, 13, 18, 19, 24]. Our study revealed that 55.6% of the BM occurred within the first year after diagnosis of the primary tumor, 66.7% in the first 2 years, and 85.2% in the first 3 years. Nearly 90% of BM was diagnosed within 3 years after diagnosis of the primary tumor. Brain imaging could be considered for at least three years; however, given the small sample size of this series, this recommendation should be interpreted with caution. In addition, the extracranial organ most frequently affected was the lung, followed by the liver and the bone. Weinberg et al. have reported that liver metastasis was an independent predictive factor for BM in EC [14]. We found that the median time interval from lung metastasis to BMs was 3 months, from liver metastasis to BMs 3.5 months, and from bone metastasis to BMs 0.5 months. Based on these findings, close attention to neurological symptoms and consideration of cranial monitoring as clinically indicated should be a component of follow-up evaluations in certain high-risk patients with ESCC, such as patients with liver or lung metastasis.

Our study was limited by the retrospective nature of its design, small sample size, single-center, the fact that data was collected over a long period, and the heterogeneity of different treatment modalities. However, given the rarity of the disease, larger sample sizes are difficult to generate, and prospective trials investigating BM in ESCC will be difficult to conduct.

In conclusion, our study found that local treatment of BMs was an independent prognostic factor for patients with BMs from ESCC. Earlier detection followed by an aggressive local therapeutic approach for BMs has a great influence on treatment outcomes as well as the long-term prognosis and quality of life for appropriately selected patients.

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