ORIGINAL RESEARCH

Sites of metastasis and overall survival in esophageal cancer: a population-based study

San-Gang Wu,[1,*] Wen-Wen Zhang,[2,*] Zhen-Yu He,[2] Jia-Yuan Sun,[2] Yong-Xiong Chen,[3] Ling Guo[4]

[1]Department of Radiation Oncology, Xiamen Cancer Hospital, The First Affiliated Hospital of Xiamen University, Xiamen, [2]Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, [3]Eye Institute of Xiamen University, Fujian Provincial Key Laboratory of Ophthalmology and Visual Science, Medical College, Xiamen University, Xiamen, [4]Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, People's Republic of China

*These authors contributed equally to this work.

Correspondence: Yong-Xiong Chen
Eye Institute of Xiamen University, Fujian Provincial Key Laboratory of Ophthalmology and Visual Science, Medical College, Xiamen University, Xiang'an South Road, Xiang'an District, Xiamen 361102, People's Republic of China
Tel +86 592 218 3761
Fax +86 592 218 6786
Email yxchen1962@xmu.edu.cn

Ling Guo
Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China
Tel +86 20 8734 3543
Fax +86 20 8734 3392
Email guolingsysucc@126.com

Background: There are few population-based studies of the sites of distant metastasis (DM) and survival from esophageal cancer (EC). The aim of this study was to assess the patterns and survival outcomes for site-specific DM from EC using a population-based approach.

Methods: Patients diagnosed with de novo stage IV EC between 2010 and 2014 were identified from the Surveillance, Epidemiology, and End Results program database. Overall survival (OS) was compared according to the site of DM.

Results: We included 3218 patients in this study; the most common site of DM was the liver, followed by distant lymph nodes, lung, bone and brain. Median OS for patients with liver, distant lymph node, lung, bone, and brain metastases was 5, 10, 6, 4, and 6 months, respectively ($p<0.001$). Site and number of distant metastases were independent prognostic factors for OS. In patients with a single site of DM, using liver metastases as reference, OS was lower for bone metastases ($p=0.026$) and higher for distant lymph node metastases ($p=0.008$), while brain ($p=0.653$) or lung ($p=0.081$) metastases had similar OS compared with liver metastases. Similar site-specific survival differences were observed in the subgroup with esophageal adenocarcinoma. However, distant lymph node metastases was associated with better survival ($p=0.002$) compared to liver, bone, or lung metastases in esophageal squamous cell carcinoma.

Conclusion: Site of metastasis affects survival in metastatic EC; OS was worst for bone metastases and greatest for distant lymph node metastases.

Keywords: esophageal cancer, SEER, bone metastases, liver metastases, lung metastases, brain metastases

Introduction

Metastasis to distant organs is the leading cause of cancer-related deaths.[1–4] Esophageal cancer (EC) is a highly lethal malignant tumor. The incidence of EC, especially the rate of esophageal adenocarcinoma (AC) in Western countries has gradually increased in recent decades.[5–7] Approximately 50% of patients present with metastases to distant lymph nodes or organs at initial diagnosis.[8,9] The prognosis of metastatic EC is poor, and the five-year survival rate is less than 5%.[10,11] Although the major mechanisms that regulate metastasis have been identified, limited advances have been made in our understanding of the epidemiology of cancer metastasis.

EC most commonly spreads to the liver, followed by lung, bone, and brain.[12–15] Therefore, knowledge of the patterns of distant metastasis (DM) is crucial to improve patient treatment and follow-up. Population-based cancer registries provide an excellent opportunity to investigate the relationship between the patterns of DM and prognosis in metastatic cancer. However, such data are rarely recorded. The purpose of this study was to assess the site-specific patterns of DM and survival outcomes of metastatic EC using the surveillance, epidemiology, and end results (SEER) database.

Methods

Data were obtained from the recent SEER-18 database, which is maintained by the National Cancer Institute and represents approximately 28% of the population of the United States.[16] We limited this study to patients diagnosed between 2010 and 2014 as detailed information about site-specific metastasis was not recorded before 2010. We identified patients with de novo stage IV esophageal squamous cell carcinoma (SCC) or AC. Patients for whom EC was not the first tumor or for whom data on sites of DM were not available were excluded. Approval for this study was obtained from the Institutional Review Board of the First Affiliated Hospital of Xiamen University.

We assessed the effect of potential demographic and clinicopathological variables (age, sex, race/ethnicity, tumor location, histological subtype, tumor grade, tumor classification, nodal classification, treatment, and sites and the number of DM) on patient survival. The sites of DM were classified as distant lymph node, bone, brain, liver, and lung. Due to the moderate sensitivity and high specificity of the radiotherapy and chemotherapy data, radiotherapy and chemotherapy are classified as "yes" or "no/unknown" in the current SEER custom database.[17] Survival time from initial diagnosis (months), specific cause of death, and vital status were also extracted from the dataset. The primary end point of this study was overall survival (OS).

Independent predictors of OS in de novo stage IV EC were assessed using a Cox proportional model. Kaplan–Meier analysis and log-rank testing were used to compare OS. $p < 0.05$ was considered statistically significant. All calculations were performed using SPSS statistical software (version 21.0; IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the patients

A total of 3218 patients with de novo stage IV EC were included. DM was diagnosed by pathological examination in 950 patients (29.5%) and clinical methods in 2268 patients (70.5%). Table 1 summarizes the demographic and clinicopathological characteristics of the 3218 patients; 2931 (91.1%) patients were aged ≥50 years, 2706 (84.1%) were males, 2703 (84.0%) were White, 2065 (64.2%) had tumors located in the lower third of the esophagus, 2357 (73.2%) had AC, and 2122 (65.9%) had node-positive disease.

Sites of distant metastases

A total of 5024 sites of DM were identified in the 3218 patients with de novo stage IV EC. The liver was the most common site of DM (1678, 33.4%), followed by distant (non-regional) lymph nodes (1334, 26.6%), lung (1028, 20.5%), bone (791, 15.7%), and brain (193, 3.8%). Overall, 1885 (58.6%) patients had DM to a single organ. The distributions of the sites of DM are shown in Table 2.

Treatment

Overall, 55/3218 (1.7%) patients underwent esophagectomy, 1319 (41.0%) received radiotherapy, 1899 (59.0%)

Table 1 Characteristics of the 3218 patients with stage IV esophageal cancer

Variable	n
Age (years)	
<50	287
≥50	2931
Sex	
Male	2706
Female	512
Race/ethnicity	
White	2703
Black	335
Other/unknown	180
Tumor location	
Upper third	126
Middle third	371
Lower third	2065
Overlapping lesion	195
Unknown	461
Histology	
SCC	861
AC	2357
Grade	
G1	74
G2	962
G3–4	1606
Unknown	576
Tumor classification	
T1	735
T2	139
T3	576
T4	544
Unknown	1224
Nodal classification	
N0	743
N1	2122
Unknown	353
Surgery	
No	3163
Yes	55
Radiotherapy	
No/unknown	1899
Yes	1319
Chemotherapy	
No/unknown	1190
Yes	2028

Abbreviations: AC, adenocarcinoma; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; N, node; SCC, squamous cell carcinoma; T, tumor.

Table 2 Patterns of distant metastases for the 3218 patients with stage IV esophageal cancer

Sites of distant metastases	n
One site of distant metastasis	
Distant lymph node	544
Bone	278
Brain	56
Liver	702
Lung	305
Two sites of distant metastasis	
Distant lymph node + bone	88
Distant lymph node + brain	18
Distant lymph node + liver	260
Distant lymph node + lung	117
Bone + brain	22
Bone + liver	118
Bone + lung	51
Brain + liver	20
Brain + lung	9
Liver + lung	233
Three sites of distant metastases	
Distant lymph node + bone + liver	62
Distant lymph node + bone + lung	32
Distant lymph node + liver + lung	142
Distant lymph node + bone + brain	5
Distant lymph node + brain + liver	2
Distant lymph node + brain + lung	3
Bone + liver+ lung	52
Bone + brain+ liver	10
Bone + brain+ lung	6
Brain + liver + lung	12
Four sites of distant metastases	
Distant lymph node + bone + liver + lung	41
Distant lymph node + bone + brain + liver	5
Distant lymph node + bone + brain + lung	6
Distant lymph node + brain + liver + lung	4
Bone + brain + liver + lung	10
Five sites of distant metastases	5

did not receive radiotherapy or their radiotherapy status was unknown, 2028 (63.0%) received chemotherapy, and the remaining 1190 (37.0%) patients did not receive chemotherapy or their chemotherapy status was unknown. In patients who received esophagectomy, 39 (70.9%) and 49 (89.1%) patients received radiotherapy (29 patients received radiotherapy prior to surgery, 8 patients underwent radiotherapy after surgery, and 2 patients had radiotherapy before and after surgery) and chemotherapy, respectively. In addition, most of patients (90.9%, 50/55) who received esophagectomy had a single site of DM, and 54% (n = 27) patients had distant lymph node metastases, followed by lung (9, 18.0%), liver (8, 16.0%), bone (3, 6%), and brain (3, 6%) metastases.

Survival outcomes and prognostic analysis

Median OS was 6 and 5 months for patients with a single site of DM and multiple sites of DM, respectively. Median OS for patients with liver, distant lymph node, lung, bone, and brain metastases was 5, 10, 6, 4, and 6 months, respectively ($p<0.001$).

In patients with a single site of DM (n = 1885), univariate analysis indicated that age, nodal classification, surgery, radiotherapy, chemotherapy, and site of DM were associated with OS (Table 3). In the entire cohort (n = 3218), age, sex, race/ethnicity, tumor location, histological subtype, nodal classification, surgery, radiotherapy, chemotherapy, and the number of DM sites were prognostic factors for OS (Table 3).

Multivariate analysis of patients with a single site of DM revealed that the site of DM was an independent prognostic factor affecting OS (Table 4). Using liver metastases as the reference, DM to bone was associated with poorer OS (hazard ratio [HR] 1.211, 95% confidence interval [CI] 1.023–1.434, $p=0.026$), while DM to distant lymph nodes was associated with better OS (HR 0.829, 95% CI 0.722–0.953, $p=0.008$). Brain (HR 1.077, 95% CI 0.779–1.490, $p=0.653$) and lung (HR 0.865, 95% CI 0.736–1.018, $p=0.081$) metastases were associated with similar OS compared to liver metastases. The corresponding survival curves are shown in Figure 1. In the entire cohort, the number of DM was an independent prognostic factor for OS; multiple sites of DM were associated with poorer OS (HR 1.388, 95% CI 1.269–1.518, $p<0.001$). In addition, surgery, radiotherapy, and chemotherapy were associated with better OS in multivariate prognostic models of patients with single or multiple sites of DM.

We further analyzed the effect of site of DM in patients with a single site of DM stratified by histological subtypes. In esophageal SCC, using liver metastases as the reference, distant lymph node metastases (HR 0.6579, 95% CI 0.503–0.858, $p=0.002$) were associated with better OS, while bone (HR 1.151, 95% CI 0.844–1.569, $p=0.374$), brain (HR 0.776, 95% CI 0.191–3.155, $p=0.723$), and lung (HR 0.891, 95% CI 0.684–1.161, $p=0.393$) metastases were associated with similar OS compared to liver metastases. The corresponding survival curves are shown in Figure 2A. In esophageal AC, using liver metastases as the reference, bone metastases were associated with poorer OS (HR 1.224, 95% *CI* 1.024–1.462, $p=0.026$), while distant lymph node metastases (HR 0.662, 95% CI 0.570–0.768, $p<0.001$) were associated with better OS. Patients with brain (HR 0.981, 95% CI 0.728–1.321, $p=0.899$) and lung (HR 0.859, 95% CI 0.698–1.058, $p=0.153$)

Table 3 Univariate Cox regression analysis of prognostic factors for overall survival in stage IV esophageal cancer

Variable	One site of distant metastases			Entire cohort		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)						
<50	I			I		
≥50	1.222	1.011–1.477	0.038	1.159	1.012–1.328	0.032
Sex						
Male	I			I		
Female	0.881	0.769–1.011	0.070	0.883	0.794–0.983	0.022
Race/ethnicity						
White	I			I		
Black	1.164	0.992–1.365	0.062	1.167	1.032–1.319	0.014
Other	0.866	0.685–1.095	0.230	0.900	0.757–1.069	0.229
Tumor location						
Upper third	I			I		
Middle third	0.904	0.680–1.203	0.490	0.946	0.758–1.181	0.623
Lower third	0.779	0.603–1.005	0.055	0.794	0.651–0.968	0.023
Overlapping lesion	0.913	0.662–1.260	0.58	1.000	0.783–1.278	0.999
Histology						
SCC	I			I		
AC	0.912	0.816–1.020	0.106	0.886	0.814–0.965	0.005
Grade						
G1	I			I		
G2	0.856	0.624–1.175	0.337	0.989	0.766–1.276	0.933
G3–4	1.086	0.796–1.482	0.603	1.239	0.964–1.592	0.094
Tumor classification						
T1–2	I			I		
T3–4	0.918	0.808–1.043	0.191	0.923	0.837–1.018	0.109
Nodal classification						
N0	I			I		
N1	0.788	0.701–0.886	<0.001	0.862	0.786–0.944	0.001
Surgery						
No	I			I		
Yes	0.316	0.213–0.470	<0.001	0.302	0.209–0.436	<0.001
Radiotherapy						
No/unknown	I			I		
Yes	0.672	0.607–0.745	<0.001	0.720	0.666–0.778	<0.001
Chemotherapy						
No/unknown	I			I		
Yes	0.288	0.259–0.321	<0.001	0.288	0.265–0.312	<0.001
Metastatic sites						
Liver	I			—		
Distant lymph node	0.677	0.596–0.770	<0.001	—	—	—
Bone	1.228	1.055–1.429	0.008	—	—	—
Brain	0.964	0.721–1.288	0.803	—	—	—
Lung	0.925	0.797–1.074	0.307	—	—	—
Number of sites of metastases (n)						
I	—			I		
>1	—	—	—	1.398	1.294–1.510	<0.001

Note: "–" indicates no data.
Abbreviations: AC, adenocarcinoma; CI, confidence interval; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; HR, hazard ratio; N, node; SCC, squamous cell carcinoma; T, tumor.

metastases had similar OS compared to patients with liver metastases. The corresponding survival curves are shown in Figure 2B.

Discussion

This population-based study indicates that the prognosis of patients with metastatic EC differs according to the site of

Table 4 Multivariate Cox regression analysis of prognostic factors for overall survival in stage IV esophageal cancer

Variable	One site of distant metastases			Entire cohort		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)						
<50	1			1		
≥50	1.063	0.866–1.306	0.558	1.110	0.947–1.301	0.196
Sex						
Male	—			1		
Female	—	—	—	0.854	0.752–0.969	0.015
Race/ethnicity						
White	—			1		
Black	—	—	—	1.060	0.905–1.242	0.470
Other	—	—	—	0.861	0.698–1.062	0.161
Tumor location						
Upper third	—			1		
Middle third	—	—	—	1.012	0.797–1.286	0.921
Lower third	—	—	—	0.934	0.743–1.173	0.555
Overlapping lesion	—	—	—	1.093	0.835–1.430	0.518
Histology						
SCC	—			1		
AC	—	—	—	0.883	0.797–0.979	0.018
Nodal classification						
N0	1			1		
N1	0.973	0.860–1.100	0.658	0.946	0.856–1.046	0.280
Surgery						
No	1			1		
Yes	0.449	0.301–0.669	<0.001	0.465	0.317–0.683	<0.001
Radiotherapy						
No/unknown	1			1		
Yes	0.798	0.712–0.896	<0.001	0.833	0.761–0.912	<0.001
Chemotherapy						
No/unknown	1			1		
Yes	0.315	0.280–0.355	<0.001	0.297	0.270–0.326	<0.001
Metastatic sites						
Liver	1			—		
Distant lymph node	0.829	0.722–0.953	0.008	—	—	—
Bone	1.211	1.023–1.434	0.026	—	—	—
Brain	1.077	0.779–1.490	0.653	—	—	—
Lung	0.865	0.736–1.018	0.081	—	—	—
Number of sites of metastases (n)						
1	—			1		
>1	—	—		1.388	1.269–1.518	<0.001

Note: "–" indicates no data.
Abbreviations: AC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; N, node; SCC, squamous cell carcinoma.

DM, and also that multimodality treatment may improve OS in metastatic EC.

Similarly to previous retrospective reports and autopsy studies of patients with metastatic EC,[12–15] the most common sites of DM in this study were the liver, followed by distant lymph nodes, lung, bone, and brain. Notably, this study was based on a much larger sample size than the previous studies. Moreover, our analysis provides additional information on the prognostic impact of site-specific DM in metastatic EC.

There are limited studies on the effect of the site of DM on survival in metastatic EC. Chen et al found that DM (not including DM to distant lymph nodes) was not associated with OS in metastatic esophageal SCC.[13] Tanaka et al also observed no significant difference in median survival for different sites of DM, including liver, bone, and lung (*p*=0.8786).[10] The study by Blank et al included patients with metastatic esophagogastric AC, and found that localization (distant hematogenous vs. peritoneal carcinomatosis vs. distant lymph nodes, *p*=0.631) and the number (*p*=0.754) of metastases were not significant prognostic factors for survival;[18] however, they did not further analyze the effect of site-specific DM on survival. In this study, patients with

distant lymph node metastases had better OS than patients with liver metastases, while bone metastases were associated with poorer OS compared to liver metastases, especially in esophageal AC. We also observed similar OS rates for patients with liver, bone, or lung metastases in esophageal SCC. Therefore, patients with stage IV EC represent a heterogeneous group that could potentially be classified by site-specific metastasis. In addition, the number of DM was also

an independent prognostic factor for OS. These observations may help physicians more accurately assess the prognosis of patients with metastatic EC.

In this study, patients with distant lymph node metastases had significantly longer OS (median, 10 months) than patients with DM to other sites. Chao et al reported a similar median OS duration of 14.2 months for patients with non-regional lymph node metastases after chemoradiotherapy.[19] Therefore, combined modality treatment may yield reasonable survival outcomes for patients with EC who have distant lymph node metastases.

In breast cancer, patients with bone metastases achieve significantly better survival than patients with metastasis to other sites.[20,21] However, in this study, patients with bone metastases had significantly poorer OS (median, 4 months) than those with metastasis to other sites. Bone metastases were also associated with poor survival in a population-based study of metastatic lung cancer.[22] The mechanism by which bone metastases lead to poorer survival compared to other sites of DM in metastatic EC is not known. Overexpression of parathyroid hormone-related protein (PTHrP) is associated with increased risk of bone metastases in small cell lung cancer.[23] Osteolytic bone metastases often overproduce PTHrP.[1] Bone metastases in EC was associated with humoral hypercalcemia and leukocytosis, which may promote rapid disease progression.[24–26]

There is no consensus on whether palliative radiotherapy or surgery is of value in metastatic EC. Several retrospective and prospective studies have suggested that palliative
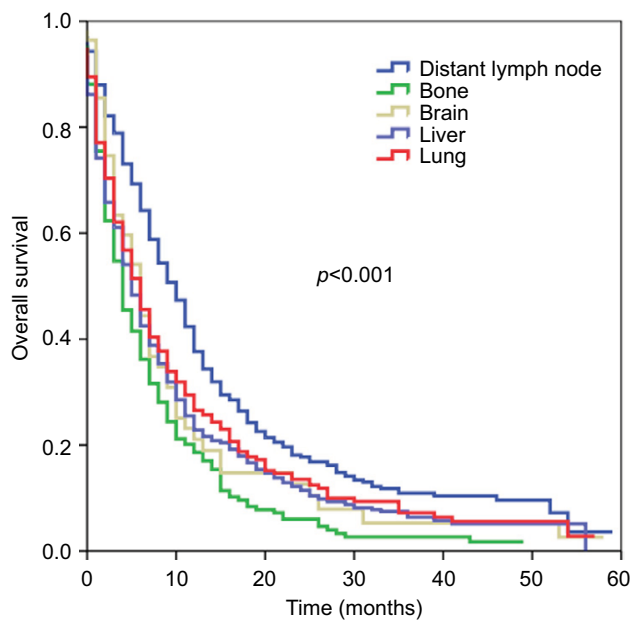
Figure 1 Kaplan–Meier survival curves for patients with metastatic esophageal cancer stratified by sites of distant metastases.
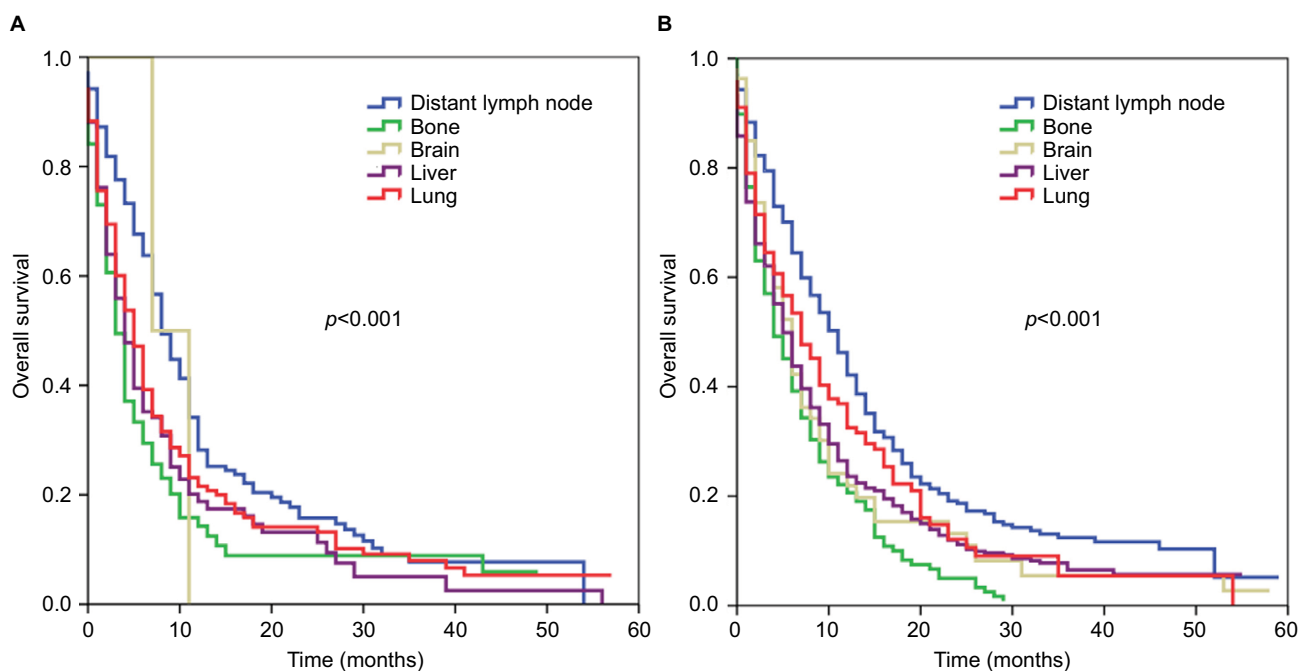
Figure 2 Kaplan–Meier survival curves for patients with metastatic esophageal squamous cell carcinoma (**A**) and adenocarcinoma (**B**) stratified by sites of distant metastases.

radiotherapy could improve survival in metastatic EC.[27–29] In addition, several recent retrospective studies found that resection of primary tumors may be considered for a select group of patients with stage IV EC who achieve a favorable response to systemic chemotherapy.[18,19,30] Our previous study of the SEER database also found that surgery and preoperative radiotherapy were associated with better survival in metastatic EC.[11] Furthermore, lymph node dissection is associated with better survival.[31] In the present study, most of patients who underwent esophagectomy also received radiotherapy and chemotherapy, and surgery. Radiotherapy and chemotherapy were independent favorable prognostic factors for OS, similarly to results in metastatic breast cancer, colorectal cancer, and renal cell carcinoma.[32–36] However, the numbers of patients who underwent surgical resection of the primary tumor in the aforementioned studies were not large enough to reach definite conclusions. In addition, these retrospective studies possess methodological defects. Therefore, further studies are required to identify the subgroups of patients who may benefit from aggressive multimodality therapy.

We should acknowledge that this study has several limitations. First, retrospective analyses may be inherently biased. Second, the SEER database lacks detailed information on comorbidities, which could lead to potential selection bias towards patients receiving a specific treatment. In addition, the SEER program only included five site-specific DM at the initial diagnosis, and we could not obtain further details concerning the other sites of DM. Third, the findings of this study can only be generalized to the United States population and are not representative of the global population, especially in endemic areas such as People's Republic of China. Moreover, the overall sensitivity of the radiotherapy and chemotherapy data in the current SEER database was 80% and 68%, respectively. However, the radiotherapy and chemotherapy data had a high specificity.[17]

Conclusion

In conclusion, in advanced EC, patients with bone metastases seem to have the poorest OS, while patients with distant lymph node metastases have the best OS. This study suggests that increased attention should be paid to the mechanisms and prognostic value of site-specific metastases. Furthermore, additional studies are required to identify the subset(s) of patients with advanced EC who may benefit from primary local treatment.

Disclosure

The authors report no conflicts of interest in this work.

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