Bone Metastasis in Esophageal Adenocarcinoma and Squamous Cell Carcinoma: A SEER-Based Study

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Abstract

Background: Esophageal cancer (EC) is a common worldwide disease with a higher mortality rate. Studies on EC patients with bone metastasis (BM) are rare. Our study focused on the clinicopathological features of EC patients with BM using the Surveillance, Epidemiology and End Results (SEER) database to further explore the risk factors and survival for BM.

Methods: According to the inclusion and exclusion criteria, EC patients with BM were extracted from the SEER database from 2010 to 2016. Univariable analysis and multivariable logistic regression were used to study the risk factors for BM. Univariable analysis and multivariable Cox regression were performed to reveal the survival and prognostic factors for BM. The competitive risk model was made to compare the association with BM among causes of death. Propensity score matching (PSM) was used to reduce the bias.

Results: A total of 5314 patients were included in this study. Patients with BM had a worse prognosis before and after PSM. Male, middle esophagus, with brain metastasis, without lung metastasis, without liver metastasis were major independent risk factors of BM. Poorly differentiated and undifferentiated, with liver metastasis, with lung metastasis and without chemotherapy were major independent prognostic factors of BM.

Conclusions: Compared to patients with other metastatic sites such as liver, brain and lung, patients with BM had a worse prognosis. Our findings provide recommendations about clinical guidelines including examination and treatment for EC patients with BM.

Introduction

Esophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of death in the world[1]. A study based on Cancer Incidence in Five Continents (CI5) shown that the highest incidence rates of EC were in Malawi, South Africa, and Iran and the highest mortality rates were in South Africa and Kazakhstan[2]. A higher incidence of EC was found in males and common histological types included adenocarcinoma (EAC) and squamous cell carcinoma (ESCC). The incidence of ESCC declined in western countries due to reducing the prevalence of smoking and drinking[3-5]. The incidence of EAC increased. Gastroesophageal reflux disease (GERD), H.pylori infection and obesity were main known risk factors for EAC[6]. Although the overall incidence of EAC and ESCC displayed a downward trend in many studies, EC imposed a tremendous public health burden globally.

EC is a tumor that is prone to distant metastases. Over fifty percent of patients have unresectable or metastatic disease at initial diagnosis[7]. At this stage, there were very few treatment choices which can only bring dismal survival advantages for patients[8]. The overall five-year survival rate for patients with distant metastases was only 5%[9]. Another study even indicated the median survival time of EC patients with metastatic disease was only 6 months and 2-year survival rate was only 11.8%[10]. Bone is a common site of metastases in malignant tumors[11-13]. Bone metastasis (BM) is the third most common

site in patients with EC[14, 15]. Compared to other metastatic sites such as liver, brain and lung, BM had worse overall survival (OS) in EC[16]. Few articles systematically analyzed BM in EC, so it requires a deeper analysis.

Our study aimed to reveal the clinical characteristics and the prognosis of EC with BM based on SEER database. SEER database registers four main metastatic organs of tumors: liver, lung, bone and brain. It is a population-based cancer registry covering about 30% of the US population, bringing much reliable information[17].

Methods

2.1 Patients selected

We collected data from 18 population-based cancer registries with additional treatment fields in SEER database (version 8.3.8). A total of 28243 patients with EC from 2010 to 2016 were identified. And 5314 patients were selected according to the inclusion and exclusion criteria. Inclusion criteria: patients diagnosed with EC between 2010 and 2015; histological types were EAC and ESCC; IV stage EC; first malignant primary cancer. Exclusion criteria: survival time was unknown, not stage metastatic EC or unknown stage EC; EC patients diagnosed in 2016. The process was presented as a flow process chart in Figure1. For at least 1-year follow-up, we selected before 2016.

2.2 Data collection

Histological types were confirmed by the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). EAC included 8140-8389 and ESCC included 8050-8089. EC patients were divided into five groups: upper esophagus including upper third and cervical, middle esophagus including middle third, lower esophagus including lower third and abdominal, overlapping and NOS including NOS and thoracic. Other clinical features were also collected including age, sex, race, primary tumor location, treatments and survival time.

2.3 Statistical methods

The risk factors were investigated by univariable and multivariable analysis. Chi-square test was used for univariable analysis. Multivariable logistic regression analysis further confirmed the risk factors for EC patients with BM. Survival estimates were performed by the Kaplan-Meier method and compared by the log-rank test. We brought factors which were statistically significant into multivariable analysis. And to avoid missing important factors, we expanded P-value to 0.1. Cox regression model was used for multivariable analysis. The competitive risk model was made by R package cmprsk. Propensity score matching (PSM) was used by R package MatchIt. Statistical analyses were performed using SPSS 25.0 and R.3.6.3. All the pictures in our study were drawn by GraphPad Prism 7.0. Statistical significance was set at two-side $P<0.05$.

Results

4.1 Epidemiological trends

The incidence of EC declined from 2010 to 2016 (Fig.2a). For both male and female, the incidence showed a similar trend (Fig.2b). Among the histological types, the incidence of ESCC declined, but the incidence of EAC still rose (Fig.2c). For all EC patients with BM from 2010 to 2015, prevalence was 7.11% (1503/21128). It peaked in patients between 31 and 40 and then displayed a downward trend. The prevalence of BM in metastatic esophageal cancer (mEC) was 23.5% (1503/6395). It rose with age and held steady in patients between 31 and 70 (Fig.2d).

4.2 Patient characteristics

A total of 21128 patients with EC were initially identified from2010 to 2015, and 5314 patients were included in the study. From 2010 to 2015, there were 23.74% (1782/7505) ESCC at stage IV, and 33.88% (4615/13623) EAC were advanced (Figure 3). At the time of diagnosis, there were 2566 (12.15%) patients with liver metastasis, 1562 (7.39%) patients with lung metastasis, 1241 (5.87%) patients with bone metastasis, and 314 (1.49%) patients with brain metastasis. Of the above four metastatic organs, 4105 (19.43%) patients had at least one metastasis (Figure 4). Characteristics of patients were shown in Table1. For BM, 440 (35.46%) patients were aged 61-70 years, 1075 (86.62%) patients were males, 725 (58.42%) patients had tumors located in the lower third of the esophagus, 928 (74.78%) patients were EAC, and 613 (49.40%) were poorly differentiated or undifferentiated.

4.3 Risk factors for BM

Univariable analysis (Table 1) showed that there were eight factors with statistically significance (P-value<0.05): age, sex, primary tumor location, brain metastasis, lung metastasis, liver metastasis, surgery and chemotherapy. BM was more common among 51-60 years old. Male patients were more likely to have BM. For tumor location, middle esophagus had higher percentage of BM. Patients with brain metastasis had a higher risk of having BM. However, EC patients with lung or liver metastasis were less likely to develop BM. Considering the logic, we did not put surgery and chemotherapy into multivariable logistic regression.

Multivariable logistic regression (Table 2) showed that with brain metastasis (vs without brain metastasis; OR, 1.546; 95%CI, 1.206-1.981; P=0.001) were associated with significantly greater odds of having BM in EC patients at the time of diagnosis. However, age 71-80 years (vs age <51 years; OR, 0.766; 95%CI, 0.599-0.980; P=0.034), female (vs male; OR, 0.718; 95%CI, 0.595-0.866; P=0.001), lower esophagus (vs middle esophagus; OR, 0.689; 95%CI, 0.566-0.840; P<0.001), with lung metastasis (vs without lung metastasis; OR, 0.801; 95%CI, 0.692-0.928; P=0.003), with liver metastasis (vs without liver metastasis; OR, 0.649; 95%CI, 0.569-0.742; P<0.001) were associated with lower rates of BM.

4.4 Survival and prognostic factors for BM

For 5314 patients with EC, the median OS was 5 (95%CI: 4.751-5.249) months, and the median CSS (cancer-specific survival) was 6 (95%CI: 5.710-6.290) months. For BM, the median OS was 4 (95%CI: 3.685-4.315) months, the median CSS was 4 (95%CI: 3.617-4.383) months. And for patients without BM, the median OS was 6 (95%CI: 5.674-6.326) months, the median CSS was 6 (95%CI: 5.664-6.336) months. Among the four metastatic sites (bone, brain, liver and lung), there were 2795 patients had only one metastasis. Among them, 556 patients had only BM, 114 patients had only brain metastasis, 1472 patients had only liver metastasis, and 653 patients suffered only lung metastasis. For BM, the median OS was 4 (95%CI: 3.334-4.666) months, the median CSS was 4 (95%CI: 3.260-4.740) months. And for the others, the median OS was 5 (95%CI: 4.609-5.391) months, the median CSS was 6 (95%CI: 5.539-6.461) months. For the numbers of metastatic sites, the median OS of one metastatic site was 5 (95%CI: 4.654-5.346) months, of two sites was 4 (95%CI: 3.599-4.401) months, of three sites was 3 (95%CI: 2.397-3.603) months, and of four sites was 2 (95%CI: 1.285-2.715) months. The median CSS of one site was 6 (95%CI: 5.582-6.418) months, of two sites was 4 (95%CI: 3.581-4.419) months, of three sites was 3 (95%CI: 2.279-3.721) months, of four sites was 2 (95%CI: 1.298-2.702) months. Figure 5 showed Kaplan-Meier analysis among EC patients. To reduce the influence of bias and confounding variables, we performed the Propensity score matching (PSM). After PSM, there were 2072 patients, the clinical features were as follows (Table 4). For BM, the median OS was 4 (95%CI: 3.579-4.421) months, and the median CSS was 4 (95%CI: 3.547-4.453) months. For EC patients without BM, the median OS was 6 (95%CI: 5.327-6.673) months, and the median CSS was 6 (95%CI: 5.319-6.681) months (Figure 6).

The cumulative incidence function curve (Figure 7) showed, compared to EC patients without BM, the cause-specific mortality was higher in BM (P<0.05). And the mortality rates of other causes were not statistically significant between the two groups (P=0.61).

The forest plot (Figure 8) showed that, for age (<51, 51-60, 61-70, 71-80 and >80), sex (male and female), race(white, black and others), site(upper esophagus, middle esophagus, lower esophagus and NOS), histology (EAC and ESCC), grade (1-2, 3-4 and unknown), brain metastasis (with and without), lung metastasis (with and without), liver metastasis (with and without), surgery (with and without) and chemotherapy (with and without), BM would increase the risk of death. However, for tumor location with overlapping, there was no statistical significance.

Univariable analysis showed, there were ten factors including age, race, tumor location, histology, grade, brain metastasis, lung metastasis, liver metastasis, surgery and chemotherapy that were statistically significant with OS. Then we put the above ten factors into the Cox regression model. The results confirmed that only four factors that were significant associated with OS: tumor grade, chemotherapy, liver metastasis and lung metastasis (Table 3).

On the multivariable Cox regression among the EC patients with BM, poorly differentiated and undifferentiated (vs highly differentiated and moderately differentiated; HR, 1.193; 95%CI, 1.044-1.364; P=0.010), with liver metastasis (vs without liver metastasis; HR: 1.365; 95%CI, 1.208-1.543; P<0.001), with lung metastasis (vs without lung metastasis; HR, 1.165; 95%CI, 1.018-1.333; P=0.027) showed worse OS.

However, those patients who received chemotherapy (vs without chemotherapy; HR, 0.308; 95%CI, 0.271-0.350; P<0.001) had better OS.

Discussion

Metastasis is one of the most important characteristics of solid tumors. Metastasis often means that malignant tumors are advanced and incurable. BM is relatively common in solid tumors, and it brings a series of skeletal-related events (SREs): pain, pathological fractures, nerve compression syndromes and hypercalcemia[18, 19].

In our study, the metastatic rate to bone from EC patients at the time of diagnosis was 5.87%. However, the actual incidence of EC patients with BM may be underestimated. Because bone imaging was not a routine imaging test, methods of examination for BM including bone scan, MRI, PET-CT and so on, which were relatively expensive. We do not recommend all patients with EC undergo these tests. Therefore, it is necessary to determine whether the EC patients have risk factors for BM. Our study showed that patients with brain metastasis were more likely to have BM. However, patients with age 71-80 years, female, lower esophagus, with lung metastasis, with liver metastasis, were relatively less likely to have BM.

During development and bone remodeling that occurs in the adult, osteoclasts and osteoblasts regulate bone modeling[20]. Malignancies may break the balance of bone physiology, and which will result in an environment that promotes metastasis[13]. BM include osteolytic metastasis and osteoblastic metastasis[19]. Osteolytic metastasis is the most common form of BM, and is associated with increased osteoclast activity and reduced osteoblast activity. In contrast, osteoblastic metastasis is rare, and was reported in prostate, breast, colon, cervical cancer and so on[18]. Imual et al. reported that in their study, multiple osteolytic BM commonly occurred in the axial skeleton in EC patients with BM, and nearly 91.4% patients suffered SREs[21]. In previous studies of EC, Ai et al. showed that in EC patients, there was no significant difference in OS among the four sites of distant metastases (liver, lung, bone and brain)[15]. Tanaka et al. also reported that there was no difference in the median survival among the three metastatic sites (liver, lung and bone)[22]. However, our study showed that in EC patients, BM was associated with poorer OS (4 vs 6 months, respectively), which was consistent with a previous study[23].Why is the OS of BM shorter than that of other metastatic sites? The mechanism is not yet clear. We think that BM is different from visceral metastases. Most patients with BM suffered SREs, which would reduce physical function and quality of life. They may bring a series of complications, and the PS score of patients would be elevated. These factors could affect patients to receive further treatments, thus shorting survival time. Similarly, Ulas et al. showed that in nonsmall cell lung cancer patients with BM, SREs were detected in 72.8% patients, and the median OS time for patients with SREs were shorter than patients without SREs (7 VS 12 months, respectively)[24]. Our study further found that for EC patients with BM, poorly differentiated and undifferentiated, with liver metastasis and with lung metastasis had poorer OS, those with chemotherapy had better OS.

With the progress of medical science, there are many treatments for EC, including surgery, chemotherapy, radiotherapy(RT), targeted therapy, immunotherapy and so on, which will improve survival[25, 26]. Due to the limitations of SEER database and our research, we only studied surgery and chemotherapy. In our study, EC patients with BM who received chemotherapy had better survival, but no significant benefit was seen in patients with surgery. There were only 1.6% (21/1241) BM patients who received surgery. We hypothesized that BM meant the disease was advanced, and it made little sense for patients to undergo surgery. In 2020, ESMO released clinical practice guidelines about bone health in cancer. Multidisciplinary management including palliative RT, radionuclide therapy, orthopaedic surgery and bone-targeted agents (BTAs)were recommended[27]. D'Oronzo et al. found that in patients with BM other than breast or prostate cancer, zoledronate would reduce the incidence of SREs, which were associated with worse survival[28]. Nowadays, bone health is becoming increasingly important in the management of cancer. We need to further research the mechanism and clinical characteristics of BM to provide guidance for clinical treatment.

Declarations

Acknowledgments

None to declare.

Authors' contributions

Ya Qin and Xiao Liang offered the idea of this study, analyzed the data, and drafted the manuscript. Nanyao Wang and Ming Yuan conducted the statistical analysis and revised the manuscript. Jiamin Zhu involved in data collection. Dan Wu and Qiong Wang were the supervisors of this study and writed the manuscript. All authors read and approved the final manuscript.

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Data Availability

The authors declare that the data supporting the findings of this study are available in this manuscript.

Ethics approval and consent to participate

Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

None declared.

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Tables

Table1: Clinical characteristics of the 5314 patients with stage IV EC.

	N	BM (%)	Without BM	Univariable analysis (P-value)
Age				<0.001*
<51	597	141 (23.62)	456(76.38)	
51-60	1398	367 (26.25)	1031(73.75)	
61-70	1799	440 (24.46)	1359(75.54)	
71-80	1059	205 (19.36)	854(80.64)	
>80	461	88 (19.09)	373(80.91)	
Sex				0.002*
male	4449	1075(24.16)	3374(75.84)	
female	865	166(19.19)	699(80.81)	
Race				0.704
White	4465	1050(23.52)	3415(76.48)	
Black	555	128(23.06)	427(76.94)	
Others[a]	294	63(21.43)	231(78.57)	
Site				<0.001*
Upper esophagus	229	51(22.27)	178(77.73)	
Middle esophagus	627	181(28.87)	446(71.13)	
Lower esophagus	3370	725(21.51)	2645(78.49)	
Overlapping	313	75(23.96)	238(76.04)	
NOS	775	209(26.97)	566(73.03)	
Histology				0.245
EAC	3906	928(23.76)	2978(76.24)	
ESCC	1408	313(22.23)	1095(77.77)	
Grade				0.167
1-2	1694	370(21.84)	1324(78.16)	
3-4	2578	613(23.78)	1965(76.22)	
Unknown	1042	258(24.76)	784(75.24)	
Brain				<0.001*
No/unknown	5000	1138(22.76)	3862(77.24)	

Yes	314	103(32.80)	211(67.20)	
lung				0.006*
No/unknown	3752	915(24.39)	2837(75.61)	
Yes	1562	326(20.87)	1236(79.13)	
Liver				<0.001*
No/unknown	2748	748(27.22)	2000(72.78)	
Yes	2566	493(19.21)	2073(80.79)	
Surgery				0.020*
No	5175	1220(23.57)	3955(76.43)	
Yes	139	21(15.11)	118(84.89)	
Chemotherapy				0.002*
No	1991	512(25.72)	1479(74.28)	
Yes	3323	729(21.94)	2594(78.06)	

EC: esophageal cancer

EAC: esophageal adenocarcinoma

ESCC: esophageal squamous cell carcinoma

BM: bone metastasis

NOS: not otherwise specified

[a] including American Indian/AK Native, Asian/Pacific Islander

*P<0.05 was statistically significant

Table2: Multivariable logistic regression for the EC patients with BM at the time of diagnosis.

Variable	N	BM	OR (95% CI)	P-value
Age				
<51	597	141	1(Reference)	NA
51-60	1398	367	1.120(0.894-1.404)	0.325
61-70	1799	440	1.029(0.826-1.282)	0.799
71-80	1059	205	0.766(0.599-0.980)	0.034*
>80	461	88	0.789(0.582-1.070)	0.127
Sex				
male	4449	1075	1(Reference)	NA
female	865	166	0.718(0.595-0.866)	0.001*
Site				
Upper esophagus	229	51	0.715(0.498-1.024)	0.067
Middle esophagus	627	181	1(Reference)	NA
Lower esophagus	3370	725	0.689(0.566-0.840)	<0.001*
Overlapping	313	75	0.749(0.546-1.028)	0.074
NOS	775	209	0.939(0.740-1.191)	0.602
Brain				
No/unknown	5000	1138	1(Reference)	NA
Yes	314	103	1.546(1.206-1.981)	0.001*
lung				
No/unknown	3752	915	1(Reference)	NA
Yes	1562	326	0.801(0.692-0.928)	0.003*
Liver				
No/unknown	2748	748	1(Reference)	NA
Yes	2566	493	0.649(0.569-0.742)	<0.001*

EC: esophageal cancer

BM: bone metastasis

NOS: not otherwise specified

OR: odds ratio

CI: confidence interval

*P<0.05 was statistically significant

Table3: Univariable analysis and multivariable Cox regression for EC patients with BM.

			Univariable analysis		Multivariable Cox regression	
Variable	N	BM	Median OS(mo)	P-value	HR(95% CI)	P-value
Age				<0.001*		
<51	597	141	5		1(Reference)	NA
51-60	1398	367	4		1.001(0.819-1.224)	0.990
61-70	1799	440	4		0.978(0.803-1.191)	0.827
71-80	1059	205	3		1.006(0.805-1.257)	0.959
>80	461	88	2		1.264(0.957-1.668)	0.098
Sex				0.126		
male	4449	1075	4		--	
female	865	166	4		--	
Race				0.085		
White	4465	1050	4		1(Reference)	NA
Black	555	128	3		1.168(0.942-1.447)	0.157
Others[a]	294	63	3		1.020(0.778-1.339)	0.884
Site				0.010*		
Upper esophagus	229	51	3		1(Reference)	NA
Middle esophagus	627	181	4		0.756(0.548-1.041)	0.087
Lower esophagus	3370	725	4		0.778(0.572-1.060)	0.111
Overlapping	313	75	2		0.906(0.622-1.321)	0.608
NOS	775	209	3		0.893(0.647-1.232)	0.489
Histology				0.005*		
EAC	3906	928	4		1(Reference)	NA
ESCC	1408	313	3		1.024(0.867-1.209)	0.782
Grade				0.007*		
1-2	1694	370	5		1(Reference)	NA
3-4	2578	613	3		1.193(1.044-1.364)	0.010*
Unknown	1042	258	3		1.005(0.852-1.185)	0.952
Brain				<0.001*		

No/unknown	5000	1138	4		1(Reference)	NA
Yes	314	103	3		1.218(0.988-1.501)	0.065
lung				0.002*		
No/unknown	3752	915	4		1(Reference)	NA
Yes	1562	326	3		1.165(1.018-1.333)	0.027*
Liver				<0.001*		
No/unknown	2748	748	4		1(Reference)	NA
Yes	2566	493	3		1.365(1.208-1.543)	<0.001*
Surgery				0.010*		
No	5175	1220	4		1(Reference)	NA
Yes	139	21	5		0.671(0.412-1.093)	0.109
Chemotherapy				<0.001*		
No	1991	512	1		1(Reference)	NA
Yes	3323	729	7		0.308(0.271-0.350)	<0.001*

EC: esophageal cancer

EAC: esophageal adenocarcinoma

ESCC: esophageal squamous cell carcinoma

BM: bone metastasis

NOS: not otherwise specified

OS: overall survival

HR: hazard ratio

CI: confidence interval

[a] including American Indian/AK Native, Asian/Pacific Islander

*P<0.05 was statistically significant

Table4: Clinical characteristics of the 2072 patients with stage IV EC after PSM.

	N	BM	Without BM	Chi-square	P-value
Age				1.276	0.865
<51	220	105	115		
51-60	576	296	280		
61-70	775	389	386		
71-80	359	174	185		
>80	142	72	70		
Sex				0.669	0.413
male	1828	920	908		
female	244	116	128		
Race				2.647	0.266
White	1822	923	899		
Black	169	77	92		
Others[a]	81	36	45		
Site				6.463	0.167
Upper esophagus	68	38	30		
Middle esophagus	237	131	106		
Lower esophagus	1356	652	704		
Overlapping	108	57	51		
NOS	303	158	145		
Histology				0.479	0.489
EAC	1621	817	804		
ESCC	451	219	232		
Grade				0.961	0.619
1-2	628	322	306		
3-4	1046	512	534		
Unknown	398	202	196		
Brain				3.038	0.081
No/unknown	1984	984	1000		

Yes	88	52	36		
lung				0.091	0.763
No/unknown	1536	771	765		
Yes	536	265	271		
Liver				0.511	0.475
No/unknown	1222	603	619		
Yes	850	433	417		
Surgery				0.156	0.693
No	2046	1022	1024		
Yes	26	14	12		
Chemotherapy				0.401	0.527
No	792	389	403		
Yes	1280	647	633		

EC: esophageal cancer

EAC: esophageal adenocarcinoma

ESCC: esophageal squamous cell carcinoma

BM: bone metastasis

PSM: propensity score matching

NOS: not otherwise specified

[a] including American Indian/AK Native, Asian/Pacific Islander

Figures

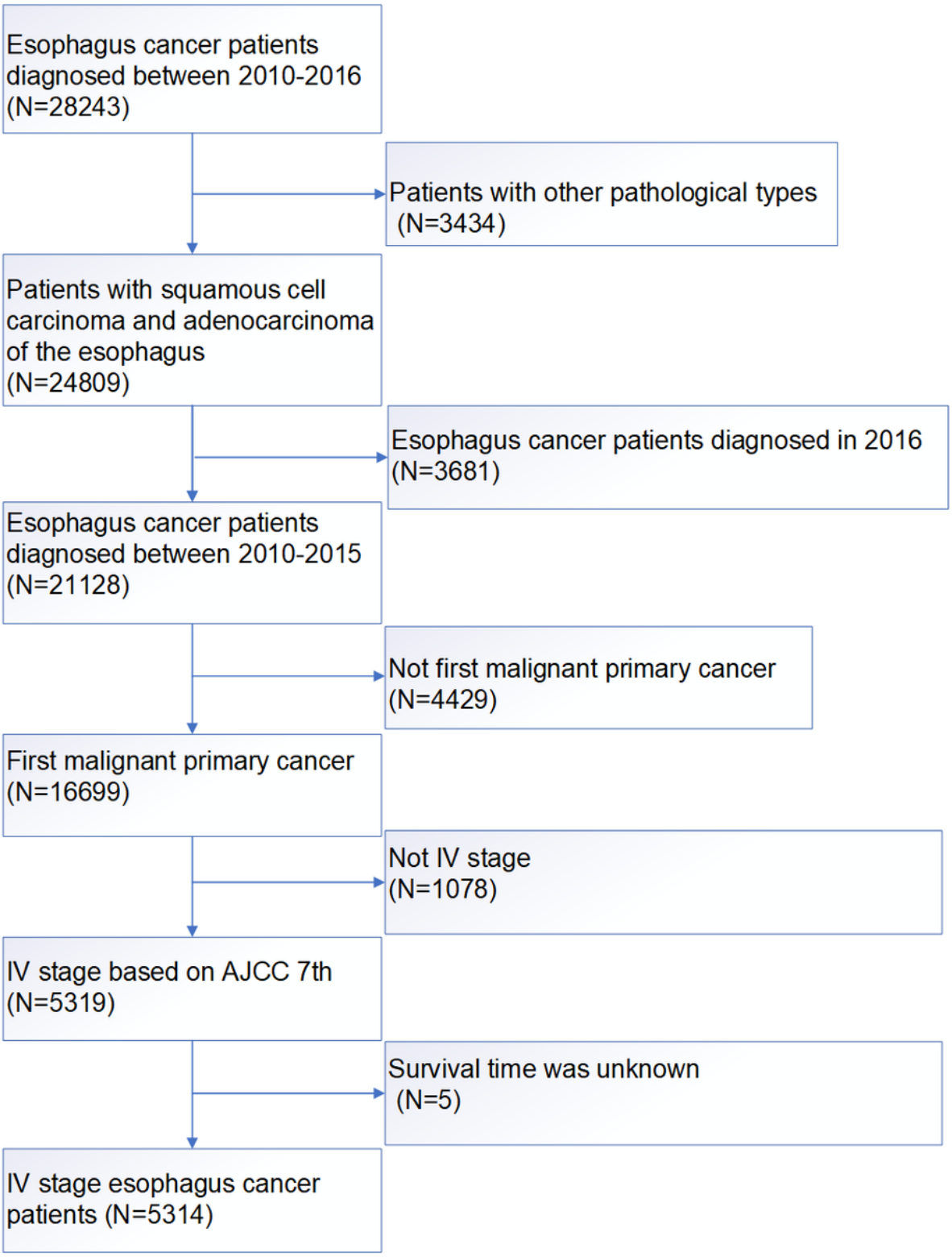

Figure 1

Patient inclusion flowchart.

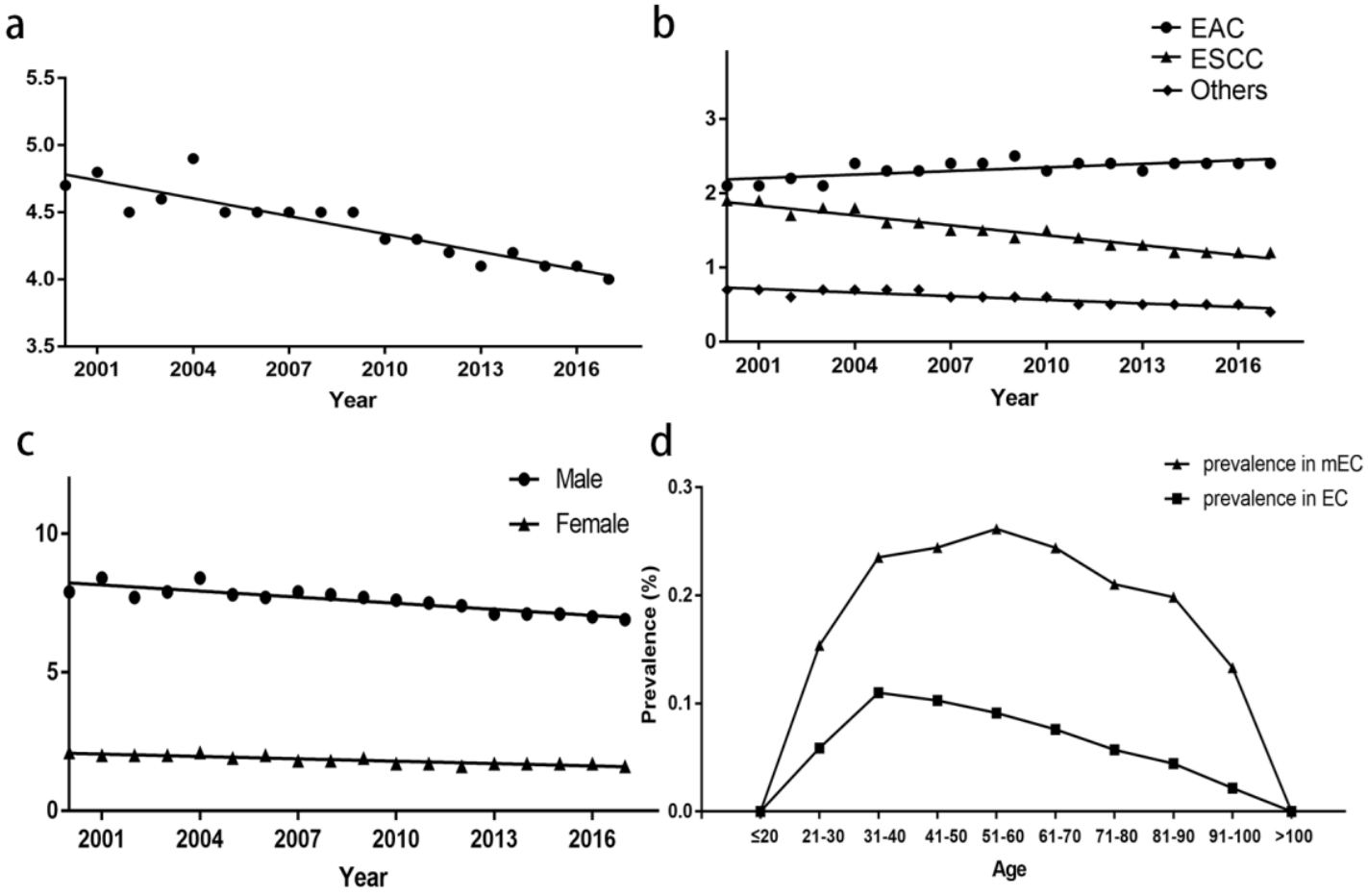

Figure 2

Epidemiological trends among EC patients. (a) Tendency about the incidence for all patients; (b) Tendency about the incidence for histological types; (c) Tendency about the incidence for sex; (d) Tendency about the prevalence for age in EC and mEC.

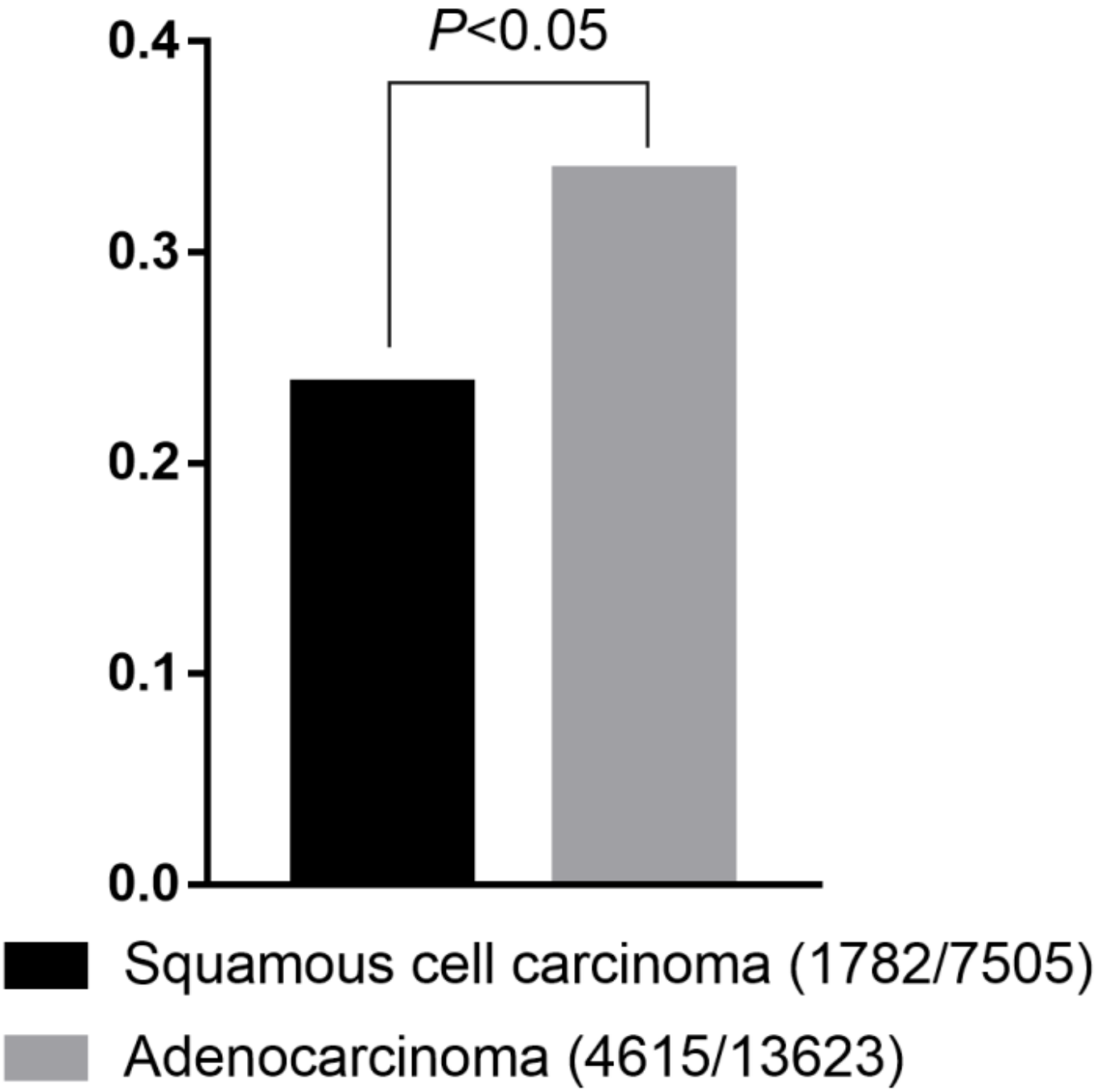

Figure 3

Comparison of advanced rates between ESCC and EAC.

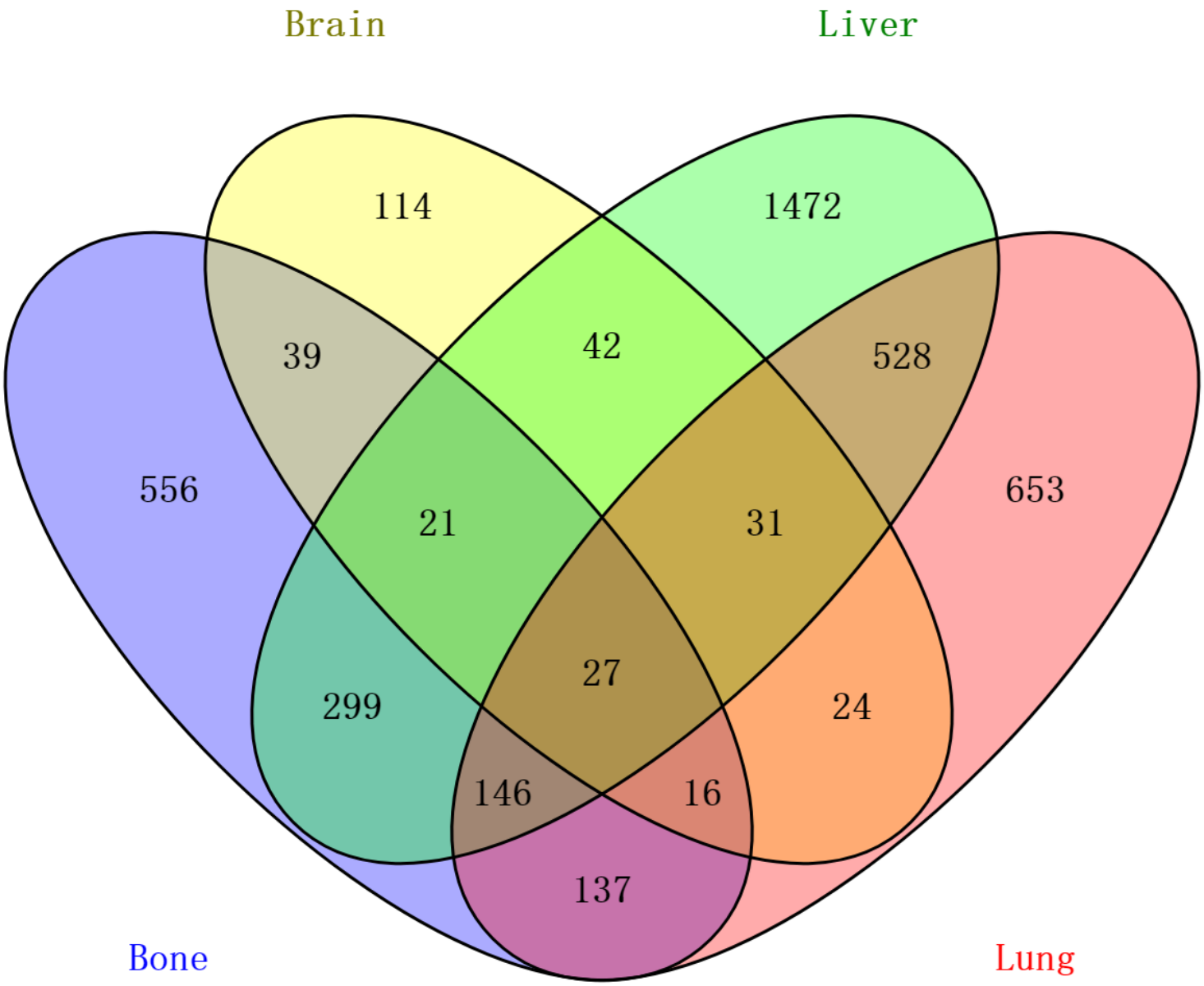

Figure 4

Distribution of metastatic sites.

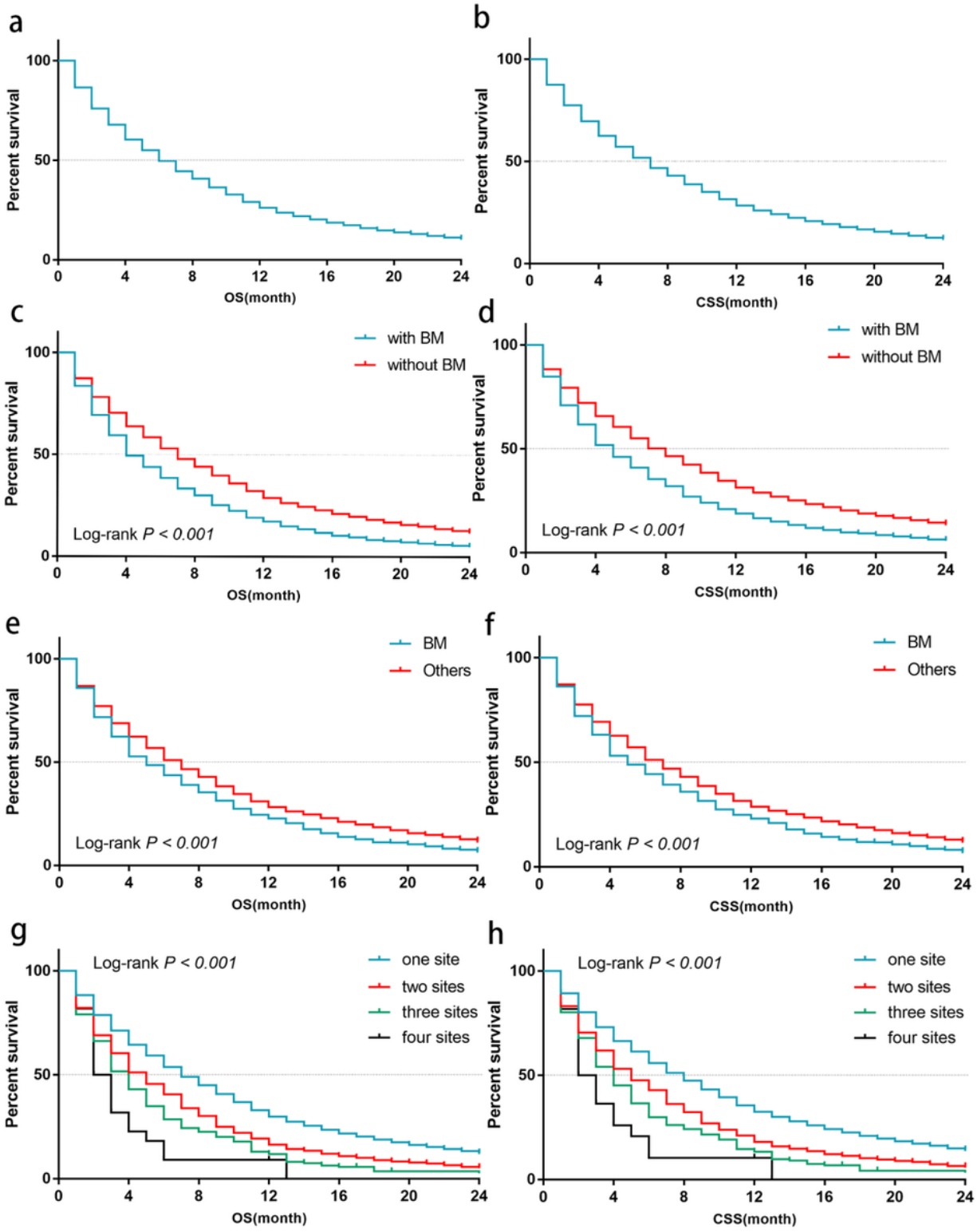

Figure 5

(a) OS for all patients; (b) CSS for all patients; (c) OS for patients with and without BM; (d) CSS for patients with and without BM; (e) OS for patients between BM and others with only one metastasis; (f) CSS for patients between BM and others with only one metastasis; (g) OS for patients with different numbers of metastatic sites; (h) CSS for patients with different numbers of metastatic sites.

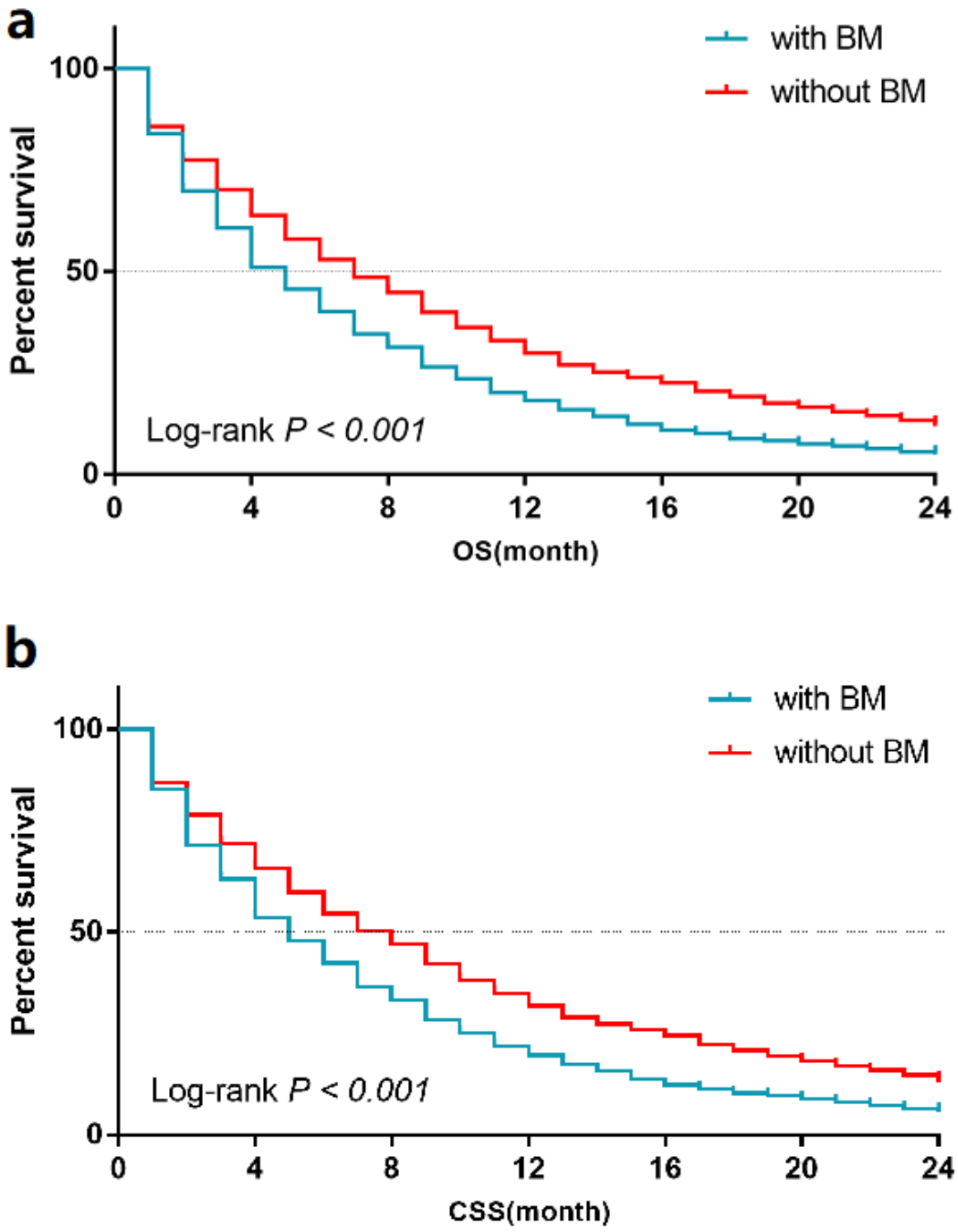

Figure 6

(a) OS for patients with and without BM after PSM; (b) CSS for patients with and without BM after PSM.

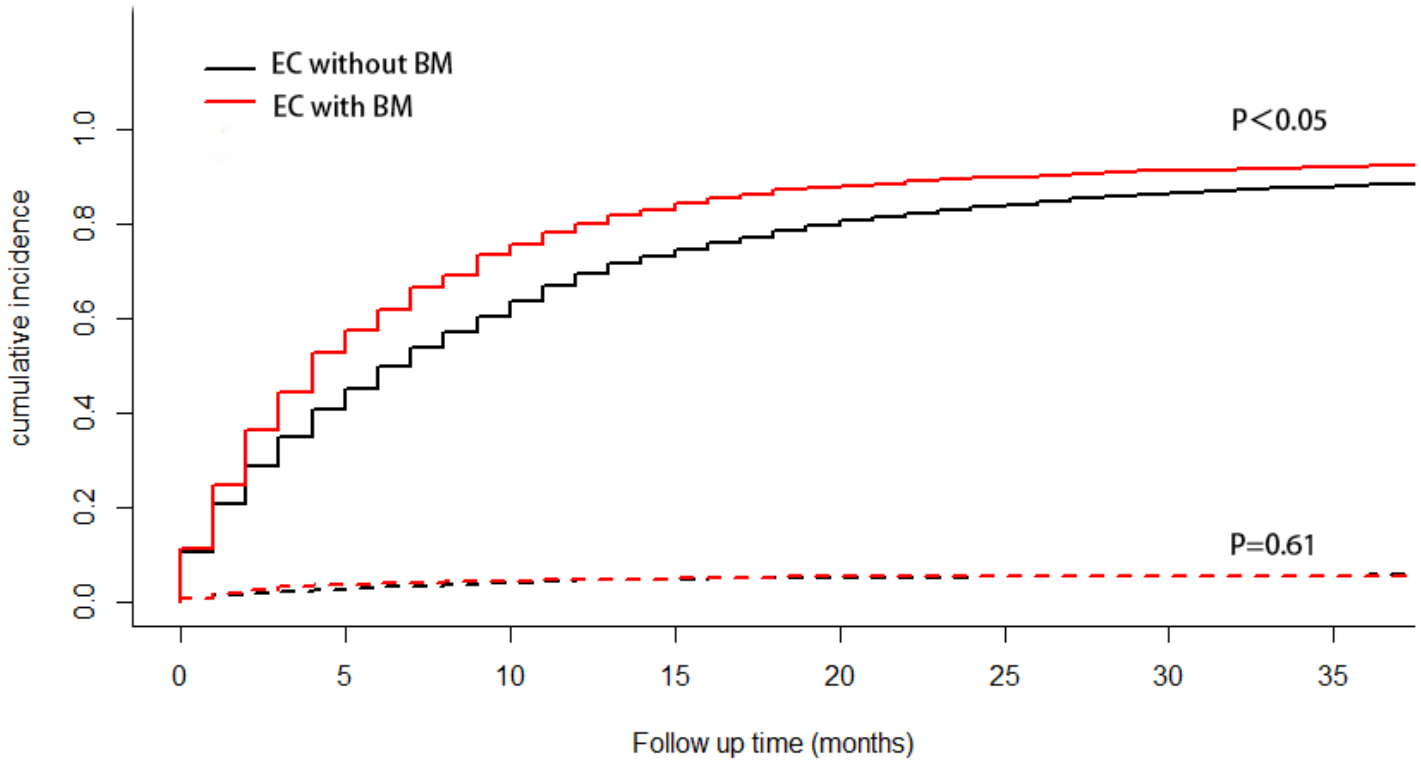

Figure 7

The cumulative incidence function curve for patients with and without BM. Solid line represents cause-specific death and dotted line represents other cause of death.

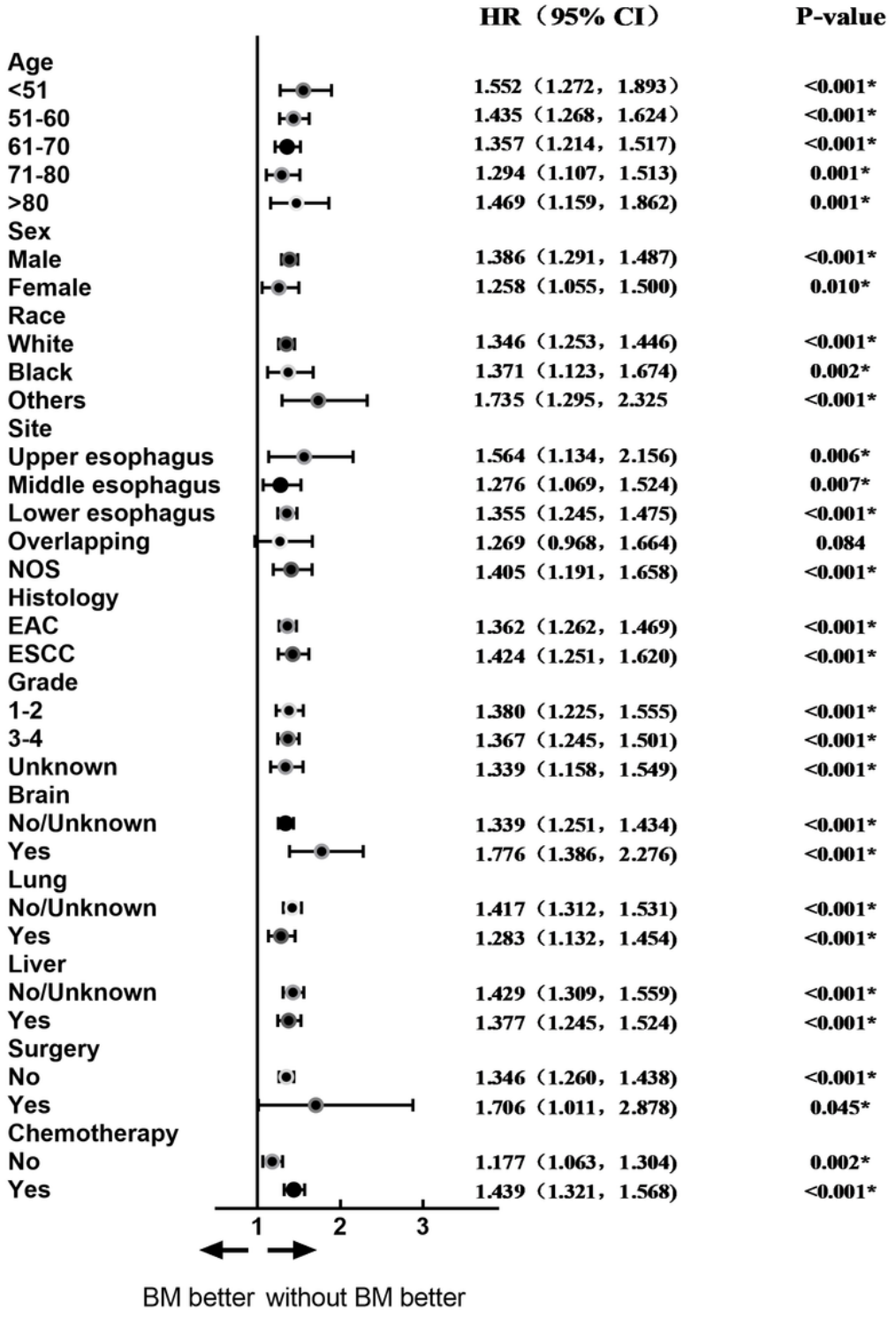

Figure 8

Forest plot of HR by the COX model for OS among patients with and without BM.