Original Article

Clinicopathological, metastatic and prognostic features of stage IV esophageal adenocarcinoma versus squamous cell carcinoma: a SEER database analysis

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Background: It is important to note that although the current treatment for advanced esophageal cancer (EC) has made great technological advances, patients' 5-year survival rates do not appear to be encouraging. Therefore, understanding the clinicopathological features and metastasis patterns of the patients with stage IV EC, combined with the prognosis of these patients, can aid in choosing the optimal treatment plan. It is well known that esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two most common pathological types. The aim of this study is to examine and compare the clinicopathological features and metastatic modes of stage IV ESCC and EAC, as well as their prognosis and survival.

Methods: Based on the Surveillance, Epidemiology, and End Results (SEER) database, we assessed the characteristics of ESCCs and EACs associated with prognosis using the Kaplan-Meier survival analysis, and the Cox regression model. Furthermore, the clinical data of 217 patients with stage IV ESCC and EAC in the Department of Gastroenterology of the Second Affiliated Hospital of Nantong University between 2014 and 2016 were reviewed.

Results: A total of 3,707 cases treated between 2010 and 2016 were included. The incidence of EAC in the United States is much higher than that of ESCC. Common metastasis patterns were lungs only, liver only, bones only, and lung & liver. The multivariate Cox analysis showed that treatment mode and metastasis patterns were independent risk factors affecting the overall survival (OS) time of patients (stage IV ESCC & EAC). EAC patients with only lung metastases may have a longer survival if chose treatment options that included surgery. In the external cohort, a total of 217 cases were included. The prevalence of ESCC is much higher than that of EAC, and the common metastasis patterns are liver only, lung only, and liver & lung. The multivariate Cox analysis showed that treatment mode was independent risk factor affecting the OS time of patients (stage IV ESCC & EAC). EAC patients treated with surgery combined with chemoradiotherapy may have a better prognosis.

Conclusions: In general, the prognosis of patients with stage IV ESCC and EAC are poor. However, surgery was found to significantly improve the OS time of patients with stage IV EAC in this study.

Keywords: Stage IV; esophageal cancer (EC); metastasis patterns; surgery; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer death and 50% of cases present with distant metastases at the time of diagnosis (1). In 2020, the global incidence of the disease was 604,000 new cases, with 544,000 deaths (2). EC has a poor prognosis, because it has often progressed into an advanced stage at diagnosis. Advanced EC is prone to distant metastasis, even multiple metastases. About 90% of EC patients in China can be classified into esophageal squamous cell carcinoma (ESCC), which is also a common subtype worldwide (3). A recent retrospective study reporting 23,804 esophageal adenocarcinoma (EAC) cases and 13,919 ESCC cases suggests an increasing incidence of EAC and a decreasing incidence of ESCC in the United States (4).

EC is prone to metastasizing to the liver, lung, bone, and brain (5). Among them, brain metastases carry the worst prognosis. The main treatment strategy for advanced EC is systemic palliative care, assisted by endoscopic therapy and nutritional support (6). Palliative care, including palliative resection or primary tumor chemoradiotherapy, is mainly performed to relieve EC-related symptoms (obstruction or bleeding) and improve the quality of life (7). In previous studies, surgeons have presented conflicting opinions on whether surgery is beneficial for the treatment of primary EC. Some studies found that surgery and non-resection groups had the same prognosis (8,9), while others reported promising outcomes following palliative resection, radiotherapy, and chemotherapy (10,11). Nonetheless, several studies have shown that patients with metastatic EC can benefit from multimodal treatment, which typically includes palliative resection, radiotherapy, and chemotherapy (12). The treatment strategy aims to alleviate symptoms, control disease progression, and improve overall survival (OS) rates. It is important to consider the patient's characteristics, the stage of his disease, and the response to treatment when evaluating the best approach to managing advanced EC (13).

Based on the data extracted from the Surveillance, Epidemiology, and End Results (SEER) database [2010–2016] and another data treated in our hospital [2014–2016] serving as the external cohort. This study aimed to analyze the clinical and epidemiological characteristics of stage IV ESCC and EAC. Moreover, we compared the survivals of patients with different metastatic patterns, and screened out treatment strategy improving stage IV EAC and ESCC prognosis. We present this article in accordance with the STROBE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-88/rc).

Highlight box

Key findings

- Stage IV esophageal adenocarcinoma (EAC) patients treated with surgery combined with chemoradiotherapy may have a better prognosis.

What is known and what is new?

- Only limited treatment outcome data about metastatic modes and therapeutic schemes have been available for patients with advanced esophageal squamous cell carcinoma (ESCC) and EAC, and thus the best therapy for this population had not previously been defined.
- This retrospective study compared the clinicopathological, metastatic and prognostic features in patients with stage IV ESCC and EAC using data from the Surveillance Epidemiology and End Results database from 2010 to 2016, with another data treated in our hospital serving as the external cohort.

What is the implication, and what should change now?

- The treatment of stage IV esophageal cancer should follow the principle of individualization, mainly according to the pathological type and metastasis pattern. Stage IV EAC patients should be considered for surgery probably.

Methods

Data

The data were extracted from the SEER program between 2010 and 2016. The program contains the population-based central cancer registries of 18 geographically defined regions. Furthermore, the clinical data of 217 patients with stage IV ESCC and EAC in the Department of Gastroenterology of the Second Affiliated Hospital of Nantong University between 2014 and 2016 were reviewed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics Committee of the Second Affiliated Hospital of Nantong University approved the protocol study (No. 2023KT259) and individual consent for this retrospective analysis was waived.

Patients

The inclusion criteria included: (I) there was only one primary tumor; (II) the histological was positive for EAC or ESCC; and (III) American Joint Committee on Cancer (AJCC) 7th edition stage was IV. The exclusion criteria included: (I) the demographic information (including race) was incomplete; (II) the clinic-pathological information was incomplete, including differentiation, AJCC stage [tumor-

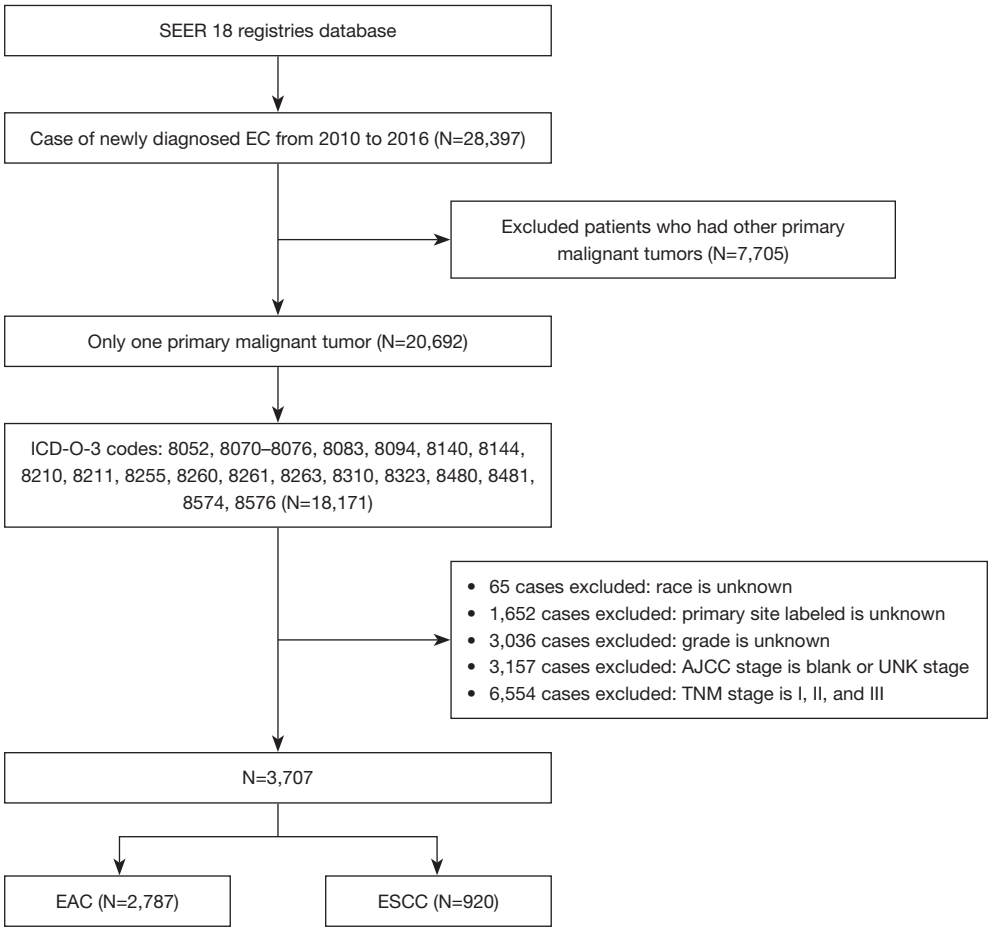

Figure 1 Flowchart of selection of patients with metastatic EC used the SEER database. SEER, Surveillance, Epidemiology, and End Results; EC, esophageal cancer; ICD-O-3, International Classification of Disease for Oncology third edition; AJCC, American Joint Committee on Cancer; UNK, unknown; TNM, tumor-node-metastasis; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

node-metastasis (TNM)], histological stage, causes of death and therapy; and (III) the information was just from autopsy or death certificate (*Figure 1*).

Patients' primary sites were defined by using the International Classification of Disease for Oncology third edition (ICD-O-3) histopathology codes. According to the age at diagnosis, we divided them into <50, 50–65, and >65 years groups.

Clinical variables

Information on demographic factors (age, race, gender), tumor-related factors (differentiation, histology, and AJCC TNM staging system), treatment methods (surgery, chemotherapy, radiotherapy, none), and follow-up were collected from the database. And follow-up period ended in 2021. According to the SEER program's surgery codes and information about other treatments, we divided treatment options into categories: no treatment, chemotherapy alone, radiotherapy alone, chemotherapy + radiotherapy, surgery (including only surgery, surgery + radiation, surgery + chemotherapy, and surgery + radiation + chemotherapy). In this study, OS time was the primary endpoint. It was calculated from the date of the first definite diagnosis to the date of death caused by any cause or the most recent follow-up.

Statistical analysis

In this cohort study, patient's OS was depicted by the Kaplan-Meier curves. Survival was defined as the time from

Table 1 Demographical characteristics and clinical data of the patients from SEER database

Variables	ESCC (n=920)	EAC (n=2,787)	χ^2/Z	P value
Age (years)			19.066	<0.001
<50	55	303		
50–65	419	1,217		
>65	446	1,267		
Gender			109.198	<0.001
Male	681	2,461		
Female	239	326		
Race			756.295	<0.001
White	529	2,609		
Black	281	94		
Asian or Pacific Islander	107	58		
American Indian/Alaska Native	3	26		
Primary site			950.454	<0.001
Upper 1/3	143	24		
Middle 1/3	362	254		
Lower 1/3	329	2,349		
Overlapping	86	160		
Differentiation			13.168	0.004
Well	22	94		
Moderately	379	976		
Poorly	511	1,680		
Undifferentiation	8	37		
T			33.843	<0.001
T_1	199	616		
T_2	35	130		
T_3	135	576		
T_4	211	442		
T_X	340	1,023		
N			33.843	<0.001
N_0	206	640		
N_1	501	1,411		
N_2	83	245		
N_3	42	177		
N_X	88	314		
Therapy			81.607	<0.001
None	271	658		
Only radiation	126	263		
Only chemotherapy	191	990		
Surgery†	16	86		
Radiation + chemotherapy	316	790		
OS			0.004	0.953
Death	890	2,695		
Alive	30	92		

†, including only surgery, surgery + radiation, surgery + chemotherapy, surgery + radiation + chemotherapy. SEER, Surveillance, Epidemiology, and End Results; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; T, tumor; N, node; OS, overall survival.

diagnosis to death from any cause. The survival curves were analyzed by the log-rank test. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), which indicated the independent prognostic factors associated with OS. Every two groups of variables were compared by χ^2/Z test. In all analyses, $P<0.05$ was considered significant, and all statistical tests were two-sided. All data were analyzed by IBM SPSS Statistics 26 software (IBM Corporation, Armonk, NY, USA).

Results

Basic information of patients

Of the 3,707 enrolled cases, all patients were diagnosed between 2010 and 2016, including 920 cases (24.8%) with ESCC and 2,787 cases (75.2%) with EAC. Stages IV ESCC and EAC were prevalent in the over 65 years age group, and more common in Caucasian men. The most prevalent primary site of ESCC was the middle of 1/3 of the esophagus and that of EAC was the lower 1/3 of the esophagus. Most cancers were in moderately or poorly differentiated. The clinical and demographic characteristics are shown in *Table 1*. Of the 3,707 cases of distant metastasis, 316 cases (34.3%) of ESCC and 790 cases (28.3%) of EAC received combined

Table 2 Demographical characteristics and clinical data of the stage IV ESCC and EAC patients from the external cohort

Variables	ESCC (n=125)	EAC (n=92)	χ^2/Z	P value
Age (years)			6.283	0.043
<50	10	7		
50–65	51	23		
>65	64	62		
Gender			8.659	0.003
Male	84	78		
Female	41	14		
Primary site			51.584	<0.001
Upper 1/3	26	5		
Middle 1/3	44	5		
Lower 1/3	40	72		
Overlapping	15	10		
Differentiation			0.787	0.375
Moderately	39	34		
Poorly	86	58		
T			9.071	0.003
T_3	29	39		
T_4	96	53		
N			19.107	<0.001
N_1	17	14		
N_2	44	9		
N_3	55	58		
N_X	9	11		
Therapy			50.155	<0.001
None	32	12		
Only radiation	5	0		
Only chemotherapy	1	25		
Surgery + radiation	10	0		
Radiation + chemotherapy	57	38		
Surgery + radiation + chemotherapy	20	17		
OS			2.113	0.146
Death	115	89		
Alive	10	3		

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; T, tumor; N, node; OS, overall survival.

chemotherapy and radiotherapy, 16 cases (1.7%) of ESCC and 86 cases (3.1%) of EAC received surgery including only surgery, surgery + radiation, surgery + chemotherapy, surgery + radiation + chemotherapy, and 990 cases (35.5%) of EAC received chemotherapy only.

A total of 217 cases from external cohort were enrolled in this research, including 125 cases (57.6%) with stage IV ESCC and 92 cases (42.4%) with stage IV EAC. The clinical and demographic characteristics are shown in *Table 2*. Of the 217 cases, 57 cases (45.6%) ESCC and 38 cases (41.3%) treated with chemoradiotherapy, 20 cases (16.0%) ESCC and 17 cases (18.5%) EAC treated with surgery followed by chemoradiotherapy, and all EAC patients did not receive surgery only or surgery combined with radiation. Furthermore, 32 cases ESCC and 12 cases EAC did not receive any treatment.

Metastasis patterns

A total of 2,717 patients presented distant metastases observed in the bone, brain, liver, and lung in the SEER database. There are 15 groups of metastatic EC, divided into single-organ metastases (bone, brain, liver, and lung), two-organ metastases (bone and brain, bone and liver, bone and lung, brain and liver, brain and lung, and liver and lung), three-organ metastases (bone, brain, and liver; bone, brain, and lung; bone, liver, and lung; and brain, liver, and lung), and four-organ metastases (bone, brain, liver, and lung). Of the 655 ESCC cases, the most common metastatic patterns included lung only (n=225, 34.4%), liver only (n=153, 23.4%), and bone only (n=89, 13.6%). Of the 2,062 EAC cases, the most common metastatic patterns included liver (n=844, 40.9%), liver and lung (n=286, 13.9%), and bone (n=270, 13.1%). The possibility of brain metastasis was lower than those of liver, lung, and bone metastases. The difference between the specific metastatic modes of ESCC and EAC is shown in *Table 3*.

In the external cohort, because of the limited sample size, metastasis patterns were divided into nine groups, single-organ metastases (bone, liver, and lung), two-organ metastases (bone and liver, bone and lung, and liver and lung), three-organ metastases (bone, brain, and liver; bone, liver, and lung), and four-organ metastases (bone, brain, liver, and lung). The most common metastatic patterns in ESCC included lung (n=40, 32.0%), liver and lung (n=30, 24.0%), and liver (n=29, 23.2%). While in EAC group, the most common metastatic patterns included liver (n=39, 42.4%), liver and lung (n=21, 22.8%), lung (n=10, 10.9%), and liver

Table 3 Compare organ metastasis patterns between ESCC and EAC with EC

Variables	ESCC (n=655), n (%)	EAC (n=2,062), n (%)	P value
Bone only	89 (13.6)	270 (13.1)	0.745†
Brain only	4 (0.6)	63 (3.1)	<0.001†
Liver only	153 (23.4)	844 (40.9)	<0.001†
Lung only	225 (34.4)	203 (9.8)	<0.001†
Bone and brain	5 (0.8)	19 (0.9)	0.706†
Bone and liver	26 (4.0)	164 (8.0)	<0.001†
Bone and lung	38 (5.8)	51 (2.5)	<0.001†
Brain and liver	1 (0.2)	23 (1.1)	0.022†
Brain and lung	2 (0.3)	12 (0.6)	0.539‡
Liver and lung	81 (12.4)	286 (13.9)	0.327†
Bone, brain, and liver	0 (0.0)	13 (0.6)	0.047‡
Bone, brain, and lung	3 (0.5)	9 (0.4)	>0.99‡
Brain, liver, and lung	2 (0.3)	15 (0.7)	0.392‡
Bone, liver, and lung	22 (3.4)	80 (3.9)	0.541†
Bone, brain, liver, and lung	4 (0.6)	10 (0.5)	0.754‡

†, Pearson's chi-squared test; ‡, Fisher exact test. ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; EC, esophageal cancer.

Table 4 Compare organ metastasis patterns between ESCC and EAC from the external cohort

Variables	ESCC (n=125), n (%)	EAC (n=92), n (%)	P value
Bone only	3 (2.4)	5 (5.4)	0.288‡
Liver only	29 (23.2)	39 (42.4)	0.003†
Lung only	40 (32.0)	10 (10.9)	<0.001†
Bone and liver	5 (4.0)	10 (10.9)	0.049†
Bone and lung	10 (8.0)	2 (2.2)	0.064†
Liver and lung	30 (24.0)	21 (22.8)	0.840†
Bone, brain, and liver	0 (0.0)	2 (2.2)	0.179‡
Bone, liver, and lung	7 (5.6)	1 (1.1)	0.142‡
Bone, brain, liver, and lung	1 (0.8)	2 (2.2)	0.575‡

†, Pearson's chi-squared test; ‡, Fisher exact test. ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

and bone (n=10, 10.9%). The difference between the specific metastatic modes of ESCC and EAC is shown in *Table 4*.

Survival

A survival analysis was conducted on patients with the above four metastatic patterns, who made up more than 80% of the sample. The median survival was 4 months for metastatic ESCC, and 5 months for metastatic EAC, which may not be clinically significant. The univariate Cox regression analysis revealed treatment mode and metastasis patterns associated with all-cause mortality in

patients with stage IV ESCC & EAC patients (P<0.05). The multivariate Cox analysis showed that treatment mode and metastasis patterns were independent risk factors affecting the OS (*Tables 5*,*6*). The OS of stage IV EAC patients with lung metastasis was longer than that of the other three metastatic patterns, with an average of 7 months (*Figure 2*). Additionally, the survival time was relatively longer in EAC patients receiving surgery, with an average of 14 months (*Figure 3*).

In the external cohort, approximately 80% of the sample had the above-mentioned metastasis patterns. It was found that survival rates between ESCC and EAC were not different. The median survival was 4 months for ESCC, and 6 months for EAC. The univariate Cox analysis showed that only treatment mode was related to the prognosis (P<0.05). The multivariate Cox analysis showed that treatment mode was independent risk factor affecting the OS (*Tables 7*,*8*). In addition, the median survival time was 11 months, relatively longer in EAC patients receiving surgery combined with chemoradiotherapy than other treatment modes (*Figure 4*).

Discussion

In this study, we found that stage IV EAC and ESCC were more prevalent in males, elderly, or Caucasians.

Table 5 Univariate and multivariate survival analysis of stage IV ESCC patients from SEER database with bone alone, liver alone, lung alone, and simultaneous liver and lung metastasis

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<50	Reference		Reference	
50–65	0.745 (0.506–1.096)	0.135	0.902 (0.601–1.352)	0.617
>65	0.942 (0.642–1.383)	0.761	1.128 (0.752–1.693)	0.559
Gender				
Male	Reference		Reference	
Female	0.908 (0.746–1.103)	0.331	0.894 (0.727–1.098)	0.285
Race				
White	Reference		Reference	
Black	1.046 (0.868–1.262)	0.636	1.007 (0.823–1.231)	0.948
Asian or Pacific Islander	0.959 (0.719–1.279)	0.778	0.882 (0.652–1.194)	0.418
American Indian/Alaska Native	0.674 (0.216–2.105)	0.497	1.066 (0.332–3.419)	0.914
Primary site				
Upper 1/3	Reference		Reference	
Middle 1/3	1.008 (0.791–1.286)	0.948	1.055 (0.808–1.377)	0.694
Lower 1/3	0.985 (0.771–1.259)	0.904	1.006 (0.756–1.339)	0.966
Overlapping	1.314 (0.930–1.859)	0.122	1.272 (0.884–1.829)	0.195
Differentiation				
Well	Reference		Reference	
Moderately	1.075 (0.600–1.925)	0.808	0.972 (0.530–1.782)	0.926
Poorly	1.096 (0.614–1.955)	0.756	1.051 (0.576–1.919)	0.871
Undifferentiation	1.243 (0.437–3.537)	0.684	1.057 (0.359–3.112)	0.921

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
T				
T_1	Reference		Reference	
T_2	0.643 (0.399–1.035)	0.069	0.640 (0.384–1.069)	0.088
T_3	0.790 (0.580–1.075)	0.134	0.970 (0.695–1.354)	0.858
T_4	1.191 (0.926–1.533)	0.174	1.240 (0.948–1.621)	0.116
T_X	0.958 (0.765–1.201)	0.712	0.969 (0.763–1.230)	0.793
N				
N_0	Reference		Reference	
N_1	0.757 (0.615–0.932)	0.009	0.782 (0.630–0.970)	0.026
N_2	0.917 (0.694–1.358)	0.864	1.177 (0.819–1.693)	0.378
N_3	0.988 (0.634–1.540)	0.959	1.027 (0.643–1.638)	0.912
N_X	1.006 (0.744–1.359)	0.971	0.913 (0.667–1.251)	0.572
Therapy				
None	Reference		Reference	
Surgery[†]	0.393 (0.193–0.801)	0.010	0.389 (0.187–0.810)	0.012
Only radiation	0.672 (0.512–0.882)	0.004	0.644 (0.487–0.850)	0.002
Only chemotherapy	0.347 (0.272–0.442)	<0.001	0.318 (0.245–0.413)	<0.001
Radiation + chemotherapy	0.302 (0.242–0.378)	<0.001	0.321 (0.254–0.406)	<0.001
Metastasis				
Bone only	Reference		Reference	
Liver only	0.761 (0.583–0.993)	0.044	0.822 (0.618–1.094)	0.179
Lung only	0.721 (0.562–0.926)	0.010	0.649 (0.497–0.848)	0.002
Liver and lung	1.076 (0.795–1.457)	0.634	0.970 (0.703–1.340)	0.855

[†], including only surgery, surgery + radiation, surgery + chemotherapy, and surgery + radiation + chemotherapy. ESCC, esophageal squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; HR, hazard ratio; CI, confidence interval; T, tumor; N, node.

ESCC was more common in the middle 1/3 esophageal segment, and EAC in the lower 1/3 segment. The number of EAC cases was larger than that of ESCC, and poorly differentiated was the most common. The minority patients received surgery (accounting for less than 5%). The SEER database is mainly based on North America, therefore, the epidemiological characteristics of EC inferred from the present study may not be representative globally. According to Lepage C's epidemiological survey, ESCC is the most common subtype of EC outside the United States, accounting for 90% of cases worldwide, and EAC in North America and Europe (14). According to the results of this study, the prevalence of EAC in the United States is indeed much higher than that of ESCC, which is in line with the characteristics of epidemiological investigation. In addition, due to the absence of a serous layer and abundant lymphatic capillary system in the esophagus, EC metastasis is prone to occurring earlier. Patients with early-stage EC have often no obvious symptoms, and EC has usually progressed into the advanced stage at diagnosis.

Therefore, we conducted a subgroup analysis of stage IV

Table 6 Univariate and multivariate survival analysis of stage IV EAC patients from SEER database with bone alone, liver alone, lung alone, and simultaneous liver and lung metastasis

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<50	Reference		Reference	
50–65	1.238 (1.040–1.474)	0.016	1.266 (1.059–1.513)	0.009
>65	1.426 (1.199–1.696)	<0.001	1.287 (1.076–1.540)	0.006
Gender				
Male	Reference		Reference	
Female	0.909 (0.775–1.066)	0.239	0.884 (0.752–1.040)	0.136
Race				
White	Reference		Reference	
Black	0.980 (0.759–1.266)	0.878	0.947 (0.728–1.231)	0.683
Asian or Pacific Islander	0.809 (0.536–1.221)	0.313	0.907 (0.598–1.376)	0.646
American Indian/Alaska Native	1.079 (0.596–1.953)	0.802	1.429 (0.785–2.603)	0.243
Primary site				
Upper 1/3	Reference		Reference	
Middle 1/3	1.374 (0.804–2.347)	0.245	1.673 (0.974–2.876)	0.062
Lower 1/3	1.268 (0.762–2.110)	0.362	1.601 (0.956–2.683)	0.074
Overlapping	1.410 (0.814–2.446)	0.221	1.624 (0.932–2.831)	0.087
Differentiation				
Well	Reference		Reference	
Moderately	1.143 (0.849–1.539)	0.380	1.151 (0.850–1.558)	0.363
Poorly	1.450 (1.081–1.945)	0.013	1.460 (1.083–1.969)	0.013
Undifferentiation	1.234 (0.738–2.065)	0.423	1.591 (0.945–2.678)	0.081
T				
T_1	Reference		Reference	
T_2	0.658 (0.504–0.861)	0.002	0.735 (0.558–0.969)	0.029
T_3	0.765 (0.656–0.892)	0.001	0.839 (0.711–0.989)	0.036
T_4	0.943 (0.803–1.108)	0.478	0.991 (0.839–1.171)	0.917
T_X	1.047 (0.918–1.194)	0.497	1.050 (0.917–1.202)	0.480
N				
N_0	Reference		Reference	
N_1	0.873 (0.773–0.985)	0.028	1.026 (0.901–1.168)	0.703
N_2	0.755 (0.614–0.929)	0.008	0.981 (0.790–1.219)	0.863
N_3	0.935 (0.741–1.179)	0.571	1.180 (0.924–1.507)	0.184
N_X	1.099 (0.922–1.309)	0.291	1.008 (0.842–1.207)	0.929

Table 6 (*continued*)

Table 6 (*continued*)

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Therapy				
None	Reference		Reference	
Surgery[†]	0.145 (0.100–0.210)	<0.001	0.161 (0.111–0.235)	<0.001
Only radiation	0.637 (0.527–0.770)	<0.001	0.653 (0.537–0.793)	<0.001
Only chemotherapy	0.262 (0.230–0.298)	<0.001	0.254 (0.222–0.290)	<0.001
Radiation + chemotherapy	0.269 (0.232–0.312)	<0.001	0.275 (0.235–0.322)	<0.001
Metastasis				
Bone only	Reference		Reference	
Liver only	0.929 (0.808–1.067)	0.296	0.934 (0.807–1.081)	0.357
Lung only	0.868 (0.721–0.945)	0.035	0.821 (0.678–0.993)	0.042
Liver and lung	1.157 (0.978–1.369)	0.089	1.123 (0.942–1.340)	0.196

[†], including only surgery, surgery + radiation, surgery + chemotherapy, and surgery + radiation + chemotherapy. EAC, esophageal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; HR, hazard ratio; CI, confidence interval; T, tumor; N, node.

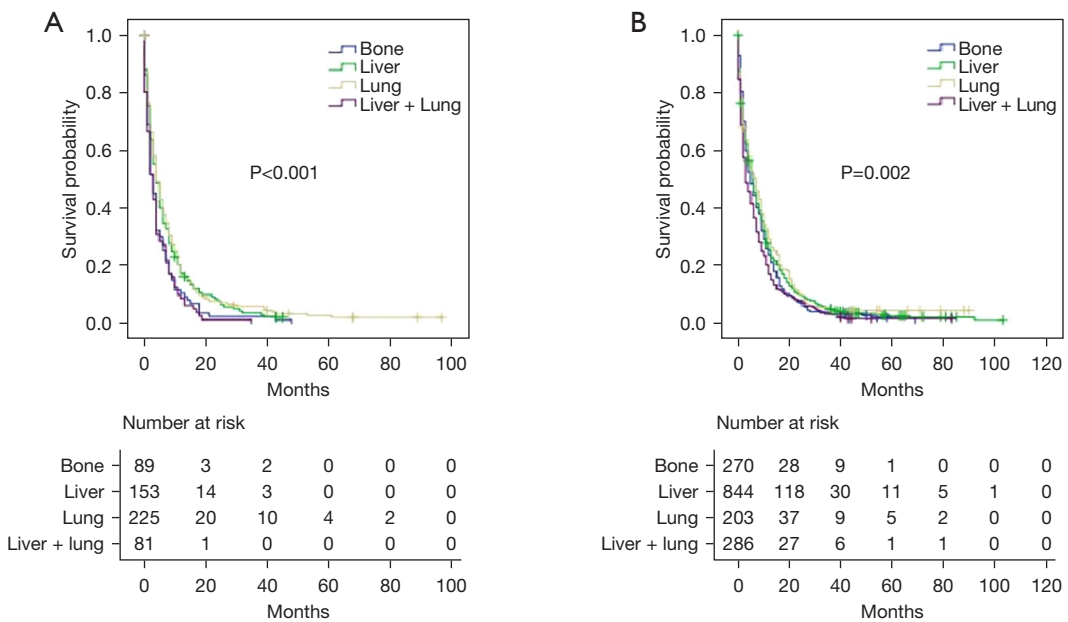

Figure 2 OS rate of ESCC and EAC patients with the common metastasis patterns. (A) ESCC; (B) EAC. OS, overall survival; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

EC patients. In this study, the incidence of EAC metastasis was compared with that of ESCC metastasis (the proportion of stage IV), finding that metastasis was more likely in males, which may be explained by that male hormones can promote the proliferation and metastasis of EC cells, and the likelihood of men drinking alcohol and smoking cigarettes is higher than that of women (15-17). In metastatic ESCC, the proportions of patients with moderately or poorly

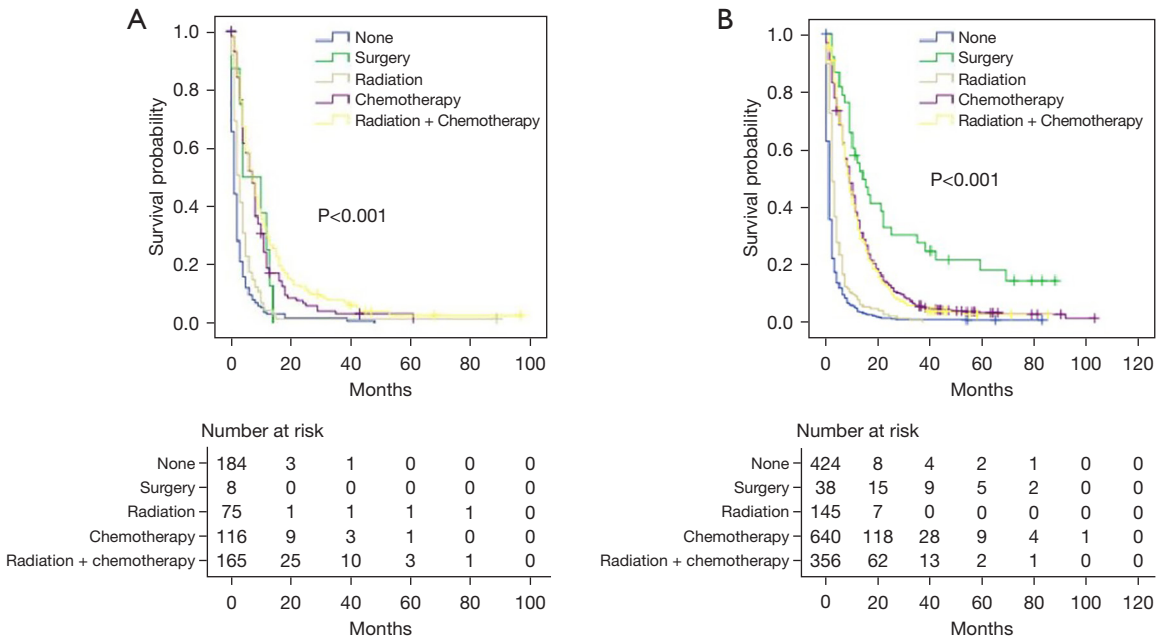

Figure 3 OS rate of different treatment regimens for ESCC and EAC from SEER database. (A) ESCC; (B) EAC. Surgery including only surgery, surgery + radiation, surgery + chemotherapy, and surgery + radiation + chemotherapy. OS, overall survival; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results.

differentiated were similar, while in metastatic EAC, the proportion of low differentiation was higher (60%), and the degree of differentiation was related to distant metastasis and prognosis. EAC is more likely to be located in the lower esophagus and ESCC in the middle esophagus. EAC generally evolves from Barrett's esophagus, which is susceptible to reflux esophagitis. The reason why ESCC tends to occur in the middle segment is currently unclear, and it is speculated to be related to physiological stenosis in this part. Due to the loss of surgical opportunities, advanced EC tends to be treated with chemotherapy and radiation therapy. Therefore, in this study, the majority of patients with stage IV ESCC and EAC chose chemotherapy combined with radiation therapy (18,19).

Then, we compared the metastatic patterns of stage IV EAC and ESCC. Overall, the most common metastatic sites were the lung, liver, and bone in EC patients, which is consistent with previous studies (5,20-23). Metastases to the liver are frequently observed in ESCC and EAC, the venous drainage of the distal esophagus drain directly into the portal vein, where the venous drainage of the distal esophagus drain directly into the portal vein. It may explain the high prevalence of liver metastases among EC patients. It is thought that the high frequency of lung metastases may be due to the fact that other parts of the venous drainage system of the distal esophagus, as well as the mid and proximal part of the esophagus, drain directly to the superior vena cava. There are no clear mechanisms behind the differences in metastatic patterns between EC subtypes. however, tumor location can pose a confounding factor as EAC originate from the distal esophagus and ESCC generally from the proximal esophagus (21). Furthermore, esophageal carcinoma had the high rate of bone metastasis. Due to its anatomical proximity to the spine and shared blood supply with it, the middle esophagus may have been affected by this finding. The vertebral vein system is interconnected and its blood flow is slow, so when the pressure increases in the thoracic or abdominal cavity, the tumor embolus can travel directly to the vertebral veins and cause metastasis (5,24).

Analysis of treatments corresponding to the top four metastatic modes found that ESCC patients with lung or bone metastasis preferred radiotherapy combined with chemotherapy, while those with liver or liver & lung metastasis preferred chemotherapy alone. Among the treatment plans corresponding to the first four metastatic modes of EAC, patients with only bone metastasis tended to choose radiotherapy combined with chemotherapy,

Table 7 Univariate and multivariate survival analysis of ESCC patients from the external cohort with liver alone, lung alone, and simultaneous liver and lung metastasis

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<50	Reference		Reference	
50–65	0.351 (0.144–0.857)	0.022	0.275 (0.096–0.787)	0.016
>65	0.547 (0.230–1.298)	0.171	0.358 (0.124–1.033)	0.058
Gender				
Male	Reference		Reference	
Female	1.448 (0.939–2.232)	0.094	1.875 (1.098–3.203)	0.051
Primary site				
Upper 1/3	Reference		Reference	
Middle 1/3	1.180 (0.656–2.123)	0.580	1.160 (0.603–2.231)	0.657
Lower 1/3	0.927 (0.506–1.700)	0.807	0.921 (0.453–1.874)	0.820
Overlapping	1.378 (0.648–2.931)	0.405	1.528 (0.656–3.556)	0.325
Differentiation				
Moderately	Reference		Reference	
Poorly	0.981 (0.644–1.495)	0.929	0.619 (0.366–1.047)	0.074
T				
T_3	Reference		Reference	
T_4	0.755 (0.491–1.160)	0.200	0.583 (0.350–0.971)	0.058
N				
N_1	Reference		Reference	
N_2	0.888 (0.463–1.705)	0.722	2.766 (1.155–6.621)	0.022
N_3	1.476 (0.788–2.764)	0.224	2.720 (1.254–5.902)	0.011
N_X	1.045 (0.416–2.624)	0.925	3.324 (0.823–13.430)	0.092
Therapy				
None	Reference		Reference	
Only radiation	0.923 (0.322–2.640)	0.881	1.189 (0.356–3.972)	0.778
Only chemotherapy	0.487 (0.066–3.606)	0.481	1.052 (0.085–13.032)	0.969
Surgery + radiation	0.315 (0.094–1.052)	0.060	0.522 (0.132–2.062)	0.354
Radiation + chemotherapy	0.291 (0.170–0.499)	<0.001	0.191 (0.091–0.401)	<0.001
Surgery + radiation + chemotherapy	0.206 (0.102–0.417)	<0.001	0.191 (0.085–0.426)	<0.001
Metastasis patterns				
Liver only	Reference		Reference	
Lung only	1.284 (0.773–2.134)	0.334	1.167 (0.614–2.218)	0.638
Liver and lung	1.250 (0.731–2.136)	0.415	0.760 (0.381–1.519)	0.437

ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; T, tumor; N, node.

Table 8 Univariate and multivariate survival analysis of EAC patients from the external cohort with liver alone, lung alone, and simultaneous liver and lung metastasis

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<50	Reference		Reference	
50–65	1.010 (0.371–2.754)	0.984	1.202 (0.338–4.278)	0.776
>65	1.048 (0.444–2.475)	0.914	1.734 (0.558–5.387)	0.341
Gender				
Male	Reference		Reference	
Female	0.436 (0.205–0.928)	0.031	0.998 (0.369–2.695)	0.997
Primary site				
Upper 1/3	Reference		Reference	
Middle 1/3	1.365 (0.274–6.797)	0.704	0.248 (0.031–1.973)	0.188
Lower 1/3	0.407 (0.125–1.333)	0.138	0.271 (0.070–1.051)	0.059
Overlapping	0.345 (0.079–1.509)	0.158	0.342 (0.062–1.897)	0.220
Differentiation				
Moderately	Reference		Reference	
Poorly	1.524 (0.849–2.734)	0.158	2.499 (1.146–5.448)	0.021
T				
T_3	Reference		Reference	
T_4	2.883 (1.587–5.237)	0.001	5.583 (2.182–14.284)	<0.001
N				
N_1	Reference		Reference	
N_2	0.279 (0.105–0.742)	0.011	0.466 (0.101–2.146)	0.327
N_3	0.422 (0.213–0.834)	0.013	0.383 (0.112–1.305)	0.125
N_X	0.332 (0.113–0.976)	0.045	1.185 (0.231–6.090)	0.839
Therapy				
None	Reference		Reference	
Only chemotherapy	0.258 (0.111–0.596)	0.002	0.271 (0.101–0.733)	0.010
Radiation + chemotherapy	0.367 (0.165–0.816)	0.014	0.622 (0.216–1.789)	0.378
Surgery + radiation + chemotherapy	0.312 (0.126–0.776)	0.012	0.087 (0.020–0.371)	0.001
Metastasis patterns				
Liver only	Reference		Reference	
Lung only	2.213 (1.051–4.661)	0.037	1.234 (0.300–5.071)	0.770
Liver and lung	1.333 (0.769–2.311)	0.306	3.875 (1.492–10.061)	0.005

EAC, esophageal adenocarcinoma; HR, hazard ratio; CI, confidence interval; T, tumor; N, node.

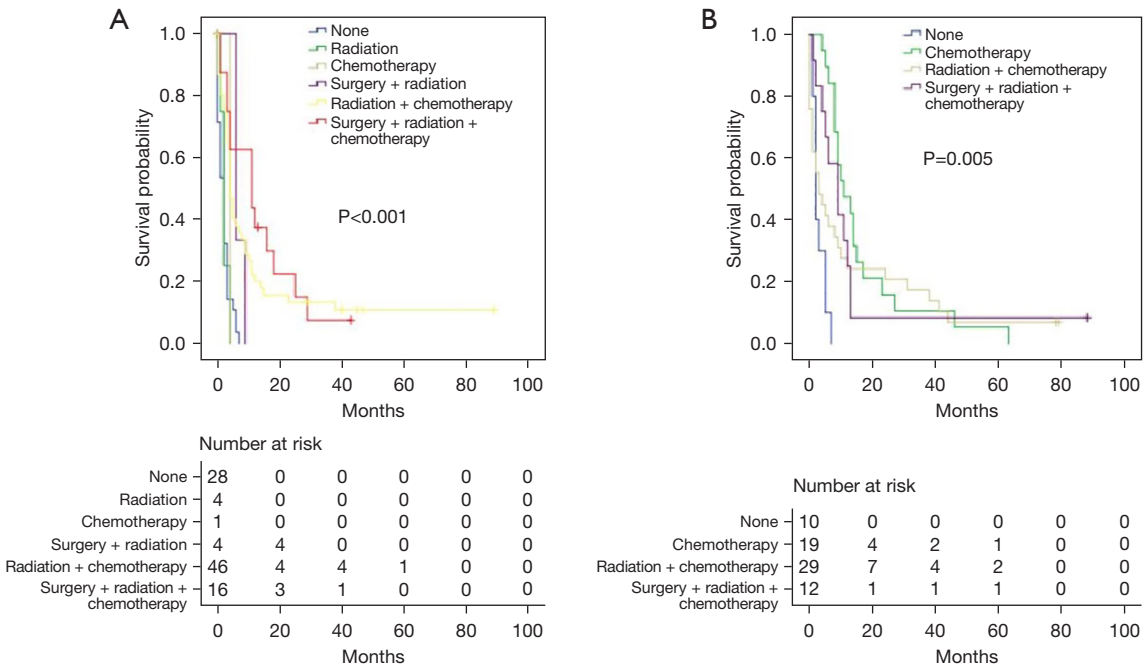

Figure 4 OS rate of different treatment regimens for ESCC and EAC from the external cohort. (A) ESCC, (B) EAC. Surgery including only surgery, surgery + radiation, surgery + chemotherapy, and surgery + radiation + chemotherapy. OS, overall survival; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

while others chemotherapy alone. Our survival analysis of the SEER database showed that EAC patients who received surgery had a longer survival time. Most stage IV EC patients often are not even considered for surgery due to perceived high risk, this finding is consistent with our data from the SEER database where only 2.8% of patients received surgery. In response to the question of whether surgery should be considered in patients with stage IV EC, the results of our external validation cohort suggest that when surgery was incorporated into patients' treatment plans, their survival was improved. Analysis of this cohort showed that surgery followed by chemoradiation therapy, had the most improved survival compared to other modalities. This finding may be because of our limited clinical sample size. But, Del Calvo *et al.* found that chemoradiation therapy followed by surgery should be considered for octogenarians who are surgically fit (25). However, the treatment paradigm with surgery was rarely used in stage IV EC patients, and most received definitive chemoradiation therapy only. Undoubtedly, there existed an increasing amount of proof indicating that individuals with metastatic tumors can experience advantages from undergoing surgery on the original tumor (13). Surgical intervention can benefit metastatic cancer patients by boosting their immune system, which is compromised by primary tumors that cause immunosuppression. Despite the presence of metastatic tumors, the immune system was restored following surgical resection of the primary tumor. Moreover, surgery can reduce the patient's tumor burden, allowing systemic therapy to have a more significant effect. Additionally, surgery can benefit patients with advanced EC by treating primary tumors locally. A surgical procedure may alleviate symptoms related to esophageal obstruction, nutrition, and metastasis of the regional lymph nodes, as well as relieve symptoms resulting from compression of the lymph nodes (13).

This study has certain limitations. First, this is a retrospective study based on the SEER database. We only obtained data on liver, lung, bone, and brain metastases, without data on other metastasis sites from the SEER database. Second, although we selected an external cohort for validation, the sample size was limited because of loss to follow-up. Third, only synchronous transfer cases were recorded, lacking data on asynchronous transfer. Fourth, since the vast majority of the samples in this study come from European and American countries, more domestic

data are needed for further research.

Conclusions

The present finding is the first large-scale report on clinicopathological, metastatic, and prognostic features of stage IV ESCC versus EAC. Metastatic patterns may differ between patients with EAC and ESCC, but the prognosis may be similar. The distant organ metastasis in EC may contribute to poor outcomes. Stage IV EAC patients treated with surgery combined with chemoradiotherapy may have a better prognosis. Thus, stage IV EAC patients should be considered for surgery probably.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-88/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-88/dss

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-88/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-88/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics Committee of the Second Affiliated Hospital of Nantong University approved the protocol study (No. 2023KT259) and individual consent for this retrospective analysis was waived.

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