Original Article

Survival benefit of radiotherapy in metastatic esophageal cancer: a population-based study

Xiangpan Li[1], Huibo Zhang[1], Xuemei Jia[2], Liming Xu[3], Huali Liu[1], Liang Chen[1], Qibin Song[1], Zhouguang Hui[4]

[1]Department of Oncology, [2]Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, China; [3]Department of Radiation Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300070, China; [4]Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing 10000, China

Contributions: (I) Conception and design: X Li, Q Song, Z Hui; (II) Administrative support: Q Song; (III) Provision of study materials or patients: X Li; (IV) Collection and assembly of data: H Zhang, X Jia, L Xu, H Liu, L Chen; (V) Data analysis and interpretation: X Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Qibin Song. Department of Oncology, Renmin Hospital of Wuhan University, No. 99, Zhangzhidong Road, Wuhan 430060, China. Email: qibinsong1@163.com; Zhouguang Hui. Department of Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing 10000, China. Email: lxp008cn@sina.com.

Background: Population-based estimates of survival benefits of radiotherapy on metastatic esophageal cancer (EC) are lacking. The aim of this study was to analyze survival benefits of radiotherapy in patients with metastatic EC at the time of cancer diagnosis.

Methods: Patients with metastatic EC were selected from Surveillance, Epidemiology, and End Results databases. The covariates included radiotherapy status, age, sex, insurance, histological type, differentiation, metastatic sites (bone, brain, liver, lung), and chemotherapy. Propensity score matching model was used to reduce bias of patients' selection. Median overall survival (OS) and cancer-specific survival (CSS) were compared and Cox regression analysis was performed.

Results: A total of 4,761 patients with metastatic EC met the selection criteria. It was found that radiotherapy significantly improved 2-year OS (P=0.020) and 2-year CSS (P=0.009) in matched patients. In the propensity score model (N=3,672), Cox regression analysis demonstrated that radiotherapy was an independent prognostic factor which associated with a longer OS (P<0.001) and esophageal cause-specific survival in matched patients (P<0.001). Additionally, age, sex, insurance status, differentiation, number of metastatic sites and chemotherapy were also found to be significantly associated with OS and CSS in matched patients.

Conclusions: The population-based study demonstrated that patients with metastatic EC might benefit from radiotherapy. This data supports the proposal to change the current management for patients with metastatic EC.

Keywords: Metastatic esophageal cancer (metastatic EC); radiotherapy; prognosis

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Introduction

Esophageal cancer (EC) is one of the most fatal malignant tumors globally, with a 5-year survival rate of 15–25% (1-3). With the improvement in diagnostic techniques, there are more than 50% patients detected at metastatic stage with incurable metastatic disease at diagnosis. For metastatic EC with distant metastasis, systematic chemotherapy is recommended as the standard therapy, however, the overall survival (OS) is still poor. External beam radiotherapy has been performed in the management for EC as definitive,

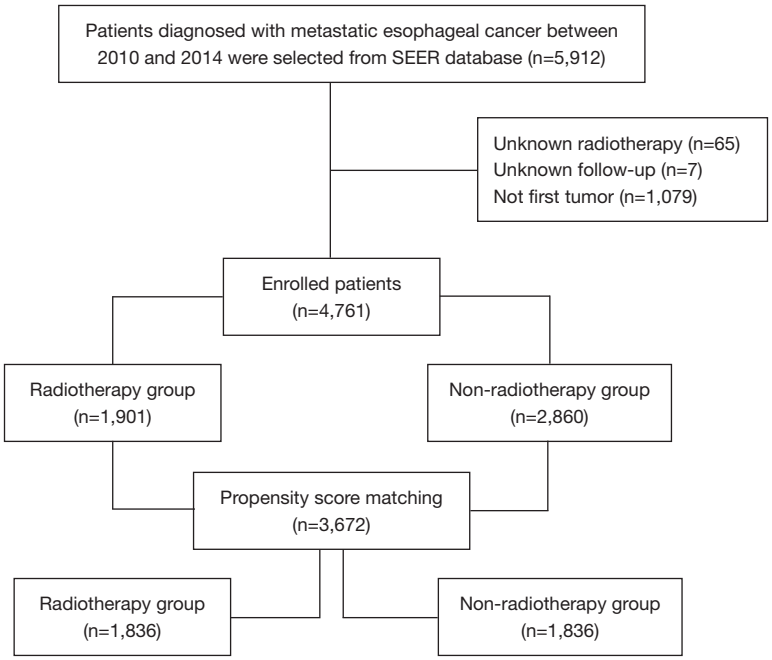

Figure 1 Flow diagram.

preoperative, postoperative, or palliative therapy combining with chemotherapy (4-7). For patients with metastatic EC, radiotherapy is used as a palliative treatment modality to relieve symptoms such as dysphagia and chest pain (8,9). However, the effect of radiotherapy on survival of patients with metastatic EC is unclear.

The purpose of this study was to assess the impact of radiotherapy on the OS of metastatic EC based on the data available in the Surveillance, Epidemiology, and End Results (SEER) database, attempting to provide a novel concept for the change of traditional treatment modality to metastatic EC.

Methods

Patients

The SEER database, one of the largest databases of oncology patients in the United States, includes cancer incidence, treatment, and survival information for approximately 30% of the US population. SEER*Stat software version 8.3.5 was used and SEER data between 1973 and 2014 ["Incidence-SEER 18 Regs Custom data (with additional treatment fields), Nov 2016 sub (1973–2014 varying)"] was chosen for this study. Adult patients diagnosed with EC who had metastatic diseases between 2010 and 2014 (n=5,912) were enrolled. Patients treated with beam radiation (combined with or without other type of radiotherapy) were included in the cohort. Patients with unknown radiotherapy data were excluded (n=65). Patients for whom the presence of follow-up was unknown were not included (n=7). In addition, patients who were presented with "N/A not first tumor" were excluded (within SEER database) (n=1,079). All authors did not have access to information that could identify individual participants (*Figure 1*).

Statistical analysis

The enrolled patients were divided into two groups, radiotherapy group and non-radiotherapy group, and were longitudinally classified by age, sex, insurance, histological type, differentiation, metastatic sites (the bone, brain, liver and lung), chemotherapy code. Absolute numbers and incidence proportions were calculated.

All statistical analyses were performed using the SPSS statistical software (version 22.0; IBM Corporation). Propensity score matching model was performed to reduce the bias of patients' selection and obtain the balanced population of radiotherapy and non-radiotherapy group. The standardized differences for matched variables were

less than 0.1. Chi-square test was used to identify the differences of two groups. Kaplan-Meier method was used to obtain survival information. Log-rank test and Cox regression analyses were implemented to evaluate covariates for OS and esophageal cause-specific survival (CSS). A value of P<0.05 were considered statistically significant for all analyses.

Results

A total of 4,761 patients were finally enrolled in this study, including 1,901 with radiotherapy and 2,870 without. The baseline features of the 4,761 eligible patients are provided in *Table 1*. The majority of the patients were 60 to 79 years old (55.1%), male (84.1%), insured (92.3%), white (84.9%), adenocarcinoma (64.5%), poorly differentiated (47.9%). As for metastatic sites (to the brain, bone, lung, and liver), 3178 (66.8%) of patients had 1 or 2 metastatic sites, 202 patients (4.2%) had 3 or 4 sites. There were 993 (20.9%) patients who had no metastasis in any site of the liver, brain, bone and lung.

The median OS (mOS) and CSS (mCSS) for the entire cohort were 4.9 and 5.0 months, and the radiotherapy group was 7.0 and 6.9 months, while 3.0 and 4.0 months in the non-radiotherapy group, respectively (P<0.001) (*Figure 2A,B*). Univariate and multivariable Cox regression demonstrated that radiotherapy was significantly associated with longer mOS and mCSS (*Tables 2,3*). In

Table 1 Clinical and pathological characteristics of enrolled metastatic esophageal cancer patients

Characteristics	Before propensity score matching, n (%)				After propensity score matching, n (%)			
	All patients (n=4,761)	Radiotherapy		P	All patients (n=3,672)	Radiotherapy		P
		Yes (n=1,901)	No (n=2,860)			Yes (n=1,836)	No (n=1,836)	
Age, year				<0.001				0.229
20–39	70 (1.5)	19 (1.0)	51 (1.8)		50 (1.4)	18 (1.0)	32 (1.7)	
40–59	1,559 (32.7)	670 (35.2)	889 (31.1)		1,257 (34.2)	636 (34.6)	621 (33.8)	
60–79	2,622 (55.1)	1,051 (55.3)	1,571 (54.9)		2,037 (55.5)	1,022 (55.7)	1,015 (55.3)	
≥80	510 (10.7)	161 (8.5)	349 (12.2)		328 (8.9)	160 (8.7)	168 (9.2)	
Sex				0.868				0.383
Male	4,002 (84.1)	1,600 (84.2)	2,402 (84.0)		3,113 (84.8)	1,547 (84.3)	1,566 (85.3)	
Female	759 (15.9)	301 (15.8)	458 (16.0)		559 (15.2)	189 (15.7)	270 (14.7)	
Insurance code				0.003				0.093
Insured	4,396 (92.3)	1,783 (93.8)	2,613 (91.4)		3,421 (93.2)	1,723 (93.8)	1,698 (92.5)	
Uninsured	235 (4.9)	82 (4.3)	153 (5.3)		160 (4.4)	77 (4.2)	83 (4.5)	
Unknown	130 (2.7)	36 (1.9)	94 (3.3)		91 (2.5)	36 (2.0)	55 (3.0)	
Race				<0.001				0.868
White	4,043 (84.9)	1,563 (82.2)	2,480 (86.7)		3,089 (84.1)	1,543 (84.0)	1,546 (84.2)	
Black	465 (9.8)	212 (11.2)	253 (8.8)		363 (9.9)	180 (9.8)	183 (10.0)	
Other	237 (5.0)	120 (6.3)	117 (4.1)		207 (5.6)	107 (5.8)	100 (5.4)	
Unknown	16 (0.3)	6 (0.3)	10 (0.3)		13 (0.4)	6 (0.3)	7 (0.4)	
Histological type				<0.001				0.002
SCC	1,118 (23.5)	547 (28.8)	571 (20.0)		913 (24.9)	492 (26.8)	421 (22.9)	
ADC	3,072 (64.5)	1,174 (61.8)	1,898 (66.4)		2,370 (64.5)	1,164 (63.4)	1,206 (65.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Before propensity score matching, n (%)				After propensity score matching, n (%)			
	All patients (n=4,761)	Radiotherapy		P	All patients (n=3,672)	Radiotherapy		P
		Yes (n=1,901)	No (n=2,860)			Yes (n=1,836)	No (n=1,836)	
Other	330 (6.9)	134 (7.0)	196 (6.9)		243 (6.6)	134 (7.3)	109 (5.9)	
Unknown	241 (5.1)	46 (2.4)	195 (6.8)		146 (4.0)	46 (2.5)	100 (5.4)	
Differentiation				<0.001				0.147
Poorly differentiated	2,282 (47.9)	929 (48.9)	1,353 (47.3)		1,801 (49.0)	901 (49.1)	900 (49.0)	
Moderately differentiated	1,261 (26.5)	542 (28.5)	719 (25.1)		961 (26.2)	518 (28.2)	443 (24.1)	
Well differentiated	102 (2.1)	48 (2.5)	54 (1.9)		84 (2.3)	46 (2.5)	38 (2.1)	
Undifferentiated	72 (1.5)	32 (1.7)	40 (1.4)		53 (1.4)	32 (1.7)	21 (1.1)	
Unknown	944 (19.8)	350 (18.4)	694 (24.3)		773 (21.1)	339 (18.5)	434 (23.6)	
Bone metastasis				<0.001				<0.001
Yes	1,123 (23.6)	564 (29.7)	559 (19.5)		884 (24.1)	550 (30.0)	334 (18.2)	
No	3,437 (72.2)	1,278 (67.2)	2,159 (75.5)		2,659 (72.4)	1,227 (66.8)	1,432 (78.0)	
Unknown	201 (4.2)	59 (3.1)	142 (5.0)		129 (3.5)	59 (3.2)	70 (3.8)	
Brain metastasis				<0.001				<0.001
Yes	256 (5.4)	181 (9.5)	75 (2.6)		226 (6.2)	181 (9.9)	45 (2.5)	
No	4,269 (89.7)	1,652 (86.9)	2,617 (91.5)		3,291 (89.6)	1,587 (86.4)	1,704 (92.8)	
Unknown	236 (5.0)	68 (3.6)	168 (5.9)		155 (4.2)	68 (3.7)	87 (4.7)	
Liver metastasis				<0.001				<0.001
Yes	2,270 (47.7)	675 (35.5)	1,595 (55.8)		1,652 (45.0)	666 (36.3)	986 (53.7)	
No	2,321 (48.8)	1,170 (61.5)	1,151 (40.2)		1,906 (51.9)	1,115 (60.7)	791 (43.1)	
Unknown	170 (3.6)	56 (3.0)	114 (4.0)		114 (3.1)	55 (3.0)	59 (3.2)	
Lung metastasis				0.001				0.291
Yes	1,375 (28.9)	526 (27.7)	849 (29.7)		1,037 (28.2)	510 (27.8)	527 (28.7)	
No	3,132 (65.8)	1,297 (68.2)	1,835 (64.2)		2,470 (67.3)	1,249 (68.0)	1,221 (66.5)	
Unknown	254 (5.3)	78 (4.1)	176 (6.2)		165 (4.5)	77 (4.2)	88 (4.8)	
Metastatic sites to the brain, bone, lung, and liver				<0.001				0.084
0	993 (20.9)	487 (25.6)	506 (17.7)		828 (22.5)	456 (24.8)	372 (20.3)	
1–2	3,178 (66.8)	1,196 (62.9)	1,982 (69.3)		2,449 (66.7)	1,163 (63.3)	1,286 (70.0)	
3–4	202 (4.2)	104 (5.5)	98 (3.4)		142 (3.9)	104 (5.7)	38 (2.1)	
Unknown	388 (8.1)	114 (6.0)	274 (9.6)		253 (6.9)	113 (6.2)	140 (7.6)	
Chemotherapy				<0.001				<0.001
Yes	2,880 (60.5)	1,403 (73.8)	1,477 (51.6)		2,494 (67.9)	1,338 (72.9)	1,156 (63.0)	
No/unknown	1,881 (39.5)	498 (26.2)	1,383 (48.4)		1,178 (32.1)	498 (27.1)	680 (37.0)	

SCC, squamous carcinoma; ADC, adenocarcinoma.

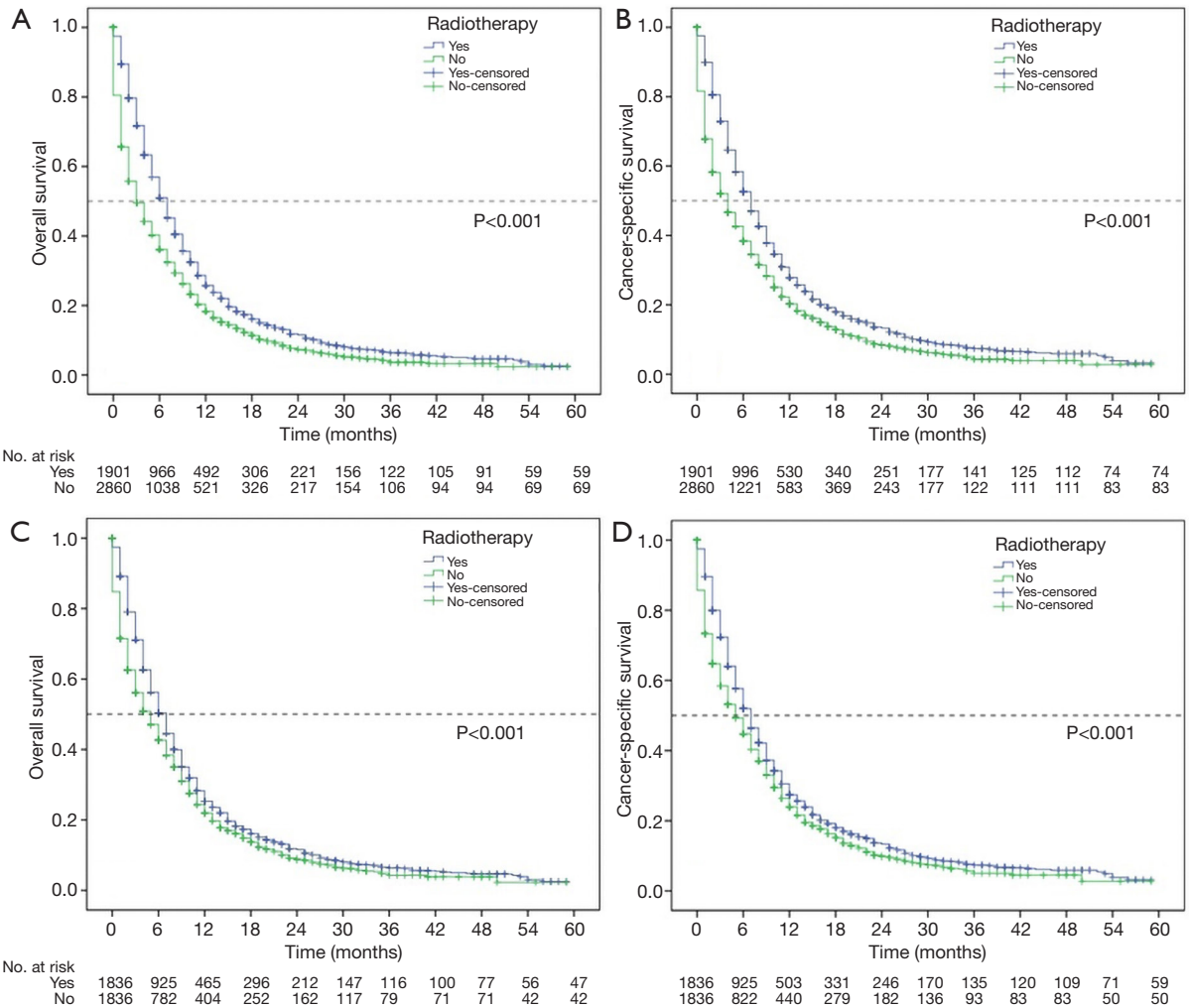

Figure 2 OS and CSS curves for the effect of radiotherapy. (A,B) Before propensity score matching; (C,D) after propensity score matching. OS, overall survival; CSS, cancer-specific survival.

addition, metastatic disease to 1–2 sites (P<0.001) or 3–4 metastatic sites (P<0.001) of the brain, bone, lung and liver, or greater than 80 years (P=0.002), uninsured status (P<0.001), and non-chemotherapy treatment (P<0.001) were significantly associated with poorer OS, while age 20 to 39 years (P=0.002), 40 to 59 years (P=0.002), 60 to 79 years (P=0.003), female (P<0.001), ADC (P=0.035), moderately differentiated (P<0.001) and well differentiated tumor (P=0.040) were significantly associated with better OS. Moreover, metastatic disease to 1–2 sites (P<0.001) or 3–4 sites (P<0.001), greater than 80 years old (P=0.016), uninsured status (P<0.001), non-chemotherapy treatment (P<0.001) were significantly associated with decreased CSS. Factors that were statistically associated with longer CSS in multivariable Cox regression analysis were female (P<0.001) and moderately differentiated tumor (P<0.001).

After propensity score matching, 3,672 of 4,761 patients were included (1,836 for each of radiotherapy or non-radiotherapy group) (*Table 1*) and also found that radiotherapy improved OS and CSS (P<0.001) (*Figure 2C,D*). Radiotherapy showed significant 2-year survival benefits in patients with age older than 80 years (2-year OS, P=0.048; CSS, P=0.018), male (2-year OS, P=0.020; CSS, P=0.011), white race (2-year OS, P=0.038; CSS, P=0.006), squamous carcinoma (2-year OS, P=0.002; CSS, P<0.001), poor differentiation (2-year OS, P=0.002; CSS, P<0.001), brain (2-year OS, P<0.001; CSS, P<0.001) metastasis, other sites (sites except for the brain, bone,

Table 2 Univariate Cox regression analysis for OS and CSS

Characteristics	Before propensity score matching						After propensity score matching					
	OS			CSS			OS			CSS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age, y												
≥80	1.000			1.000			1.000			1.000		
60–79	0.665	0.601–0.735	<0.001	0.688	0.620–0.765	<0.001	0.714	0.629–0.809	0.001	0.753	0.660–0.860	<0.001
40–59	0.604	0.543–0.673	<0.001	0.628	0.562–0.703	<0.001	0.644	0.564–0.735	<0.001	0.686	0.597–0.788	<0.001
20–39	0.496	0.371–0.663	<0.001	0.531	0.396–0.712	<0.001	0.570	0.405–0.803	<0.001	0.617	0.435–0.875	<0.001
Sex												
Male	1.000			1.000			1.000			1.000		
Female	0.915	0.839–0.997	0.043	0.990	0.823–0.984	0.021	0.882	0.797–0.977	0.016	0.867	0.780–0.963	0.008
Insurance code												
Insured	1.000			1.000			1.000			1.000		
Uninsured	1.376	1.198–1.581	<0.001	1.386	1.202–1.598	<0.001	1.446	1.224–1.708	<0.001	1.444	1.217–1.714	<0.001
Unknown	1.175	0.975–1.418	0.091	1.132	0.931–1.378	0.214	1.173	0.937–1.469	0.165	1.160	0.919–1.464	0.211
Race												
White	1.000			1.000			1.000			1.000		
Black	1.127	1.017–1.248	0.023	1.142	1.028–1.268	0.013	1.143	1.017–1.284	0.025	1.151	1.021–1.297	0.021
Other	0.869	0.752–1.004	0.056	0.842	0.724–0.979	0.025	0.917	0.785–1.071	0.273	0.900	0.767–1.057	0.200
Unknown	0.994	0.577–1.714	0.984	0.970	0.550–1.709	0.915	0.940	0.505–1.749	0.844	0.892	0.464–1.717	0.733
Histological type												
SCC	1.000			1.000			1.000			1.000		
ADC	0.881	0.818–0.949	0.001	0.880	0.815–0.950	0.001	0.865	0.787–0.929	<0.001	0.853	0.783–0.929	<0.001
Other	1.059	0.928–1.209	0.396	1.070	0.934–1.225	0.330	1.081	0.927–1.261	0.318	1.083	0.926–1.268	0.318
Unknown	1.576	1.364–1.821	<0.001	1.511	1.299–1.757	<0.001	1.512	1.264–1.810	<0.001	1.459	1.210–1.759	<0.001
Differentiation												
Poor	1.000			1.000			1.000			1.000		
Moderate	0.792	0.734–0.855	<0.001	0.798	0.738–0.862	<0.001	0.741	0.679–0.808	<0.001	0.753	0.689–0.823	<0.001
Well	0.802	0.647–0.995	0.045	0.810	0.650–1.009	0.061	0.802	0.632–1.018	0.069	0.816	0.639–1.040	0.101
Undifferentiated	1.030	0.800–1.326	0.820	1.054	0.815–1.364	0.686	1.010	0.753–1.354	0.947	1.048	0.779–1.410	0.759
Unknown	0.964	0.891–1.044	0.373	0.958	0.882–1.040	0.303	0.880	0.802–0.966	0.007	0.877	0.796–0.965	0.007
Bone metastasis												
No	1.000			1.000			1.000			1.000		
Yes	1.391	1.293–1.495	<0.001	1.399	1.29801.507	<0.001	1.436	1.332–1.560	<0.001	1.143	1.326–1.571	<0.001
Unknown	1.108	0.950–1.292	0.191	1.069	0.911–1.255	0.413	1.045	0.861–1.267	0.658	1.033	0.846–1.262	0.748

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Before propensity score matching						After propensity score matching					
	OS			CSS			OS			CSS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Brain metastasis												
No	1.000			1.000			1.000			1.000		
Yes	1.255	1.097–1.435	0.001	1.255	1.093–1.441	0.001	1.282	1.109–1.482	0.001	1.287	1.109–1.493	0.001
Unknown	1.060	0.920–1.221	0.421	1.024	0.883–1.188	0.751	0.987	0.827–1.178	0.888	0.978	0.815–1.174	0.813
Liver metastasis												
No	1.000			1.000			1.000			1.000		
Yes	1.246	1.170–1.327	<0.001	1.265	1.185–1.350	<0.001	1.264	1.176–1.359	<0.001	1.282	1.190–1.381	<0.001
Unknown	1.109	0.938–1.313	0.226	1.058	0.886–1.264	0.530	0.988	0.803–1.215	0.907	0.939	0.754–1.168	0.570
Lung metastasis												
No	1.000			1.000			1.000			1.000		
Yes	1.279	1.194–1.370	<0.001	1.274	1.187–1.368	<0.001	1.295	1.196–1.402	<0.001	1.294	1.193–1.404	<0.001
Unknown	1.090	0.948–1.253	0.228	1.086	0.941–1.253	0.261	0.985	0.827–1.173	0.865	0.994	0.831–1.189	0.951
Metastatic sites to the brain, bone, lung, and liver												
0	1.000			1.000			1.000			1.000		
1–2	1.458	1.346–1.579	<0.001	1.473	1.357–1.600	<0.001	1.499	1.371–1.639	<0.001	1,157	1.384–1.664	<0.001
3–4	2.268	1.932–2.664	<0.001	2.290	1.941–2.701	<0.001	2.253	1.945–2.847	<0.001	2.377	1.954–2.892	<0.001
Unknown	1.556	1.378–1.780	<0.001	1.563	1.370–1.784	<0.001	1.435	1.229–1.676	<0.001	1.452	1.238–1.704	<0.001
Radiotherapy												
Yes	1.000			1.000						1.000		
No	1.407	1.320–1.499	<0.001	1.405	1.316–1.500	<0.001	1.231	1.146–1.322	<0.001	1.293	1.146–1.327	<0.001
Chemotherapy												
Yes	1.000			1.000			1.000			1.000		
No/unknown	3.367	3.153–3.596	<0.001	3.341	3.123–3.575	<0.001	3.331	3.083–3.600	<0.001	3.314	3.060–3.590	<0.001

OS, overall survival; CSS, cancer-specific survival.

Table 3 Multivariate Cox regression analysis for OS and CSS

Characteristics	Before propensity score matching						After propensity score matching					
	OS			CSS			OS			CSS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age, y												
≥80	1.000			1.000			1.000			1.000		
60–79	0.853	0.769–0.947	0.003	0.875	0.785–0.975	0.016	0.867	0.762–0.986	0.030	0.915	0.799–1.048	0.198
40–59	0.837	0.749–0.937	0.002	0.859	0.765–0.966	0.011	0.835	0.727–0.958	0.010	0.889	0.769–1.027	0.111
20–39	0.623	0.465–0.835	0.002	0.661	0.491–0.890	0.006	0.653	0.462–0.923	0.016	0.915	0.799–1.048	0.198

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Before propensity score matching						After propensity score matching					
	OS			CSS			OS			CSS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sex												
Male	1.000			1.000			1.000			1.000		
Female	0.854	0.782–0.934	<0.001	0.840	0.766–0.920	<0.001	0.828	0.746–0.920	<0.001	0.815	0.731–0.908	<0.001
Insurance code												
Insured	1.000			1.000			1.000			1.000		
Uninsured	1.343	1.166–1.547	<0.001	1.332	1.151–1.540	<0.001	1.404	1.184–1.663	<0.001	1.387	1.165–1.652	<0.001
Unknown	0.881	0.727–1.068	0.197	0.854	0.698–1.045	0.126	0.958	0.758–1.210	0.718	0.953	0.749–1.213	0.696
Race												
White	1.000			1.000						1.000		
Black	1.073	0.959–1.202	0.220	1.083	0.965–1.217	0.175	1.052	0.925–1.197	0.439	1.051	0.921–1.199	0.461
Other	0.894	0.771–1.036	0.137	0.865	0.741–1.009	0.064	0.897	0.765–1.051	0.177	0.879	0.746–1.036	0.124
Unknown	0.881	0.507–1.534	0.655	0.858	0.482–1.527	0.602	0.804	0.424–1.523	0.503	0.750	0.382–1.470	0.402
Histological type												
SCC	1.000			1.000			1.000			1.000		
ADC	0.920	0.852–0.994	0.035	0.925	0.848–1.009	0.078	0.933	0.848–1.026	0.151	0.924	0.838–1.018	0.110
Other	1.019	0.889–1.169	0.787	1.048	0.908–1.210	0.521	1.130	0.959–1.331	0.144	1.132	0.957–1.340	0.149
Unknown	1.258	1.081–1.464	0.003	1.221	1.038–1.435	0.016	1.330	1.101–1.607	0.003	1.285	1.055–1.564	0.013
Differentiation												
Poor	1.000			1.000			1.000			1.000		
Moderate	0.767	0.710–0.828	<0.001	0.772	0.713–0.835	<0.001	0.766	0.701–0.837	<0.001	0.778	0.711–0.853	<0.001
Well	0.798	0.643–0.990	0.040	0.804	0.645–1.003	0.053	0.785	0.618–0.997	0.047	0.795	0.622–1.105	0.065
Undifferentiated	0.855	0.660–1.109	0.238	0.888	0.681–1.158	0.380	0.809	0.594–1.102	0.179	0.845	0.618–1.155	0.290
Unknown	0.798	0.735–0.867	<0.001	0.800	0.735–0.871	<0.001	0.772	0.702–0.849	<0.001	0.771	0.699–0.851	<0.001
Metastatic sites to the brain, bone, lung, and liver												
0	1.000			1.000			1.000			1.000		
1–2	1.357	1.251–1.471	<0.001	1.363	1.253–1.482	<0.001	1.414	1.291–1.548	<0.001	1.427	1.300–1.567	<0.001
3–4	2.365	2.012–2.781	<0.001	2.379	2.014–2.810	<0.001	2.460	2.029–2.981	<0.001	2.477	2.032–3.019	<0.001
Unknown	1.290	1.132–1.471	<0.001	1.291	1.127–1.478	<0.001	1.153	0.982–1.353	0.082	1.162	0.986–1.370	0.074
Radiotherapy												
Yes	1.000			1.000			1.000			1.000		
No	1.229	1.151–1.313	<0.001	1.227	1.147–1.313	<0.001	1.218	1.132–1.310	<0.001	1.219	1.131–1.314	<0.001
Chemotherapy												
Yes	1.000			1.000			1.000			1.000		
No/unknown	3.211	2.995–3.442	<0.001	3.204	2.982–3.441	<0.001	3.195	2.944–3.467	<0.001	3.204	2.946–3.485	<0.001

OS, overall survival; CSS, cancer-specific survival.

lung, and liver, 2-year OS, P<0.001; CSS, P<0.001), however, there were no statistically significant survival differences in patients with bone and liver metastasis, 1–2 or 3–4 metastatic sites (*Table 4*). Interestingly, no survival difference was found between chemotherapy alone and radiotherapy combined with chemotherapy (2-year OS, P=0.177; CSS, P=0.080). Cox regression demonstrated that radiotherapy was an independent prognostic factor which was significantly associated with longer mOS and mCSS in matched patients (*Tables 2,3*). In addition, metastatic disease to 1–2 sites (P<0.001) or 3–4 metastatic sites (P<0.001) of the brain, bone, lung and liver, age greater than 80 years (P≤0.030), uninsured status (P<0.001), male (P<0.001), poor differentiation (P≤0.047), non-chemotherapy treatment (P<0.001) were associated with poorer OS. While metastatic disease to 1–2 sites (P <0.001) or 3–4 sites (P<0.001), uninsured status (P<0.001), male (P<0.001), poor differentiation (P<0.001), non-chemotherapy treatment (P<0.001) were significantly associated with decreased CSS.

Discussion

This is the first large population-based study evaluating the effect of radiotherapy in the management of metastatic EC based on the SEER database, revealing that radiotherapy was an independent prognostic factor associated with survival benefits of patients with metastatic EC. EC is one of the leading cause of cancer deaths worldwide with poor prognosis (3,10,11). In general, radiotherapy plays an important role in the treatment of local EC. A study reported a 5-year OS rate of 21% in 101 patients with locally EC receiving radiotherapy alone (12). Then chemoradiotherapy became the preferred treatment and had been shown to improve the quality of life and prolong survival for patients with local metastatic or unresectable EC. Systemic therapy is the standard treatment for metastatic disease, but symptoms caused by metastasis disease often require multidisciplinary management including radiotherapy. However, the value of radiotherapy in the treatment of

Table 4 Z test for the effects of radiotherapy on OS and CSS in matched patients

Characteristics	2-year OS				2-year CSS			
	RT (%)	Non-RT (%)	Z	P	RT (%)	Non-RT (%)	Z	P
RT	11.6	8.8	2.325	0.020	13.4	9.9	2.602	0.009
Age								
20–39	8.4	15.6	0.65	0.517	9.3	15.6	−0.54	1.410
40–59	12.3	10.6	0.83	0.407	13.6	11.9	0.75	0.452
60–79	11.5	8.4	1.90	0.057	13.2	9.3	2.29	0.022
≥80	9.1	2.9	1.98	0.048	13.8	4.2	2.37	0.018
Sex								
Male	10.9	8.1	2.33	0.020	12.5	9.1	2.53	0.011
Female	15.1	13.6	0.43	0.665	17.7	15.4	0.59	0.554
Insurance code								
Insured	11.7	9.2	2.08	0.038	13.4	10.3	2.30	0.021
Uninsured	8.2	0.0	2.28	0.023	10.2	0.0	2.43	0.015
Unknown	15.3	7.5	1.00	0.320	16.7	8.1	1.01	0.312
Race								
White	12.0	8.7	2.45	0.014	13.6	9.7	2.74	0.006
Black	7.0	8.9	0.60	0.551	8.8	9.4	0.17	0.865
Other	13.8	10.3	0.65	0.515	17.0	12.5	0.73	0.465
Unknown	20.0	0.0	1.12	0.264	40.0	0.0	1.826	0.068

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	2-year OS				2-year CSS			
	RT (%)	Non-RT (%)	Z	P	RT (%)	Non-RT (%)	Z	P
Histological type								
SCC	12.1	5.6	3.04	0.002	13.8	6.0	3.51	0.000
ADC	12.1	10.6	0.96	0.335	13.8	11.7	1.24	0.216
Other	7.1	6.0	0.28	0.782	9.4	7.2	0.48	0.633
Unknown	4.9	3.0	0.51	0.609	8.7	4.8	0.76	0.448
Differentiation								
Poor	12.1	5.6	3.04	0.002	10.8	7.1	3.51	0.000
Moderate	12.1	10.6	0.96	0.335	18.2	12.3	2.14	0.032
Well	7.1	6.0	0.28	0.782	16.4	8.2	1.03	0.301
Undifferentiated	4.9	3.0	0.51	0.609	0.0	15.1	1.61	0.108
Unknown	12.1	5.6	3.04	0.002	13.6	13.1	0.16	0.870
Bone metastasis								
Yes	4.2	4.6	0.26	0.798	5.1	5.5	0.20	0.841
No	14.6	9.7	0.87	0.384	16.5	10.8	3.48	0.001
Unknown	14.9	9.4	0.82	0.411	21.9	9.8	1.65	0.099
Brain metastasis								
Yes	8.1	0.0	3.52	0.000	10.7	0.0	3.82	0.000
No	11.6	9.0	2.16	0.031	13.2	10.1	2.30	0.021
Unknown	18.9	9.5	1.45	0.148	23.1	10.0	1.89	0.059
Liver metastasis								
Yes	7.0	8.7	1.04	0.296	8.4	9.7	0.71	0.481
No	13.7	8.6	3.01	0.003	15.3	9.6	3.10	0.002
Unknown	20.7	11.9	1.16	0.244	30.0	12.8	2.07	0.038
Lung metastasis								
Yes	8.3	7.0	0.66	0.511	9.7	8.3	2.27	0.023
No	12.4	9.4	2.02	0.044	14.1	10.4	1.78	0.076
Unknown	20.1	12.3	1.20	0.229	24.6	12.7	1.78	0.076
Metastatic sites to the brain, bone, lung, and liver								
0	19.5	9.0	3.80	0.000	21.2	9.9	3.80	0.000
1–2	8.6	9.1	0.37	0.710	10.1	10.3	0.81	0.420
3–4	2.6	0.0	1.44	0.149	3.8	0.0	1.52	0.129
Unknown	17.2	7.7	2.00	0.045	21.1	8.2	2.51	0.012
Chemotherapy								
Yes	14.8	12.6	1.35	0.177	16.8	13.7	1.75	0.080
No/unknown	2.8	2.2	0.55	0.579	3.5	2.7	0.59	0.556

OS, overall survival; CSS, cancer-specific survival.

metastatic EC has not yet been fully evaluated before. This present study can complement the treatment recommended in the current guidelines.

Although the research from Wu *et al*. (13) found that combining surgery with radiotherapy could improve survival in metastatic EC, it based on older populations, older methods of radiotherapy, and did not analyze the clinical benefits of chemotherapy combined with radiation therapy. A phase II study compared concurrent chemoradiation therapy (CCRT) with chemotherapy alone in stage IV esophageal squamous cell carcinoma, demonstrating that CCRT significantly prolonged median progression-free survival (mPFS, 9.3 *vs*. 4.7 months, P=0.021) and mOS (18.3 *vs*. 10.2 months, P=0.001) (14). This study challenged the status of standard treatment modality for metastatic EC treated with chemotherapy alone. The results showed that metastatic EC patients had good tolerance to concurrent chemoradiotherapy, and both OS and PFS were higher than chemotherapy alone. The possible mechanisms for radiotherapy to prolong the survival of metastatic disease may be improve local control rate under the premise of effective systemic therapy, produce certain cytokines that further inhibit the proliferation and metastasis of tumor cells. However, the phase II study was presented only in an abstract format, and the value of radiotherapy in the treatment of metastatic EC has not yet been fully evaluated. Thus, it was initially confirmed that the survival benefits of radiotherapy in metastatic EC based on this retrospective and propensity-matched study, which laid the foundation for the following clinical studies.

However, the addition of radiotherapy to chemotherapy showed no survival benefits, which was significantly inconsistent with the study mentioned above. The reason for the discrepancy between the two conclusions may be that the specific combination modalities of chemotherapy and radiotherapy such as concurrent or sequential therapy were unknown in this study which might influence survival, and that chemotherapy plays a leading role in the treatment of metastatic EC rather than radiotherapy.

The liver is the most common metastatic site of metastatic EC (47.7% of all enrolled patients), there are only few case reports that have reported the local treatment of hepatic metastasis with good clinical efficacy (15,16), while this study showed no survival benefits in matched patients with liver metastasis when radiotherapy was applied. As for patients with more than 3 metastatic sites, radiotherapy did not improve survival, indicating the limitations of local treatment for patients with multiple metastases.

The majority of studies found that the prognosis of patients with ADC is much better than the patients with SCC (17,18), however, these studies included all clinical stages of EC, but there was no significant prognostic difference between ADC and SCC in matched patients with advanced stage, and patients of both two types showed survival benefits from radiotherapy. Besides, the multivariable Cox regression analysis demonstrated that age, sex, insurance status, differentiation, chemotherapy were also important prognostic factors for metastatic EC.

There were few limitations in this study. Firstly, The SEER database does not provide information about the sites (both primary and metastatic sites) and dose of radiation therapy. Thus, there were no data of treatment response of radiotherapy, which might affect the results of analysis. Secondly, information relating to comorbidities and performance status was not available in the SEER database, which may influence the treatment approach, resulting in selective bias. Thirdly, the impact of chemotherapy regimens was unknown as no data was available in the SEER database. Last, the combination modalities of radiation and chemotherapy had not been shown in the SEER database, which is worthy of further investigations to maximize the survival benefits of radiotherapy in metastatic EC.

Conclusions

This large population-based study demonstrated that radiotherapy could improve the survival of patients with metastatic EC, which provides a line of evidence to guide the current treatment. Further randomized studies are warranted to assess the value of radiotherapy in the management of metastatic EC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.15). 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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were retrieved from SEER database. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University. Informed consent was waived.

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