Nomogram to predict overall survival for patients with non-metastatic cervical esophageal cancer: a SEER-based population study

Dezuo Dong[1#^], Dan Zhao[1#], Shuai Li[1], Weixin Liu[1], Feng Du[2], Xiaolong Xu[1], Shaowen Xiao[1], Baomin Zheng[1], Yan Sun[1], Weihu Wang[1]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, Beijing, China; [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), The VIP-II Gastrointestinal Cancer Division of Medical Department, Peking University Cancer Hospital and Institute, Beijing, China

Contributions: (I) Conception and design: W Wang, Y Sun; (II) Administrative support: W Wang; (III) Provision of study materials or patients: D Dong, D Zhao; (IV) Collection and assembly of data: D Dong; D Zhao; (V) Data analysis and interpretation: D Dong, D Zhao, S Li, W Liu, F Du, X Xu, S Xiao, B Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Weihu Wang; Yan Sun. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, No. 52 Fucheng Road, Haidian District, Beijing 100142, China. Email: wangweihu88@163.com; ysunemail@yahoo.com.

Background: Cervical esophageal cancer (CEC) is an uncommon malignancy with poor prognosis, and there is no specific model that can be used to accurately predict the survival of patients with CEC.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was searched for patients with non-metastatic CEC from 2004 to 2015. Overall survival (OS) and disease-specific survival (DSS) rates were calculated using the Kaplan-Meier method. Predictive factors were analyzed by Cox's proportional hazards regression, and a nomogram was created to predict survival probability using R software.

Results: We identified 601 patients with CEC, 94.3% of whom had squamous cell carcinoma (SCC). The median follow-up time was 71 months. The median OS and DSS for the overall population were 15 and 18 months, respectively. There was a statistically significant decrease in surgical rates over time, from 16.7% in 2004 to 8% in 2015 (P=0.035). Comprehensive strategies consisting of two or three treatment modalities were correlated with significantly better OS and DSS (P<0.001 for both). We randomly assigned half of the patients to the training cohort (n=300) and the other half to the validation cohort (n=301). Multivariate Cox regression analysis was performed using the training cohort. Age, sex, tumor size, stages in the 7th edition of the American Joint Committee on Cancer (AJCC) staging system, and treatment with surgery, radiotherapy, or chemotherapy were identified as independent risk factors for OS. These factors were incorporated into the development of a nomogram for predicting 1-, 3-, and 5-year OS rates. The C-index of the nomogram was 0.743, which was statistically higher than that of the AJCC staging system. The internal validation, using bootstrap resampling and external validation, demonstrated the accuracy of the nomogram.

Conclusions: We developed and validated the first nomogram for CEC. This nomogram could be used to predict the OS of CEC patients with a relatively high accuracy.

Keywords: Cervical esophageal cancer (CEC); nomogram; surgery; comprehensive treatment; prognosis

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^ ORCID: 0000-0001-6008-7193.

Introduction

Cervical esophageal cancer (CEC) is a relatively uncommon malignancy, accounting for approximately 5% of all esophageal cancers (1). Squamous cell carcinoma (SCC) is a major histologic type of CEC, accounting for approximately 95% of CEC cases. The 5-year overall survival (OS) of patients with CEC is lower than that of patients with other SCCs of the head and neck region (2), and is more comparable to the 5-year OS of patients with SCC located in other regions of the esophagus, which is approximately 26% (3). However, CEC differs from cancers of the thoracic esophagus in other aspects, such as genetic alterations, prognostic factors, and cancer management (4,5). Therefore, CEC is a unique disease that has specific characteristics.

Nomograms have been widely used for predicting prognoses in a diverse range of cancers with success. Compared to the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system, nomograms quantify risk by incorporating all clinicopathological variables, allowing for individualized prognostic predictions for various types of cancer (6-11). However, to the best of our knowledge, no specific nomogram has yet been developed for CEC. The present study is the first to develop a prognostic nomogram for CEC based on a large cohort of patients from the Surveillance, Epidemiology, and End Results (SEER) database. The present study was performed in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2505).

Methods

To identify the population of interest, we collected data from the recent SEER 18 database. Patients with non-metastatic CEC (C150) from 2004 to 2015 were chosen. The following histological subtypes were included: (I) adenocarcinoma (8,050 to 8,052, 8,123, 8,140 to 8,147, 8,210 to 8,211, 8,255, 8,260 to 8,263, 8,310, 8,480 to 8,481, 8,490, 8,550, and 8,570 to 8,575), and (II) SCC (8,032, 8,070 to 8,077, 8,083, and 8,094). Information on patient characteristics (age, sex, race, and year of diagnosis), primary tumor features (histology, grade, T stage, N stage, and tumor size), treatment approaches (surgery, radiation, and chemotherapy), and clinical outcomes (cancer-specific survival and OS) were collected.

Continuous variables were summarized as medium (range), and categorical variables were summarized as number (percentage). Survival was evaluated using the Kaplan-Meier method and the log-rank test. Univariate and multivariate analyses of clinicopathological factors were performed using Cox proportional hazards model to identify risk factors for OS and disease-specific survival (DSS). For statistical testing, we used a two-sided significance level (alpha) of 0.05. We selected the optimum cutoff score for the tumor size using X-tile plots (version 3.6.1; Yale University School of Medicine, New Haven, CT, USA).

For the development of the nomogram, we randomly assigned half of the patients into a training cohort (n=300) and the other half into a validation cohort (n=301). A nomogram was created based on the results of the multivariable analysis. Predictive performance was assessed based on the C-index and external calibration plots with samples in the validation cohort. We compared the nomogram with the TNM stage system using the rcorr.cens function in the R package Hmisc. All statistical analyses were performed using IBM SPSS software (version 23.0; IBM, Armonk, NY, USA) and R software (version 3.1.1; http://www.r-project.org). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Patient characteristics and treatment

The patient selection process is shown in *Figure 1*. A total of 601 patients were included in the present study. The demographic and clinicopathological characteristics of the study cohort are provided in *Table 1*. The median age at diagnosis was 68 years, and 59.4% of the patients were male. SCC was the predominant histological type; 567 (94.3%) patients were diagnosed with SCC, whereas 34 (5.7%) patients had adenocarcinoma (AC). Of the 498 patients with documented tumor size, the median size was 40 mm. The majority of patients presented with locally advanced primary cancer, with 62.1% having a primary tumor classification of T3 or T4. Most of the patients (58.6%) had no nodal involvement.

A total of 83 patients (13.8%) underwent surgery, and 453 patients (75.4%) were treated with radiotherapy (RT). Patients were evaluated to determine whether treatment decisions were related to demographic or clinicopathological factors. We found that patients were more likely to undergo surgery if they were diagnosed before 2009, had AC, had relatively small primary tumors, presented with early-stage

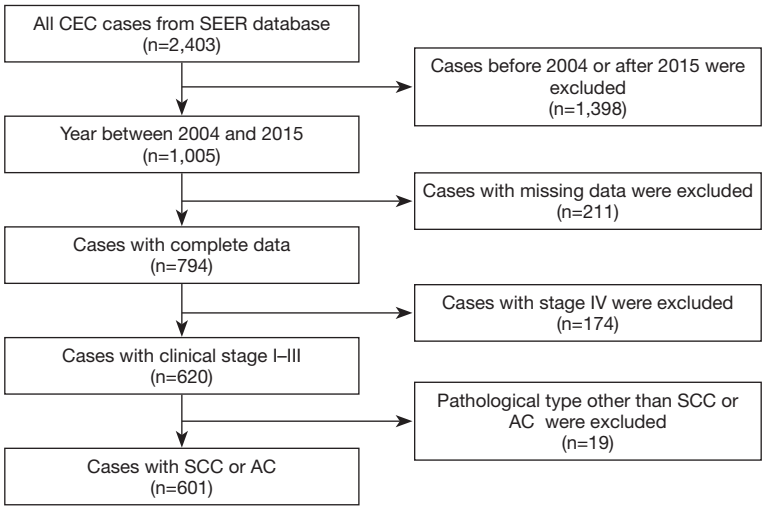

Figure 1 Flow diagram of the patient selection process for the study.

disease, or had no nodal involvement (*Table 2*). We observed a statistically significant decrease in the incidence of surgery between 2004 and 2015, from 16.7% in 2004 to 8% in 2015 (P=0.035) (*Figure 2*).

Survival analysis

The median follow-up time was 71 months. The median OS and DSS for the overall population were 15 and 18 months, respectively. Most of the patients (64.4%) underwent comprehensive treatment consisting of surgery, RT, or chemotherapy. There was a significant improvement in OS and DSS among patients who underwent comprehensive treatment (*Figure 3A*,*B*). In a subgroup of patients with SCC, trimodal therapy consisting of surgery and chemoradiotherapy showed the best DSS, although there was no improvement in OS over dual therapy (*Figure 3C*,*D*). Patients who underwent surgery usually had earlier-stage disease and smaller tumor size (*Table 3*); however, there was no significant difference in OS or DSS between those who underwent surgery only and those who underwent surgery and chemoradiotherapy (*Figure 3E*,*F*).

Prognostic factors for OS and DSS in the overall cohort

Univariate analysis demonstrated that older age (P=0.002), male sex (P=0.006), SCC (*vs.* AC) (P=0.008), larger tumor size (P<0.046), higher T (7th) stage (P<0.001), higher AJCC (7th) stage (P<0.001) and the absence of RT (P=0.025), chemotherapy (P<0.001), or surgery (P=0.010) were all associated with decreased OS (*Table 4*).

Multivariate regression analysis revealed that older age (P=0.015), male sex (P=0.038), larger tumor size (P=0.010), higher AJCC (7th) stage (P=0.017), and the absence of RT (P=0.030), chemotherapy (P<0.001), or surgery (P<0.001) were independent risk factors for decreased OS (*Table 4*).

Nomogram for predicting locoregional recurrence and validation

To predict the survival risk for patients with CEC, a nomogram was established by multivariate Cox regression analysis, incorporating all independent factors that were significant for OS (*Figure 4*). The C-index for the prediction of OS was 0.743, which was significantly higher (P<0.001) than either the 7th edition of the AJCC staging system (C-index =0.559) or the 6th edition of the AJCC staging system (C-index =0.532). Calibration curves demonstrated good agreement between prediction and observation in the probability of 3- and 5-year OS (*Figure 5*). In the external validation cohort, the C-index of the nomogram was 0.706, indicating that the nomogram demonstrates reasonably good discrimination in prognostic prediction.

Discussion

In the present study, we collected data from the SEER database to evaluate prognostic factors for non-metastatic CEC, and then used these risk factors to construct a nomogram to predict the OS of patients with CEC. We

Table 1 Demographics and clinicopathological characteristics of patients with non-metastatic cervical esophageal carcinoma

Characteristics	Training set (n=300), n (%)	Validation set (n=301), n (%)	Total (n=601), n (%)
Age (years), median (range)	67 (25 to 98)	69 (42 to 99)	68 (25 to 99)
<65	131 (43.7)	115 (38.2)	246 (40.9)
≥65	169 (56.3)	186 (61.8)	355 (59.1)
Sex			
Male	178 (59.3)	179 (59.5)	357 (59.4)
Female	122 (40.7)	122 (40.5)	244 (40.6)
Race/region			
White	227 (75.9)	242 (80.4)	469 (78.2)
Black	53 (17.7)	36 (12.0)	89 (14.8)
Other	19 (6.3)	23 (7.6)	42 (7.0)
Year of diagnosis			
2004 to 2009	147 (49.0)	145 (48.2)	293 (48.8)
2010 to 2015	153 (51.0)	156 (51.8)	308 (51.2)
Histology			
Squamous	285 (95.0)	282 (93.7)	567 (94.3)
Adenocarcinoma	15 (5.0)	19 (6.3)	34 (5.7)
Tumor size (mm)			
<55	149 (76.4)	159 (74.6)	308 (75.5)
≥55	46 (23.6)	54 (25.4)	100 (24.5)
Differentiation			
Well	15 (6.5)	12 (5.3)	27 (5.9)
Moderate	136 (58.9)	142 (62.8)	278 (60.8)
Poor	78 (33.8)	72 (31.9)	150 (32.8)
Undifferentiated	2 (0.9)	0 (0.0)	2 (0.4)
T^{6th} stage†			
T1	89 (29.7)	91 (30.2)	180 (30.0)
T2	27 (9.0)	21 (7.0)	48 (8.0)
T3	86 (28.7)	87 (28.9)	173 (28.8)
T4	98 (32.7)	102 (33.9)	200 (33.3)
N^{6th} stage†			
N0	169 (57.3)	178 (59.9)	347 (58.6)
N1	126 (42.7)	119 (40.1)	245 (41.4)
$AJCC^{6th}$ stage†			
I	68 (22.7)	70 (23.3)	138 (23.0)
IIa	59 (19.7)	64 (21.3)	123 (20.5)
IIb	31 (10.3)	25 (8.3)	56 (9.3)
III	142 (47.3)	142 (47.2)	284 (47.3)
T^{7th} stage‡			
T1a	14 (4.7)	12 (4.0)	26 (4.3)
T1b	12 (4.0)	11 (3.7)	23 (3.8)
T1-NOS	63 (21.0)	68 (22.6)	131 (21.8)
T2	27 (9.0)	21 (7.0)	48 (8.0)
T3	86 (28.7)	87 (28.9)	173 (28.8)
T4a	22 (7.3)	20 (6.6)	42 (7.0)
T4b	23 (7.7)	19 (6.3)	42 (7.0)
T4-NOS	53 (17.7)	63 (20.9)	116 (19.3)
N^{7th} stage‡			
N0	169 (67.6)	179 (70.8)	348 (69.2)
N1	64 (25.6)	62 (24.5)	126 (25.0)
N2	13 (5.2)	8 (3.2)	21 (4.2)
N3	4 (1.6)	4 (1.6)	8 (1.6)
$AJCC^{7th}$ stage‡			
Ia	20 (8.8)	24 (10.8)	44 (9.8)
Ib	48 (21.2)	47 (21.2)	95 (21.2)
IIa	18 (8.0)	15 (6.8)	33 (7.4)
IIb	64 (28.3)	61 (27.5)	125 (27.9)
IIIa	30 (13.3)	34 (15.3)	64 (14.3)
IIIb	4 (1.8)	5 (2.3)	9 (2.0)
IIIc	42 (18.6)	36 (16.2)	78 (17.4)
Surgery			
Yes	37 (12.3)	46 (15.3)	83 (13.8)
No	263 (87.7)	255 (84.7)	518 (86.2)
Radiation			
Yes	225 (75.0)	226 (75.1)	453 (75.4)
No	75 (25.0)	75 (24.9)	148 (24.6)
Chemotherapy			
Yes	199 (66.3)	205 (68.1)	404 (67.2)
No	101 (33.7)	96 (31.9)	197 (32.8)

†, from the AJCC 6th edition staging system; ‡, from the AJCC 7th edition staging system. AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

Table 2 Correlation between demographic or clinicopathologic factors and treatment decisions

Factors	Surgery (n)	Non-surgery (n)	P value	Chemotherapy (n)	Non-chemotherapy (n)	P value	Radiotherapy (n)	Non-radiotherapy (n)	P value
Age (year)			0.151			<0.001			0.035
<65	206	40		52	194		50	196	
≥65	312	43		145	210		100	255	
Sex			0.719			0.860			0.702
Male	212	32		81	163		63	181	
Female	306	51		116	241		150	451	
Race/region			0.036			0.930			0.680
White	397	72		153	316		120	349	
Black	83	6		31	58		21	68	
Other	37	5		13	29		9	33	
Year of diagnosis			0.045			0.082			0.573
2004–2009	243	49		106	186		76	216	
2010–2015	275	34		91	218		74	235	
Histology			0.017			1.000			0.157
Squamous	494	73		186	381		138	429	
Adenocarcinoma	24	10		11	23		12	22	
Tumor size (mm)			0.014			0.542			0.894
<55	248	60		103	205		77	231	
≥55	91	9		30	70		24	76	
Differentiation			0.657			0.742			0.828
Well	21	6		10	17		6	21	
Moderate	233	45		89	189		74	204	
Poor	129	21		48	102		38	112	
Undifferentiated	2	0		0	2		1	1	
T^{6th} stage†			0.591			0.001			<0.001
T1	159	21		78	102		61	119	
T2	39	9		11	37		8	40	
T3	147	26		42	131		27	146	
T4	173	27		66	134		54	146	
N^{6th} stage†			0.001			<0.001			<0.001
N0	285	62		139	208		106	241	
N1	224	21		55	190		42	203	
$AJCC^{6th}$ stage†			0.024			<0.001			0.025
I	119	19		66	72		48	90	
IIa	97	26		40	83		28	95	
IIb	53	3		14	42		13	43	
III	249	35		77	207		61	223	

Table 2 *(continued)*

Table 2 *(continued)*

Factors	Surgery (n)	Non-surgery (n)	P value	Chemotherapy (n)	Non-chemotherapy (n)	P value	Radiotherapy (n)	Non-radiotherapy (n)	P value
T^{7th} stage‡			0.009			0.001			<0.001
T1a	19	7		12	14		12	14	
T1b	14	9		15	8		14	9	
T2	39	9		11	37		8	40	
T3	147	26		42	131		27	146	
T4a	36	6		15	27		8	34	
T4b	40	2		13	29		14	28	
N^{7th} stage‡			0.045			<0.001			0.005
N0	284	64		139	209		105	243	
N1	114	12		24	102		20	106	
N2	18	3		6	15		2	19	
N3	5	3		4	4		2	6	
AJCC^{7th} stage‡			0.011			<0.001			<0.001
Ia	34	10		24	20		20	24	
Ib	86	9		42	53		27	68	
IIa	31	2		11	22		3	30	
IIb	96	29		36	89		33	92	
IIIa	58	6		10	54		6	58	
IIIb	7	2		2	7		1	8	
IIIc	70	8		26	52		20	58	

†, from the AJCC 6th edition staging system; ‡, from the AJCC 7th edition staging system. AJCC, American Joint Committee on Cancer.

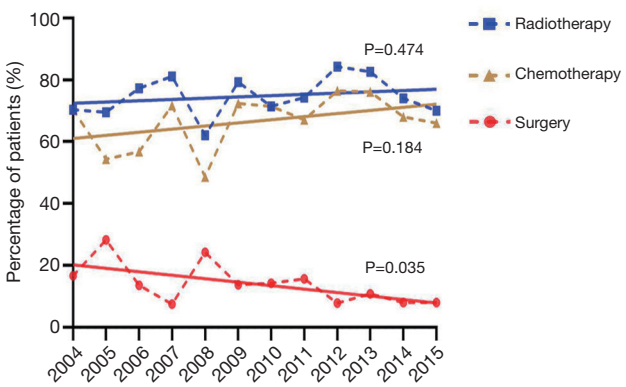

Figure 2 Rates of use of surgery, radiotherapy, and chemotherapy between the years 2004 and 2015 in non-metastatic CEC. P values represent the comparison of the linear regression line and a line with slope equal to 0 for each treatment modality.

included age, sex, tumor size, TNM staging, and treatment modalities when creating the nomogram. The nomogram had a relatively high accuracy which was supported by the C-index (0.743 for the training cohort and 0.706 for the validation cohort, respectively) and calibration plots.

The demographic and clinicopathological characteristics of this cohort resemble those of a previous study, which was also based on the SEER database (12). The median age of the whole group at diagnosis was 68 years, and the proportion of males to females was about 6:4. We set 65 years as the cutoff age because it presented the most significant difference in OS. Most of the cases were moderately differentiated, followed by cases with poor differentiation, whereas only 2 cases were documented as undifferentiated. We found no difference in survival among those who had well-, moderately, or poorly differentiated tumors, although both patients with undifferentiated tumors survived for only 2 months. The majority of patients

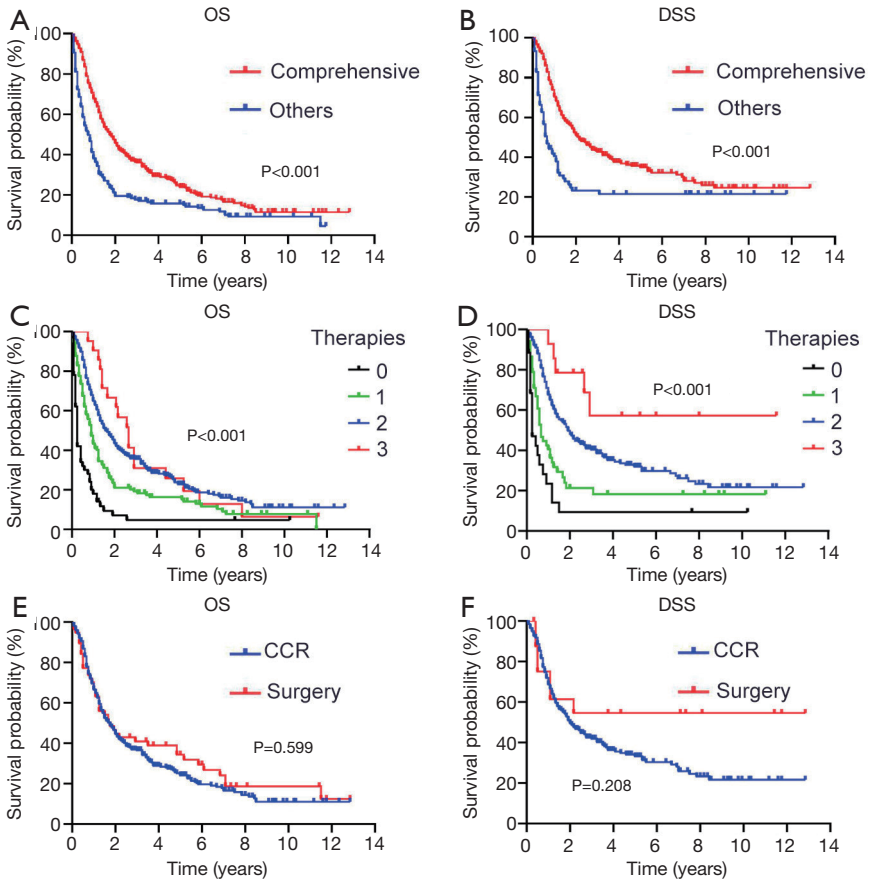

Figure 3 OS and DSS for patients with non-metastatic CEC. (A,B) OS and DSS among patients who underwent comprehensive treatment and those who did not. (C,D) OS and DSS among patients whose number of treatment modalities was different. (E,F) OS and DSS among patients who underwent surgery alone and those who underwent definitive chemoradiotherapy in the SCC subgroup.

were stage III (47.3%) and stage II (stage IIA: 20.5%, stage IIB: 9.3%) at diagnosis, which was consistent with reports from other studies (12-16).

SCC and AC represent two primary histological subtypes of thoracic esophageal cancer that are significantly different in clinicopathology and prognosis (17,18). In our cohort of patients with CEC, SCC was the predominant histological type, whereas AC accounted for only 5.7% of patients; these findings are consistent with previously reported data (2). The median OS and DSS for patients with AC were 44 and 84 months, respectively, compared to 15 and 17 months for those with SCC. The 5-year OS for patients with SCC and AC of the cervical esophagus were 19.8% and 46.1%, respectively (data not shown). These results confirmed that patients with AC had a better prognosis compared to those with SCC.

The tumor size of CEC may play a critical role in determining survival; however, the optimal cutoff value has not been established. Performance status and tumor length (≤6 or >6 cm) have previously been described as factors that are significantly related to survival (14). Other cutoff values of tumor length, such as 3 cm or 3.5 cm, have also been reported (19-21). In the present study, a total of 498 patients (82.9%) had documented tumor size. Using Cox regression analysis, we identified tumor size as an independent risk factor for survival. By using X-tile plot software, we set 5.5 cm as the cutoff value, which is close to previously reported values (14). In contrast to breast cancer, tumor size is not currently included in the TNM staging system for esophageal cancer (22,23). Based on our findings, we propose that it be considered for inclusion in future editions.

Historically, surgery has been the preferred treatment for CEC. However, we identified a decreased trend in the implementation of surgery; this may be due to the high risk

Table 3 Correlation between clinicopathologic factors and treatment decisions.

Factors	Surgery alone (n)	CCR† (n)	P value
Tumor size (mm)			0.024
<55	45	177	
≥55	5	60	
T^{7th} stage‡			<0.001
T1a	5	9	
T1b	9	7	
T2	5	31	
T3	21	121	
T4a	5	25	
T4b	1	24	
N^{7th} stage‡			0.007
N0	49	178	
N+	10	168	
N2	2	14	
N3	1	2	
$AJCC^{7th}$ stage‡			0.033
Ia	9	19	
Ib	7	46	
IIa	1	21	
IIb	20	73	
IIIa	6	53	
IIIb	1	6	
IIIc	4	43	

†, definitive chemoradiotherapy; ‡, from the AJCC 7th edition staging system. AJCC, American Joint Committee on Cancer.

of major complications and the high rates of morbidity and mortality associated with surgical treatment, although data pertaining to this is not available from the SEER database. In our cohort, 13.8% of patients underwent surgical resection. These patients had significantly longer survival compared to those who did not, which could be attributed to an earlier stage at diagnosis and smaller primary tumors.

Chemoradiotherapy has become the current mainstay for the treatment of CEC. We found that there was no significant difference in prognosis between those who underwent surgery and those who underwent radical chemoradiotherapy, although patients who underwent surgery were more likely to have AC, a smaller tumor size, less lymph node involvement, and lower TNM staging. These results underline the critical role of chemoradiotherapy in CEC, especially among patients who have a greater number of high-risk factors. However, it remains controversial whether OS improves with chemoradiotherapy followed by surgery versus chemoradiotherapy alone for patients with SCC of the esophagus (24-27). Our results showed that trimodal therapy significantly improved DSS when compared with double or single therapy in the SCC subgroup, although no significant difference in OS was found between the trimodal- and dual-therapy groups. This provides favorable evidence for the use of trimodal therapy for CEC patients with SCC.

Nomograms have advantages over the AJCC TNM staging system in predicting patient prognosis, and they

Table 4 Univariable and multivariable Cox proportional hazards regression for overall survival of the training set

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥65 years	1.52 (1.17–1.6)	0.002	1.85 (1.13–3.04)	0.015
Male *vs.* female	1.45 (1.11–1.89)	0.006	1.71 (1.03–2.83)	0.038
AC *vs.* SCC	0.38 (0.19–0.78)	0.008	–	–
Tumor size ≥55 mm	1.44 (1.01–2.06)	0.046	2.10 (1.20–3.69)	0.010
T^{7th} stage†	1.27 (1.10–1.46)	<0.001	–	–
AJCC VII stage	1.16 (1.06–1.26)	<0.001	1.34 (1.05–1.71)	0.017
Surgery (yes *vs.* no)	0.71 (0.55–0.92)	0.010	0.17 (0.08–0.39)	<0.001
Chemotherapy (yes *vs.* no)	0.56 (0.43–0.73)	<0.001	0.26 (0.14–0.49)	<0.001
Radiotherapy (yes *vs.* no)	0.72 (0.54–0.95)	0.025	0.49 (0.26–0.93)	0.030

†, from the AJCC 7th edition staging system. AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; AC, adenocarcinoma; SCC, squamous cell carcinoma.

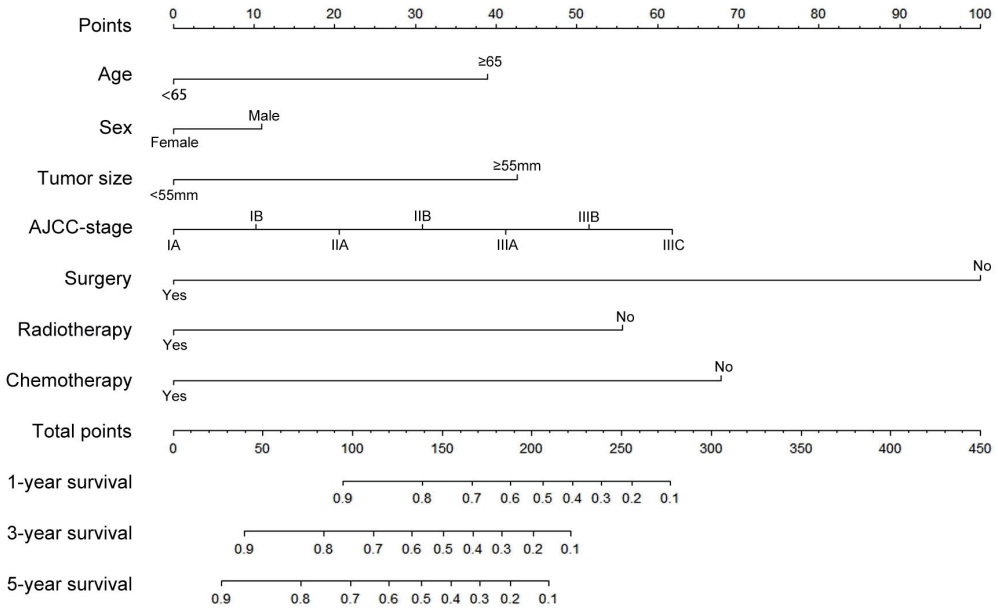

Figure 4 Nomogram for predicting 1-, 3-, and 5-year OS for non-metastatic CEC. To calculate the survival rate of each individual patient, points for each of the factors were first identified on the uppermost point scale, and then the total points from all factors were added up and projected on the bottom point scale to indicate the probability survival.

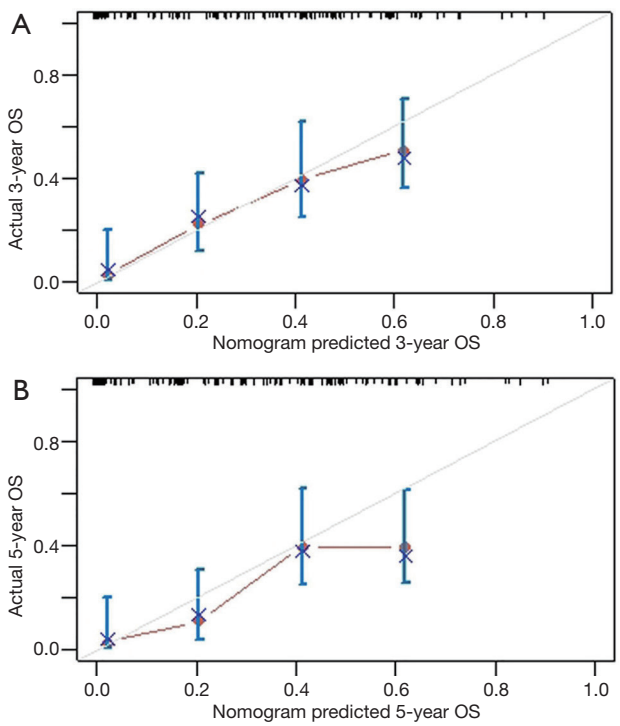

Figure 5 Calibration curve for predicting patient OS at 3 years (A) and 5 years (B) in the training cohort. Nomogram-predicted probability of OS is plotted on the X-axis; actual OS is plotted on the Y-axis.

have been applied in numerous types of cancers. To the best of our knowledge, no nomogram has been developed specifically for CEC. The present study represents the first effort to develop a prognostic nomogram for CEC, based on a large cohort of patients from the SEER database. The nomogram showed good discrimination in the external validation cohort. In addition, we compared the predictive accuracy of our nomogram with the 7th edition of AJCC TNM staging system, and showed that our nomogram outperformed the TNM staging system in the prognostic prediction of OS in CEC patients. These results suggest that our nomogram has a relatively good discrimination in identifying high-risk populations and predicting prognosis.

The present study has several limitations. First, the SEER database does not include information on treatment toxicities, comorbidities, and failure patterns; therefore, these parameters could not be analyzed in the present study. Second, detailed information about cancer management was not available. We were therefore unable to separate patients who did not undergo surgery, RT, or chemotherapy, or those who underwent these treatments, but were not documented. Information on surgical procedure, radiation dose, and chemotherapy regimens were also not available. Therefore, our nomogram did not include details about treatment. Finally, selection bias and confounding bias

should be considered when interpreting the results from the present study based on the SEER database.

Conclusions

We developed a prognostic nomogram to produce an individualized survival prediction for non-metastatic CEC patients. The nomogram had a relatively high accuracy and can likely be used to help identify high-risk patient populations and supplement the current TNM staging system.

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Footnote

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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).

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