Patterns of care and prognostic evaluation for stage I–III upper esophageal squamous cell carcinoma: a population-based study

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Background: There is no strong evidence regarding the optimal treatment and specific prognosis prediction model for upper esophageal squamous cell carcinoma (UESCC). This study aimed to investigate the real-world treatment patterns and develop models to predict overall survival (OS) and esophageal cancer-specific survival (ECSS) in patients with stage I–III UESCC.

Methods: Patients with T1-4N0-3M0 UESCC in the Surveillance, Epidemiology, and End Results (SEER) database were identified from 2010 to 2017, and randomized to a training cohort and a validation cohort. The effect of treatment patterns on survival were comprehensively analyzed. Nomograms were developed by incorporating independent prognostic factors analyzed by Cox regression in the training cohort and evaluated by the concordance index (C-index), receiver operating characteristic (ROC) curves, calibration curves, and decision curve analyses (DCA) in two cohorts.

Results: A total of 677 patients were identified, including 452 in the training cohort and 225 in the validation cohort. Among all populations, 71.9% (487) received chemoradiotherapy without surgery, and chemoradiotherapy or/and surgery showed better survival than other treatments. However, surgery was rarely carried out for patients with stage II–III. T stage, N stage, surgery, chemotherapy, and radiotherapy were independent risks for both OS and ECSS, while age was also an independent risk for OS. The C-indexes for nomograms to predict OS (0.71 and 0.72) and ECSS (0.70 and 0.73) were greater than 7th AJCC staging system to predict OS (0.61 and 0.64) and ECSS (0.64 and 0.64) in both the training cohort and the validation cohort. Time-dependent ROC curves and DCA also suggested that nomograms performed consistently better than 7th AJCC staging system. The calibration curves demonstrated good consistency in predicting survival.

Conclusions: Chemoradiotherapy was a major treatment with preferable survival for patients with stage I–III UESCC. We have firstly developed and validated prognostic nomograms in patients with stage I–III UESCC, which would play a supplementary role in the current staging system.

Keywords: Esophageal cancer; nomogram; Surveillance, Epidemiology, and End Results (SEER); prognosis; chemoradiotherapy

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Introduction

Esophageal carcinoma (EC) is the 7th most common type of cancer and ranks 6th in cancer-related death worldwide. Its incidence has a striking geographic variation with a particularly high burden in eastern Asia and in eastern and southern Africa (1,2). It is usually not recognized until the disease has become advanced or metastatic, resulting in a poor survival. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the esophagus are the most common histologic subtypes with quite different etiologies (3). In lower income countries (high burden regions), the majority of EC are SCC; AC predominates in high-income countries, and has risen sharply over the past decades (2). The prognostic factors include the characteristics of the patient (including performance status and comorbidities) and those of the tumor (stage, histology, subsite, etc.).

Upper EC is relatively uncommon compared to the high incidence of middle esophageal SCC (ESCC) in high burden regions and the high incidence of lower esophageal AC in western countries. Upper EC consists of EC in the cervical segment and upper thoracic segment, which accounts for 8.8–19.6% of all EC (4-7), and about 90% patients are ESCC (4,6,7). It has been found that tumor location is an important prognostic factor for ESCC and upper ESCC (UESCC) has the worst survival (8-10). Therefore, tumor location was incorporated into staging recommendations for ESCC in the 7th and 8th edition American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classifications. Definitive chemoradiotherapy is recommend for patients with non-metastatic cervical ESCC, and the treatment of patients with upper thoracic ESCC is the same as that of those with other thoracic ESCC in the guideline of the National Comprehensive Cancer Network (NCCN). However, there is no strong evidence regarding the best treatment for UESCC. The sample sizes of patients with UESCC in clinical trials have been very small (11-14).

An accurate prognostic model for UESCC is essential for both clinicians and patients. The AJCC TNM staging systems are commonly employed to predict the prognosis of malignant tumors. However, many import factors are not included in the stage system. Nomograms, which can incorporate multiple prognostic factors, have shown better prognostic prediction than TNM staging systems in EC (15,16). To the best of our knowledge, there is no specific nomogram developed for UESCC.

In the present study, we systematically reviewed the real-world treatment strategies and their outcomes of patients with stage I–III UESCC using the Surveillance, Epidemiology, and End Results (SEER) database. We then evaluated the associations of clinicopathological variables with outcomes and developed nomograms to predict overall survival (OS) and esophageal cancer-specific survival (ECSS). These results should provide more evidence on the decision-making of treatment guidance for UESCC. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4577/rc).

Methods

Data sources

Data was extracted from the SEER database using the SEER*Stat program version 8.3.9 (https://seer.cancer.gov/). We used the EC data (Site recoded ICD-O-3/WHO 2008 = "Esophagus" and Behavior Code ICD-O-3 = "Malignant") based on the recent incidence-SEER Research Plus Data (18 Registries, Nov 2020 Sub). We collected information on patient's general characteristics (age, gender, race, year of diagnosis and marital status), tumor features (histology, primary site, grade, AJCC T stage, AJCC N stage and AJCC stage), treatment methods (surgery, chemotherapy and radiotherapy) and clinical outcomes (overall survival and cancer specific survival).

Assessment of variables and endpoints

Upper EC was defined when the primary tumor was located at the upper third of the esophagus (code: C15.3) and the cervical esophagus (code: C15.0). Diagnosis of the tumor was based on the histological results. Primary tumor grade was classified into well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3),

undifferentiated (G4) and unknown. Marital status was divided into married and others (single, widowed, divorced, etc.). Treatment without surgery was defined when the cancer-directed surgery information was not recommended or not performed. Treatment without chemotherapy was defined when the chemotherapy record was no/unknown. Treatment without radiotherapy was defined when the radiation record was no/unknown or refused.

The death and EC-specific death were regarded as observed endpoints. OS and ECSS were defined as the intervals between the date of diagnosis and the occurrence of any-cause or esophageal cancer-specific death, respectively. Survivors are censored as of the last follow-up.

Patient selection

Patients with UESCC diagnosed between 2010 and 2017 were included. The inclusion criteria were as follows: (I) patients with histologically confirmed SCC; (II) patients with stage T1-T4aN0-3M0, according to the 7th edition AJCC TNM classifications. The exclusion criteria were as follows: (I) patients with two or more in situ/malignant tumors; (II) patients with unknown information on treatment; (III) patients with unknown T stage, N stage, or M stage; (IV) patients with survival time less than 1 month; (V) patients with unknown or missing cause-specific death classification. The detailed flowchart of study population selection is presented in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment definitions

In this study, treatment strategies for patients were divided into the following groups: surgery alone (S); radiotherapy alone (RT); chemotherapy alone (CT); surgery and radiotherapy (S + RT); surgery and chemotherapy (S + CT); chemotherapy and radiotherapy (CRT); surgery, chemotherapy, and radiotherapy (S + CRT); and others. The treatments of S + RT, S + CT, and S + CRT were defined as patients receiving preoperative or postoperative RT, CT, and CRT, respectively, whereas CRT referred to patients receiving concurrent or sequential RT with CT. The treatment of others included all patients without any treatment of surgery, chemotherapy, or radiotherapy.

Statistical analysis

Statistical analyses were performed using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R software 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). For comparison of categorical variables, either Pearson's chi-square test or Fisher's exact test was used. Survival analyses were performed using the Kaplan-Meier method with the log-rank test. All included patients were randomly divided into a training cohort and a validation cohort in a ratio of 2:1. The training cohort was used to develop nomograms, while the validation cohort was used to validate the results. Univariate Cox regression analyses were performed to identify the risk variables associated with OS and ECSS, and variables with a P value less than 0.10 were included in the multivariate Cox regression analyses. A P value <0.05 was considered statistically significant and all tests were two-sided.

Nomograms were developed by incorporating independent prognostic variables analyzed by multivariate Cox regression analyses in the training cohort. The predictive accuracy and discriminative ability of nomograms was evaluated by the concordance index (C-index), receiver operating characteristic (ROC) curves, and calibration curves. In the calibration curve analyses, a bootstrap method with 1000 replications was used to test the association between the predicted probability and the actual probability. Decision curve analyses (DCA) were used for evaluating their clinical application.

Results

Patient characteristics

After systematic screening, a total of 677 patients with UESCC were included in this study. Most patients were aged above 50 years at diagnosis (94.7%), White (71.3%), stage II–III (85.5%), and G2-3 differentiation (73.6%). Totals of 54 (8.0%), 537 (79.3%), and 569 (84.0%) patients received surgery, chemotherapy, and radiotherapy, respectively. The baseline demographics and clinical characteristics of patients with different treatments are listed in *Table 1*. There were significant differences in age, primary site, stage, T stage, and vital status between patients with and without surgery, in age, race, stage, T stage, N stage, marital status, and vital status between patients with and without chemotherapy, and in age, race, primary site, stage, T stage, N stage, and vital status between patients with and without radiotherapy. The baseline demographics and clinical characteristics of patients in the training cohort and validation cohort are listed in *Table 2*.

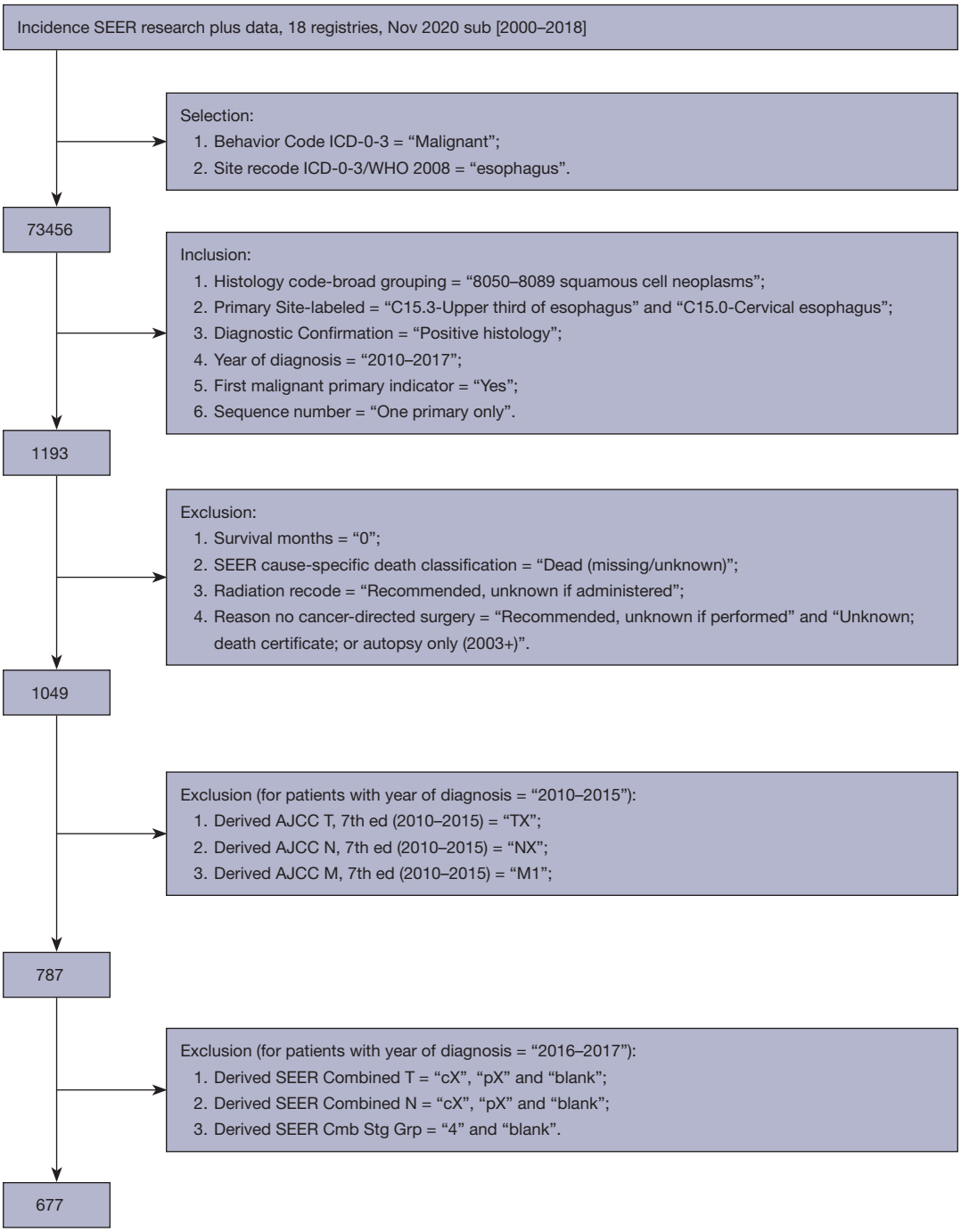

Figure 1 Flowchart of patient's selection. SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; T, tumor; N, node; M, metastasis.

Table 1 The clinical baselines of patients with different treatments

Variables	Treatments								
	Surgery			Chemotherapy			Radiotherapy		
	Yes (N=54)	No (N=623)	P value	Yes (N=537)	No (N=140)	P value	Yes (N=569)	No (N=108)	P value
Age (years)			0.018			<0.001			0.005
<65	33 (4.9)	277 (40.9)		266 (39.3)	44 (6.5)		274 (40.5)	36 (5.3)	
≥65	21 (3.1)	346 (51.1)		271 (40.0)	96 (14.2)		295 (43.6)	72 (10.6)	
Gender			0.529			0.061			0.172
Male	32 (4.7)	396 (58.5)		349 (51.6)	79 (11.7)		366 (54.1)	62 (9.2)	
Female	22 (3.2)	227 (33.5)		188 (27.8)	61 (9.0)		203 (28.19)	46 (6.8)	
Race			0.726			0.006			<0.001
White	41 (6.1)	442 (65.3)		386 (57.0)	97 (14.3)		412 (60.9)	71 (10.5)	
Black	8 (1.2)	106 (15.7)		80 (11.8)	34 (5.0)		83 (12.3)	31 (4.6)	
Others	5 (0.7)	75 (11.1)		71 (10.5)	9 (1.3)		74 (10.9)	6 (0.9)	
Primary site			0.014			0.133			0.015
Cervical	7 (1.0)	177 (26.1)		153 (22.6)	31 (4.6)		165 (24.4)	19 (2.8)	
Upper third	47 (6.9)	446 (65.9)		384 (56.7)	109 (16.1)		404 (59.7)	89 (13.1)	
Stage			0.001			<0.001			<0.001
IA	6 (0.9)	16 (2.4)		12 (1.8)	10 (1.5)		14 (2.1)	8 (1.2)	
IB	13 (1.9)	63 (9.3)		37 (5.5)	39 (5.8)		40 (5.9)	36 (5.3)	
IIA	2 (0.3)	32 (4.7)		28 (4.1)	6 (0.9)		30 (4.4)	4 (0.6)	
IIB	13 (1.9)	160 (23.6)		147 (21.7)	26 (3.8)		159 (23.5)	14 (2.1)	
IIIA	14 (2.1)	169 (25.0)		161 (23.8)	22 (3.2)		165 (24.4)	18 (2.7)	
IIIB	3 (0.4)	39 (5.8)		39 (5.8)	3 (0.4)		41 (6.1)	1 (0.1)	
IIIC	3 (0.4)	144 (21.3)		113 (16.7)	34 (5.0)		120 (17.7)	27 (4.0)	
T stage			0.013			<0.001			<0.001
T1	19 (2.8)	125 (18.5)		86 (12.7)	58 (8.6)		92 (1.6)	52 (7.7)	
T2	5 (0.7)	66 (9.75)		62 (9.2)	9 (1.3)		68 (10.0)	3 (0.4)	
T3	25 (3.7)	275 (40.6)		267 (39.4)	33 (4.9)		278 (41.1)	22 (3.2)	
T4	5 (0.7)	157 (23.2)		122 (18.0)	40 (5.9)		131 (19.4)	31 (4.6)	
N stage			0.052			<0.001			<0.001
N0	32 (4.7)	271 (40.0)		208 (30.7)	95 (14.0)		228 (34.2)	75 (11.1)	
N1	19 (2.8)	268 (39.6)		249 (36.8)	38 (5.6)		259 (38.3)	28 (4.1)	
N2	3 (0.4)	66 (9.7)		64 (9.5)	5 (0.7)		67 (9.9)	2 (0.3)	
N3	0 (0.0)	18 (2.7)		16 (2.4)	2 (0.3)		15 (2.2)	3 (0.4)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Treatments								
	Surgery			Chemotherapy			Radiotherapy		
	Yes (N=54)	No (N=623)	P value	Yes (N=537)	No (N=140)	P value	Yes (N=569)	No (N=108)	P value
Grade			0.429			0.346			0.171
G1	3 (0.4)	37 (5.5)		32 (4.7)	8 (1.2)		35 (5.2)	5 (0.7)	
G2	30 (4.4)	279 (41.2)		236 (34.9)	73 (10.8)		250 (36.9)	59 (8.7)	
G3	12 (1.8)	177 (26.1)		159 (23.5)	30 (4.4)		168 (24.8)	21 (3.1)	
G4	1 (0.1)	3 (0.4)		3 (0.4)	1 (0.1)		3 (0.4)	1 (0.1)	
Unknown	8 (1.2)	127 (18.8)		107 (15.8)	28 (4.1)		113 (16.7)	22 (3.2)	
Marital status			0.183			0.021			0.160
Married	29 (4.3)	276 (40.8)		254 (37.5)	51 (7.5)		263 (38.8)	42 (6.2)	
Others	25 (3.7)	347 (51.3)		283 (41.8)	89 (13.1)		306 (45.2)	66 (9.7)	
Vital status			<0.001			0.003			0.002
Dead	27 (4.0)	460 (67.9)		372 (54.9)	115 (17.0)		396 (58.5)	91 (13.4)	
Alive	27 (4.0)	163 (24.1)		165 (24.4)	25 (3.7)		173 (25.6)	17 (2.5)	

Data are shown as n (%). G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.

Treatment patterns and survival analyses in overall populations

Of all patients included in this study, 17 (2.5%), 16 (2.4%), 47 (6.9%), 2 (0.3%), 3 (0.4%), 32 (4.7%), 487 (71.9%), and 73 (10.8%) received treatment of S, CT, RT, S + CT, S + RT, S + CRT, CRT, and others, respectively. The treatment strategies for patients with different stages, T stages, N stages, ages, primary sites, and races are shown in *Figure 2* (Figure S1 shows treatment strategies for patients of different gender, marital status, grade, and vital status). It was found that 71.9% (487/677) of patients received CRT. Treatment of S alone was performed solely in patients with T1-3, N0, stage I–II (mainly for stage I), and in patients with White or Black ancestry. Treatment of CT, RT, S + CT, and S + RT were not routinely used in all patients. The S + CRT treatment was performed in patients aged less than 80 years and N0-2, and rarely in patients with cervical ESCC. For early staged or aged UESCC, there was a relatively high percentage of patients without surgery, chemotherapy, or radiotherapy. Furthermore, relatively older patients received RT.

Among all patients, 487 patients had died, and 426 patients had died of UESCC. The median follow-up time for living patients was 40.0 (2.0 to 107.0) months. The 1-, 3-, 5-year OS rates, and median OS for all patients were 58.3%, 29.5%, 23.7%, and 15.0 months, respectively (*Figure 3A*). The 1-, 3-, 5-year ECSS rates, and median ECSS for all patients were 61.7%, 34.6%, 29.6%, and 17.0 months, respectively (*Figure 3B*). The survival for patients with different treatments are shown in *Figure 3C,3D*. Since there were only 2 and 3 patients received S + CT and S + RT, respectively, they were not included in survival analyses of treatments. The OS and ECSS for patients with S, S + CRT, or CRT were better than patients with CT, RT, or others (P<0.05 for all comparison among groups). There were no OS and ECSS differences between patients with S and patients with S + CRT or CRT. However, patients with S + CRT showed better OS and ECSS than patients with CRT (P=0.003 and 0.005, respectively).

For patients with stage I UESCC, the treatment of S, S + CRT, or CRT tended to show better OS and ECSS. However, there were no significant survival differences among patients with S, S + CRT, CRT, RT, or CT (*Figure 4A,4B*). For patients with stage II UESCC (*Figure 4C,4D*), there were only 4 patients with S and 2 patients with CT. Patients with S + CRT or CRT had

Table 2 The clinical baselines of patients in different cohorts.

Variables	Total patients	Training cohort	Validation cohort
Age (years)			
<65	310 (45.8)	196 (29.0)	114 (16.8)
≥65	367 (54.2)	256 (37.8)	111 (16.4)
Gender			
Male	428 (63.2)	280 (41.4)	148 (21.9)
Female	249 (36.8)	172 (25.4)	77 (11.4)
Race			
White	483 (71.3)	322 (47.6)	161 (23.8)
Black	114 (16.8)	82 (12.1)	32 (4.7)
Others	80 (11.8)	48 (7.1)	32 (4.7)
Primary site			
Cervical	184 (27.2)	117 (17.3)	67 (9.9)
Upper third	493 (72.8)	335 (49.5)	158 (23.3)
Stage			
IA	22 (3.2)	16 (2.4)	6 (0.9)
IB	76 (11.2)	57 (8.4)	19 (2.8)
IIA	34 (5.0)	23 (3.4)	11 (1.6)
IIB	173 (25.6)	111 (16.4)	62 (9.2)
IIIA	183 (27.0)	120 (17.7)	63 (9.3)
IIIB	42 (6.2)	29 (4.3)	13 (1.9)
IIIC	147 (21.7)	96 (14.2)	51 (7.5)
T stage			
T1	144 (21.3)	107 (15.8)	37 (5.5)
T2	71 (10.5)	45 (6.6)	26 (3.8)
T3	300 (44.3)	192 (28.4)	108 (16.0)
T4	162 (23.9)	108 (16.0)	54 (8.0)
N stage			
N0	303 (44.8)	208 (30.7)	95 (14.0)
N1	287 (42.4)	186 (27.5)	101 (14.9)
N2	69 (10.2)	45 (6.6)	24 (3.5)
N3	18 (2.7)	13 (1.9)	5 (0.7)
Grade			
G1	40 (5.9)	26 (3.8)	14 (2.1)
G2	309 (45.6)	201 (29.7)	108 (16.0)
G3	189 (27.9)	128 (18.9)	61 (9.0)
G4	4 (0.6)	4 (0.6)	0 (0.0)
Unknown	135 (19.9)	93 (13.7)	42 (6.2)
Marital status			
Married	305 (45.1)	186 (27.5)	119 (17.6)
Others	372 (54.9)	266 (39.3)	106 (15.7)
Surgery			
Yes	54 (8.0)	32 (4.7)	22 (3.2)
No	623 (92.0)	420 (62.0)	203 (30.0)
Chemotherapy			
Yes	537 (79.3)	348 (51.4)	189 (27.9)
No	140 (20.7)	104 (15.4)	36 (5.3)
Radiotherapy			
Yes	569 (84.0)	373 (55.1)	196 (29.0)
No	108 (16.0)	79 (11.7)	29 (4.3)
Vital status			
Dead	487 (71.9)	327 (48.3)	160 (23.6)
Alive	190 (28.1)	125 (18.5)	65 (9.6)

Data are shown as n (%). G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.

better survival than those with RT or others. Moreover, there were no OS and ECSS differences between patients with CRT and patients with S + CRT (P=0.443 and 0.092, respectively). For patients with stage III UESCC (*Figure 4E,4F*), S was not performed. Patients with S + CRT or CRT showed better OS and ECSS than patients with RT, CT, or others (P<0.05 for all comparisons among groups). There were no OS and ECSS differences between patients with CRT and patients with S + CRT (P=0.128 and 0.055, respectively).

Prognostic factors for OS and ECSS in the training cohort

Cox regression analyses were performed to identify the variables associated with OS and ECSS in the training cohort (*Table 3*). Univariate Cox regression analyses suggested that T stage, N stage, grade, surgery, chemotherapy, and radiotherapy are associated with OS and ECSS and age was also associated with OS. Variables with a P-value less than 0.10 in univariate analyses were incorporated into multivariate Cox regression analyses. It was found that T

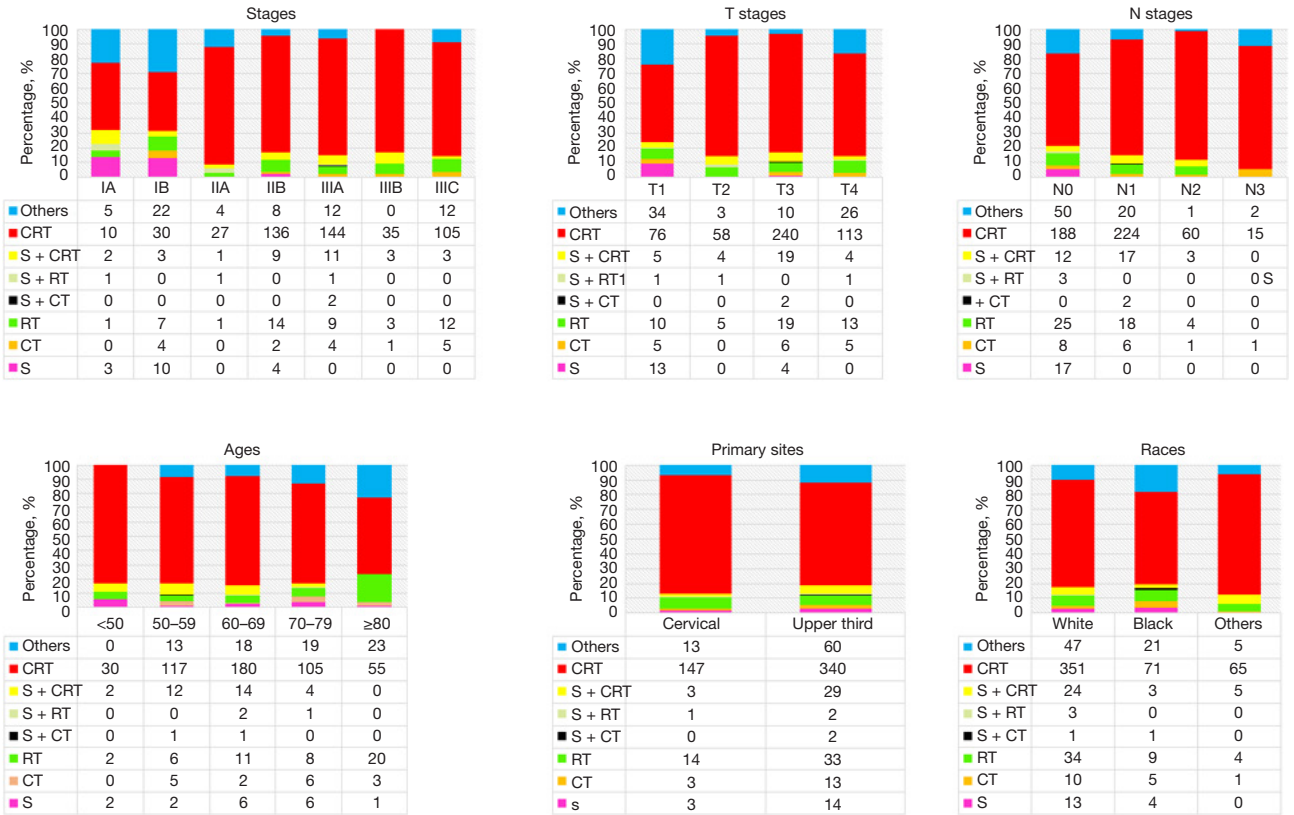

Figure 2 Treatment strategies among patients with different stages, ages, T stages, N stages, primary sites, and races. S, surgery alone; RT, radiotherapy alone; CT, chemotherapy alone; S + RT, surgery and radiotherapy; S + CT, surgery and chemotherapy; CRT, chemotherapy and radiotherapy; S + CRT, surgery, chemotherapy, and radiotherapy; T, tumor; N, node.

stage, N stage, surgery, chemotherapy, and radiotherapy were independent risk factors for OS and ECSS and age was also independent risk factor for OS. The survival analyses for patients with different ages, gender, races, T stages, N stages, marital status, surgery, chemotherapy, and radiotherapy are shown in Figures S2,S3.

Nomograms development and validation

Based on the independent risk factors found on multivariate Cox regression analyses, predictive nomograms were constructed to predict the 1-, 3-, and 5-year OS and ECSS for stage I–III UESCC (*Figure 5A*,*5B*). The C-indexes of nomograms for predicting OS (0.71 in the training cohort and 0.70 in the validation cohort) and ECSS (0.72 in the training cohort and 0.73 in the validation cohort) were significantly greater than that of 7th AJCC staging system to predict OS (0.61 in the training cohort and 0.64 in the validation cohort) and ECSS (0.64 in the training cohort and 0.64 in the validation cohort). Time-dependent ROC curves also suggested that nomogram for predicting OS performed consistently better than 7th AJCC staging system throughout the investigated period in both the training cohort and validation cohort (*Figure 6A*,*6B*). The calibration curves showed good consistency between the observed and nomogram-predicted 1-, 3-, and 5-year OS in the training cohort (*Figure 6C*) and in the validation cohort (*Figure 6D*). In addition, DCA suggested that nomogram had great positive net benefits and higher net benefit than 7th AJCC staging system across most of the threshold probabilities at 1-, 3-, and 5-year OS in both cohorts (Figure S4A-S4D and *Figure 6E*,*6F*), indicating the superiority of the nomogram utility over 7th AJCC staging system in clinical practice. Time-dependent ROC curves (*Figure 7A*,*7B*), calibration curves (*Figure 7C*,*7D*) and DCA (Figure S5A-S5D and *Figure 7E*,*7F*) indicated

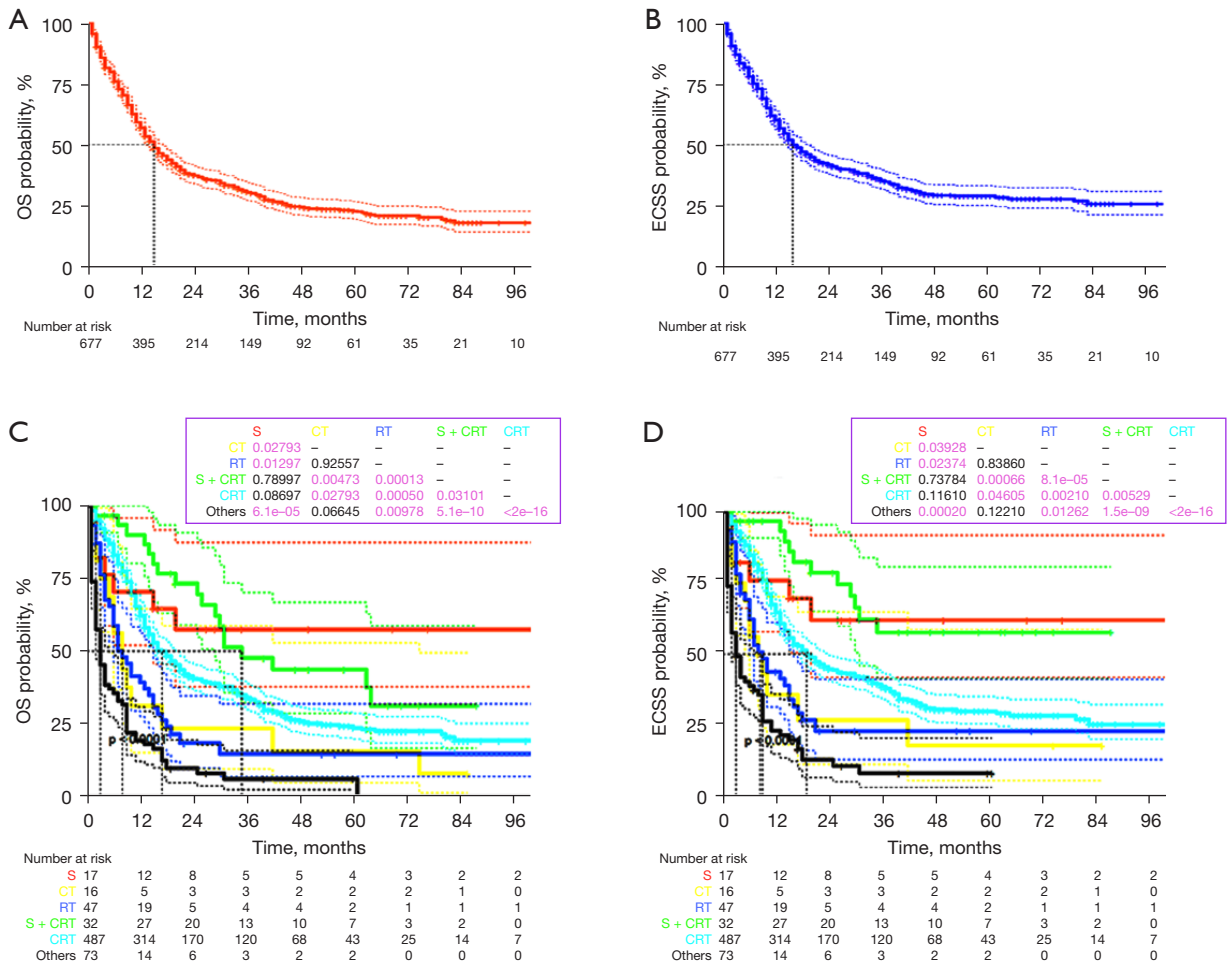

Figure 3 Kaplan-Meier survival curves for patients with UESCC: (A) OS, (B) ECSS, (C) OS in patients with different treatments, and (D) ECSS in patients with different treatments. OS, overall survival; ECSS, esophageal cancer-specific survival; UESCC, upper esophageal squamous cell carcinoma; S, surgery alone; RT, radiotherapy alone; CT, chemotherapy alone; CRT, chemotherapy and radiotherapy; S + CRT, surgery, chemotherapy, and radiotherapy.

that nomogram for predicting ECSS also showed good performance in both cohorts.

Discussion

In the present study, patients with stage I–III UESCC from the SEER database were comprehensively reviewed. Treatment strategies for patients with different characteristics and their survival outcomes were analyzed. Then, we conducted nomograms to predict the OS and ECSS, which can accurately and effectively predict individual survival for patients with stage I–III UESCC.

The majority of patients received radiotherapy (79.3%) and chemotherapy (84.0%), whereas only 9.0% patients received surgery. Unlike the esophageal AC, the ESCC resembles the squamous carcinoma of other organs (3). Some believe that patients with UESCC should be treated like patients with squamous carcinomas of the head and neck. UESCC has a high risk of local invasiveness to adjacent structures, and is located in an area of abundant lymphatic drainage (17). Further, the surgical procedure has many drawbacks for patients with UESCC because of the complexity of anatomical structures in this area and the limitations of the surgery itself. Therefore, radical surgery is usually precluded and associated with high rates of morbidity, mortality (18), and recurrence (19-21).

Patients with upper thoracic ESCC have rarely been studied as a single group in clinical trials due to the

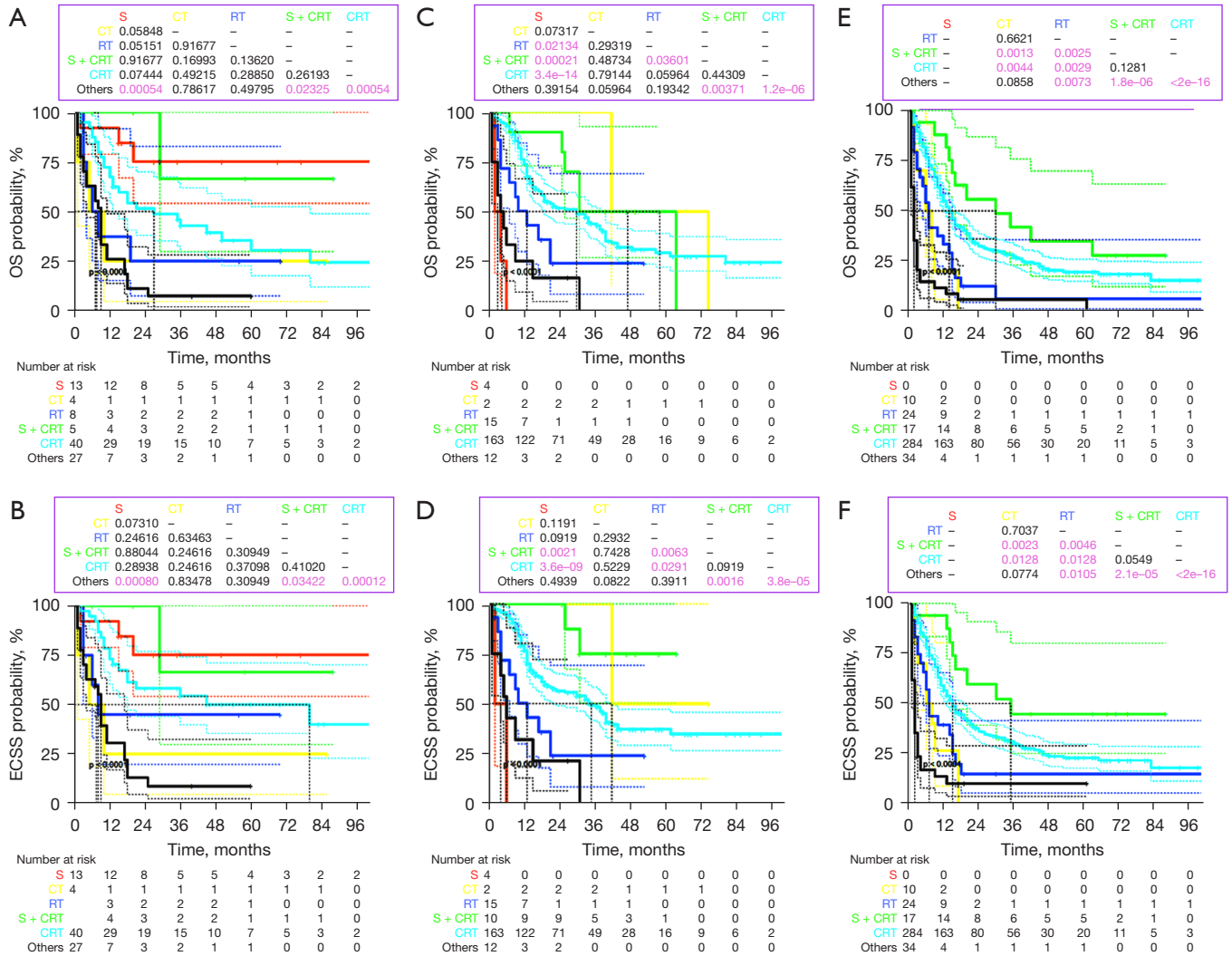

Figure 4 Kaplan-Meier survival curves for patients with different stages received different treatments. (A) OS curves for stage I UESCC, (B) ECSS curves for stage I UESCC, (C) OS curves for stage II UESCC, (D) ECSS curves for stage II UESCC, (E) OS curves for stage III UESCC, and (F) ECSS curves for stage III UESCC. S, surgery alone; RT, radiotherapy alone; CT, chemotherapy alone; CRT, chemotherapy and radiotherapy; S + CRT, surgery, chemotherapy, and radiotherapy; OS, overall survival; ECSS, esophageal cancer-specific survival; UESCC, upper esophageal squamous cell carcinoma.

Table 3 Cox regression analyses of OS and ECSS in the training cohort

Variables	OS						ECSS					
	Univariate Cox			Multivariate Cox			Univariate Cox			Multivariate Cox		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95%CI	P value
Age (years)			0.007			0.025			0.093			0.163
<65	1			1			1			1		
≥65	1.356	1.087–1.692		1.307	1.034–1.651		1.223	0.967–1.549		1.194	0.931–1.531	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	OS						ECSS					
	Univariate Cox			Multivariate Cox			Univariate Cox			Multivariate Cox		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95%CI	P value
Gender			0.128						0.185			
Male	1						1					
Female	0.839	0.670–1.052					0.849	0.666–1.082				
Race			0.093			0.360			0.083			0.205
White	1			1			1			1		
Black	1.266	0.954–1.679		1.238	0.920–1.667		1.395	1.038–1.749		1.328	0.972–1.815	
Others	1.050	0.735–1.498		0.995	0.694–1.425		1.143	0.786–1.661		1.063	0.729–1.550	
T stage			<0.001			<0.001			<0.001			<0.001
T1/2	1			1			1			1		
T3	1.031	0.797–1.333		1.189	0.902–1.566		1.004	0.738–1.367		1.303	0.962–1.765	
T4	1.718	1.296–2.278		2.146	1.588–2.900		1.843	1.332–2.552		2.549	1.846–3.520	
N stage			0.015			0.002			0.008			0.001
N0	1			1			1			1		
N1	1.139	0.900–1.443		1.126	0.881–1.438		1.238	0.960–1.597		1.222	0.939–1.591	
N2/3	1.625	1.172–2.255		1.855	1.313–2.620		1.720	1.214–2.437		1.979	1.369–2.860	
Grade			0.022			0.106			0.037			0.192
G1/2	1			1			1			1		
G3/4	0.731	0.566–0.945		0.800	0.616–1.039		0.728	0.553–0.959		0.816	0.616–1.081	
Unknown	0.741	0.556–0.987		0.772	0.579–1.031		0.750	0.552–1.019		0.786	0.577–1.071	
Marital status			0.259						0.306			
Married	1						1					
Others	1.136	0.910–1.419					1.133	0.892–1.438				
Primary site			0.956						0.657			
Cervical	1						1					
Upper third	0.993	0.777–1.270					0.943	0.726–1.223				
Surgery			<0.001			<0.001			0.001			<0.001
No	1			1			1			1		
Yes	0.381	0.223–0.652		0.282	0.161–0.492		0.389	0.218–0.694		0.289	0.158–0.528	
Chemotherapy			<0.001			0.001			<0.001			0.002
No	1			1			1			1		
Yes	0.566	0.441–0.727		0.575	0.410–0.806		0.545	0.418–0.711		0.556	0.385–0.802	
Radiotherapy			<0.001			0.002			<0.001			0.001
No	1			1			1			1		
Yes	0.551	0.419–0.723		0.556	0.383–0.806		0.516	0.387–0.688		0.501	0.335–0.750	

G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; OS, overall survival; ECSS, esophageal cancer-specific survival; HR, hazard ratio; CI, confidence interval.

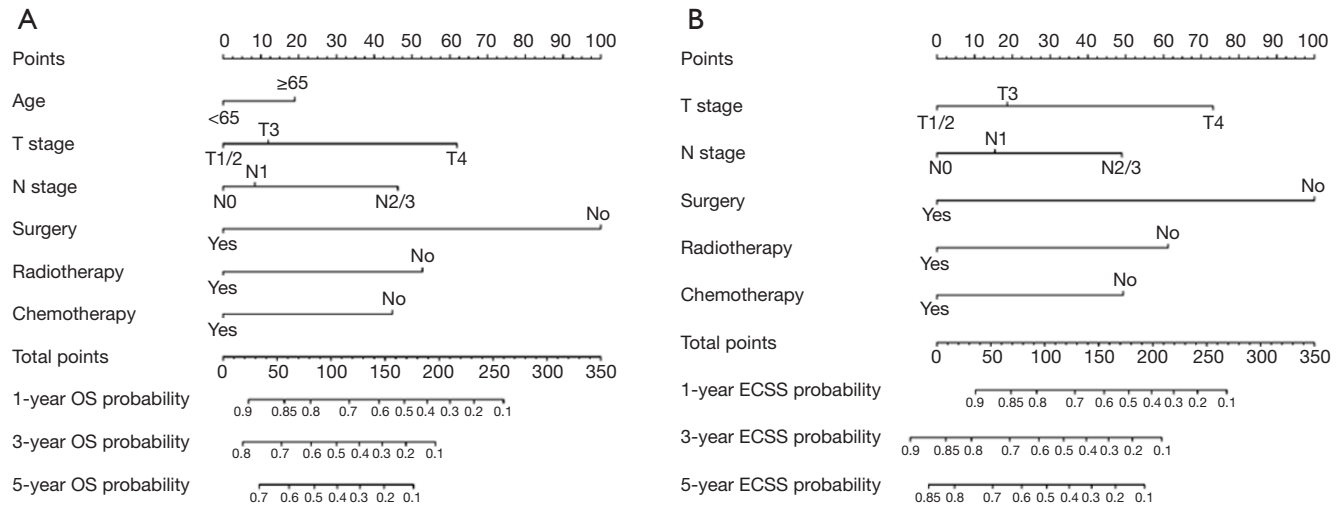

Figure 5 Nomograms for predicting 1-,3-, and 5-year OS and ECSS for patients with stage I–III UESCC in the training cohort. (A) OS nomogram; (B) ECSS nomogram. OS, overall survival; ECSS, esophageal cancer-specific survival; UESCC, upper esophageal squamous cell carcinoma.

low incidence. Though the treatment guideline is the same as that of other thoracic ESCC, the survival of patients with upper thoracic ESCC is much lower (8-10). Therefore, there is a trend toward more patients with upper thoracic ESCC receiving treatment without surgery in clinical practice. In this study, 4.8% (7/184) of patients with cervical ESCC (code: C15.0) and 9.5% (47/493) patients with UESCC (code: C15.3) received surgery (3/184 *vs.* 14/493 for S and 3/184 *vs.* 29/493 for S + CRT), respectively (P<0.05), which may suggest that more patients with upper thoracic ESCC received surgery. However, chemoradiotherapy without surgery was still the main treatment for all patients (79.9% for cervical ESCC and 69.0% for UESCC, respectively).

The 5-year OS and ECSS were 23.7% and 29.6% for the overall population in this study, which is comparable to a study performed in patients with upper EC who received chemoradiotherapy (22). Other studies have reported a 5-year OS of about 20.0% for non-metastatic cervical ESCC (17,23,24). The 5-year OS of UESCC is relatively poor compared to squamous carcinomas in the head and neck region (25,26). Moreover, ESCC shows lower survival than esophageal AC (23,27).

Surgery alone is recommended for patients with cT1b-T2M0 thoracic EC without poor prognostic factors in the NCCN guidelines. In this study, surgery alone was performed mainly for patients with early stage UESCC (13/17 for T1N0 and 4/17 for T3N0). Although there were no significant differences of OS and ECSS, surgery alone had a trend toward OS benefit compared to CRT (P=0.07) and RT (P=0.05) for patients with stage I UESCC. However, surgery may be associated with increased mortality and poorer quality of life. Similar to the results of another study (28), a prospective nonrandomized controlled study also suggested that chemoradiotherapy was noninferior to surgery and should be considered for the treatment of T1bN0M0 ESCC (29). About half of all patients with stage I UESCC received radiotherapy alone (8/98) or chemoradiotherapy (40/98) without surgery in the present study.

Chemoradiotherapy is recommend for patients with non-metastatic cervical ESCC, and chemoradiotherapy followed by surgery is a standard treatment for patients with resectable stage II–III thoracic ESCC. As shown in *Figure 4*, CRT (447/579) or S + CRT (27/579) showed better survival in patients with stage II–III UESCC. Previous studies have indicated that chemoradiotherapy should be selected as the initial larynx-preserving treatment and that surgery should be a treatment of choice for patients with non-complete response after chemoradiotherapy for cervical EC (18,30). Although the CROSS trial and NEOCRTEC5010 trial suggested that chemoradiotherapy followed by surgery showed significantly better survival compared to surgery alone for locally advanced ESCC (11,14), the superiority of trimodality therapy over definitive chemoradiotherapy is controversial, especially for patients with clinical

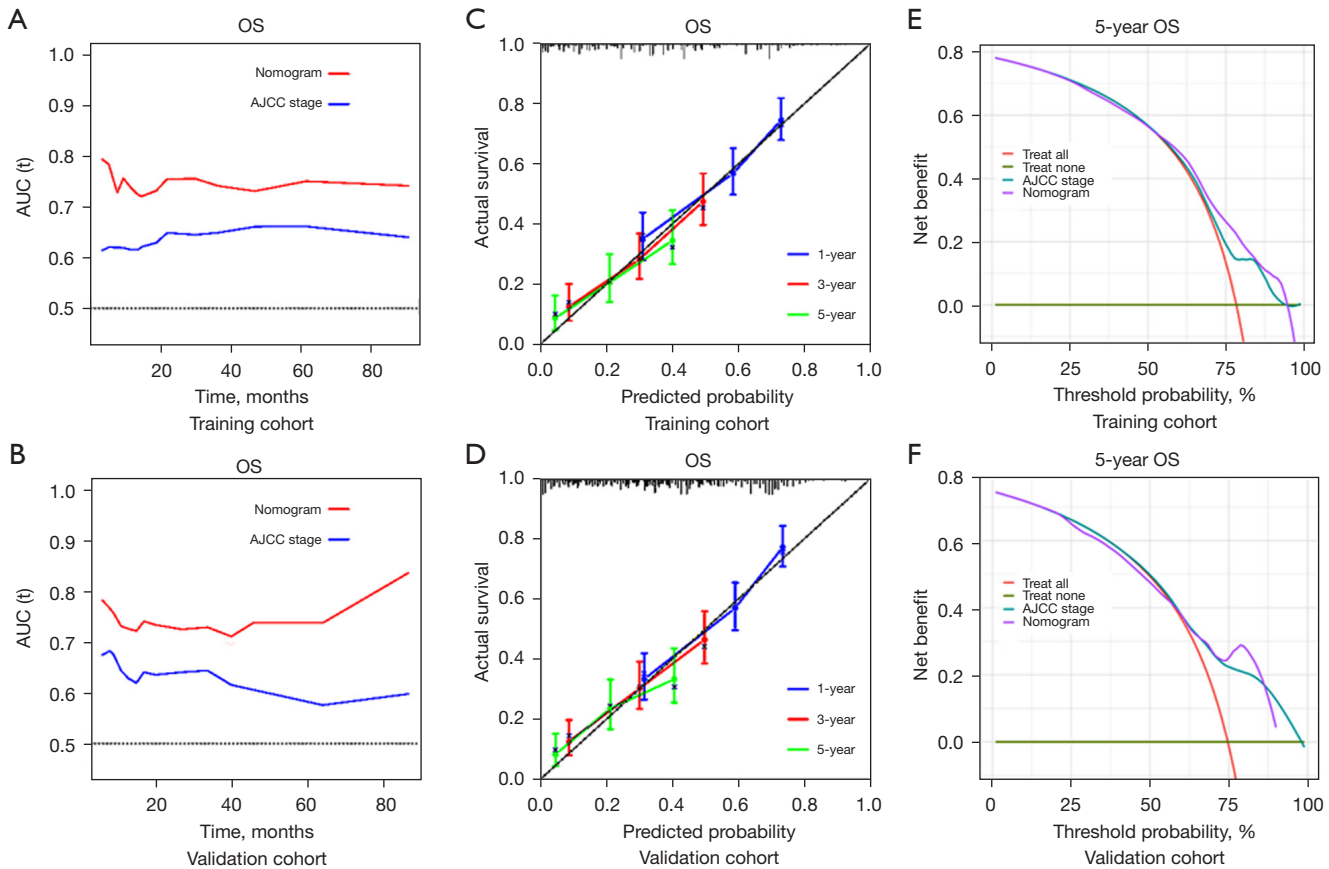

Figure 6 Time-dependent ROC curves, calibration curves and DCA of nomogram and 7th AJCC staging system for predicting OS in the training cohort and validation cohort. (A) Time-dependent ROC curves in the training cohort; (B) time-dependent ROC curves in the validation cohort; (C) calibration curves for predicting 1-, 3-, and 5-year OS in the training cohort; (D) calibration curves for predicting 1-, 3-, and 5-year OS in the validation cohort; (E) DCA for predicting 5-year OS in the training cohort; (F) DCA for predicting 5-year OS in the validation cohort. AJCC, American Joint Committee on Cancer; DCA, decision curve analyses; ROC, receiver operating characteristic; OS, overall survival.

complete response to chemoradiotherapy (31) and patients with proton beam radiotherapy (32). Interestingly, a retrospective study indicated that patients with upper EC had a significantly higher rate of complete response to chemoradiotherapy compared to patients with middle EC (33). In the present study, trimodality therapy also showed no significant survival differences compared to chemoradiotherapy for patients with stage II or III UESCC.

The AJCC TNM staging system comprises the currently accepted criteria for reference in diagnosis, treatment, and prognosis of malignant tumors. However, this staging system has many limitations, such as the accuracy of clinical stages, and ignorance of non-tumor and other tumor factors. Nomograms, which can incorporate multiple prognostic factors, have been widely used to predict prognosis in a diverse range of cancers. In this study, we conducted nomograms to predict OS and ECSS by incorporating independent risk analyzed by Cox regression analyses.

Based on the findings of previous studies (34,35), women have lower incidence and better survival than men in ESCC. However, gender was not an independent risk factor for both OS and ECSS in the present study. Although age is always a prognostic factor in most studies, it is not an independent risk factor for ECSS in our study. Additionally, the OS and ECSS differences were significant among patients with different treatments (*Figures 3*,*4*), which was similar to the results of another study (23). The ROC

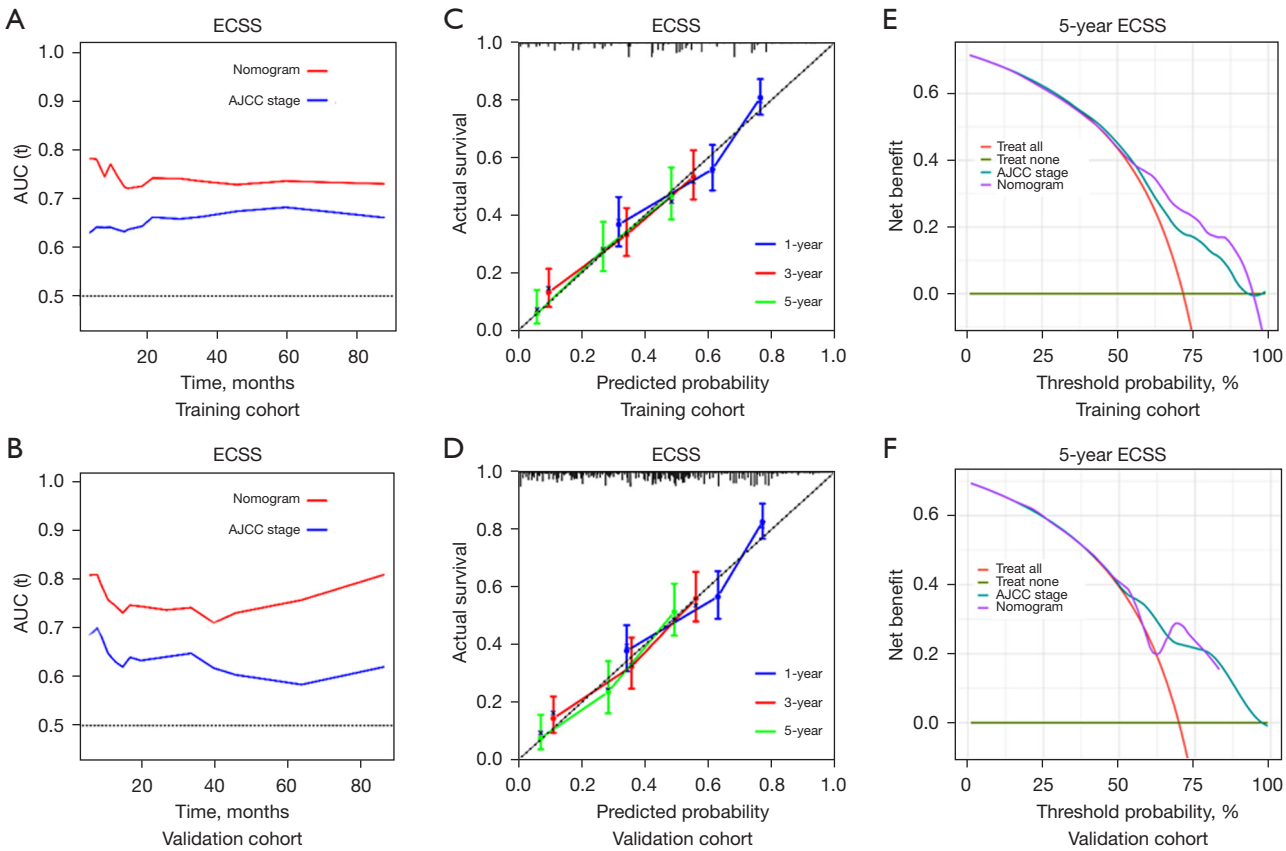

Figure 7 Time-dependent ROC curves, calibration curves and DCA of nomogram and 7th AJCC staging system for predicting ECSS in the training cohort and validation cohort. (A) Time-dependent ROC curves in the training cohort; (B) time-dependent ROC curves in the validation cohort; (C) calibration curves for predicting 1-, 3-, and 5-year ECSS in the training cohort; (D) calibration curves for predicting 1-, 3-, and 5-year ECSS in the validation cohort; (E) DCA for predicting 5-year ECSS in the training cohort; (F) DCA for predicting 5-year ECSS in the validation cohort. AJCC, American Joint Committee on Cancer; DCA, decision curve analyses; ROC, receiver operating characteristic; ECSS, esophageal cancer-specific survival.

curves, calibration curves, and DCA of nomograms showed considerable performance, indicating the good predictive ability and favorable clinical application.

Our study has addressed many strengths, as follows: (I) we reviewed data of patients with stage I–III UESCC in the SEER database with a large sample size and long-term follow-up period; (II) the patterns and outcomes of care in different subgroups were comprehensively analyzed, which may provide more reliable evidence on the decision-making of treatment guidance for patients with UESCC; and (III) compared to AJCC staging system, we developed nomograms with better predictive ability for OS and ECSS in patients with stage I–III UESCC. However, our study has many limitations. First, inherent selection bias and unmeasured confounding factors were inevitable in this retrospective study. Second, except for the CRT group, it was difficult to accurately evaluate the efficacy of patients with different treatments due to their small sample sizes. Third, the detailed information of chemotherapy, radiotherapy, surgery, and combabilities was missing in the SEER database, which limited further analyses of efficacy and prognosis. Finally, a validation of the predictive models using external data is still necessary.

Conclusions

In this SEER-based population study, we found that chemoradiotherapy was the main treatment for patients with stage I–III UESCC. Although it may be an alternative treatment choice for patients with stage I UESCC to

receive surgery alone and patients with stage II–III UECSS to receive trimodality therapy, their superiorities over chemoradiotherapy and surgery related complications need to be evaluated in future studies. We successfully developed nomograms to predict OS and ECSS for patients with stage I–III UESCC by incorporating independent risk analyzed by Cox regression analyses. The nomograms showed better predictive ability than 7th AJCC staging system, indicating promising clinical applications.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4577/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4577/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).

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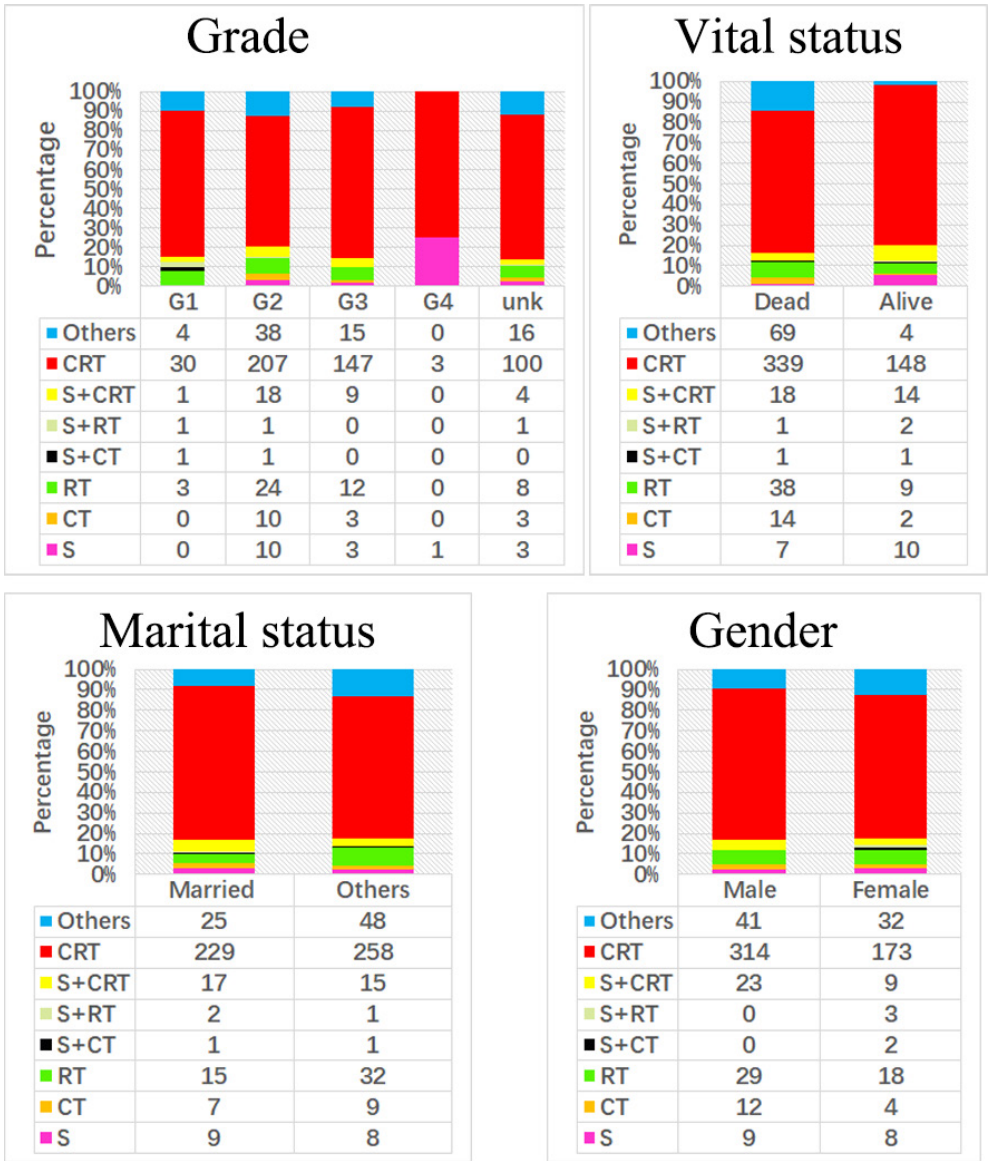

Figure S1 Treatment strategies among patients with different grade, vital status, marital status, and gender. S, surgery alone; RT, radiotherapy alone; CT, chemotherapy alone; S+RT, surgery and radiotherapy; S+CT, surgery and chemotherapy; CRT, chemotherapy and radiotherapy; S+CRT, surgery, chemotherapy, and radiotherapy.

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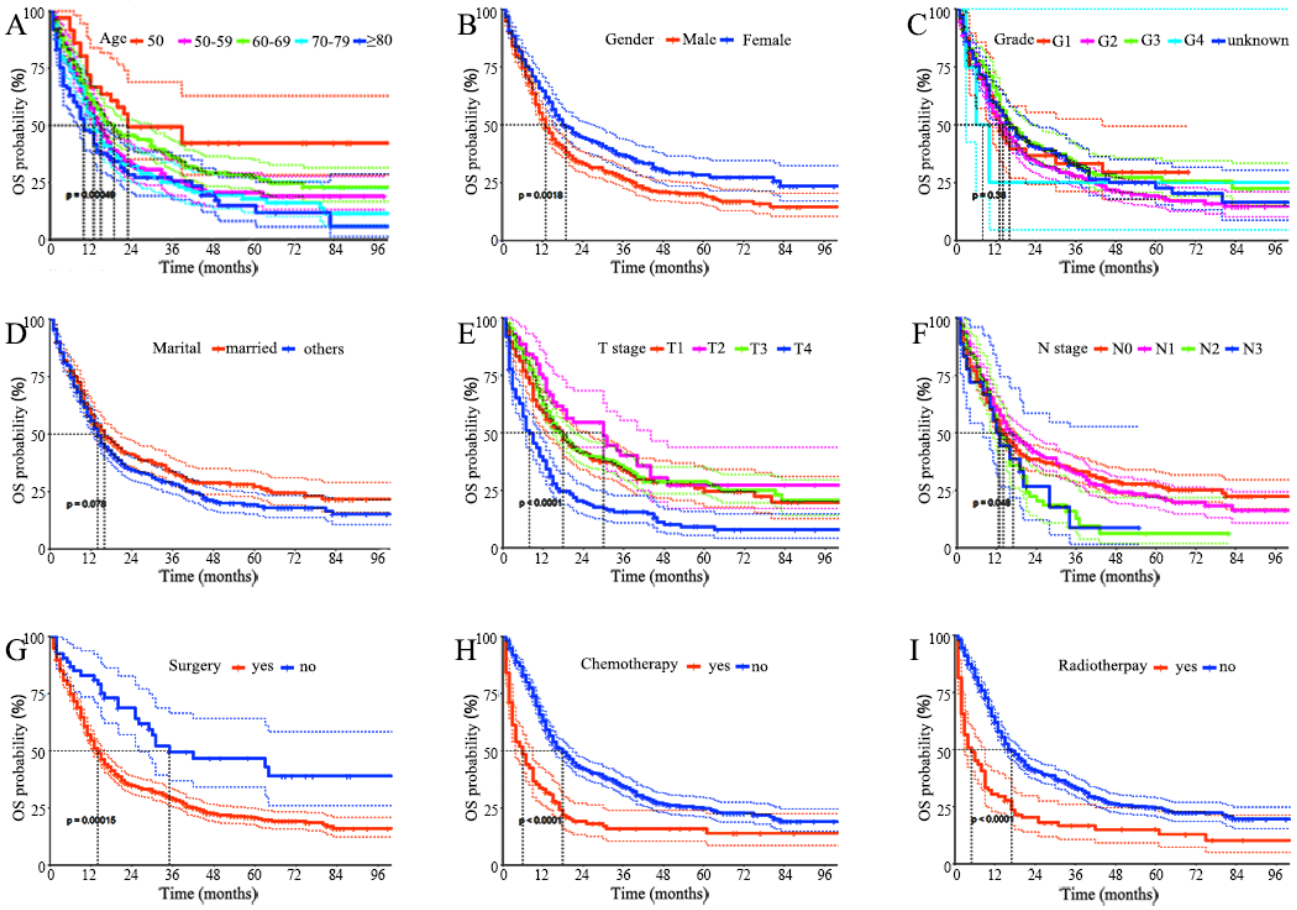

Figure S2 Kaplan-Meier OS curves for patients with different subgroups. (A) age, (B) gender, (C) grade, (D) marital status, (E) T stage, (F) N stage, (G) surgery, (H) chemotherapy, and (I) radiotherapy. OS, overall survival; ECSS, esophageal cancer-specific survival.

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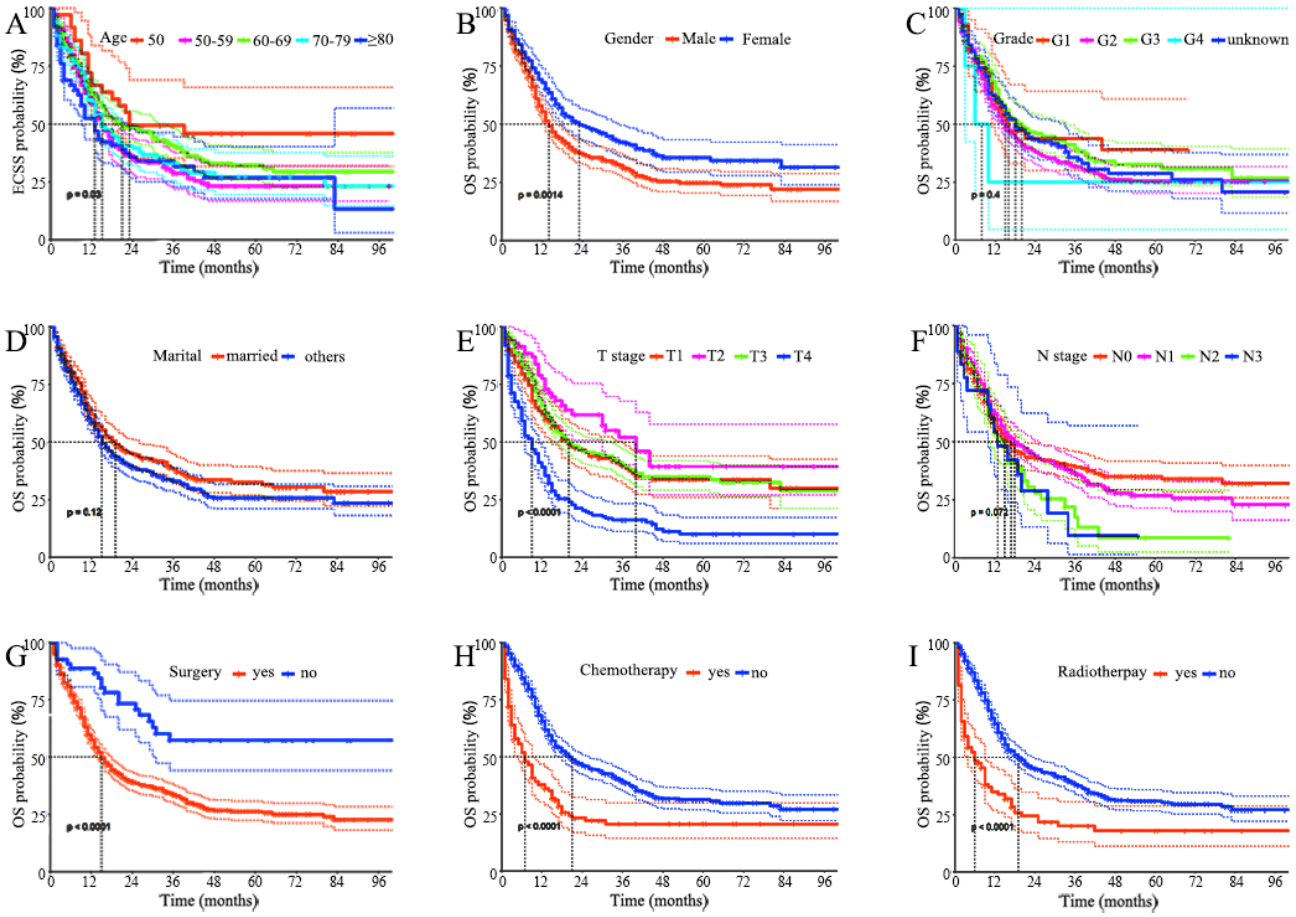

Figure S3 Kaplan-Meier ECSS curves for patients with different subgroups. (A) age, (B) gender, (C) grade, (D) marital status, (E) T stage, (F) N stage, (G) surgery, (H) chemotherapy, and (I) radiotherapy. OS, overall survival; ECSS, esophageal cancer-specific survival.

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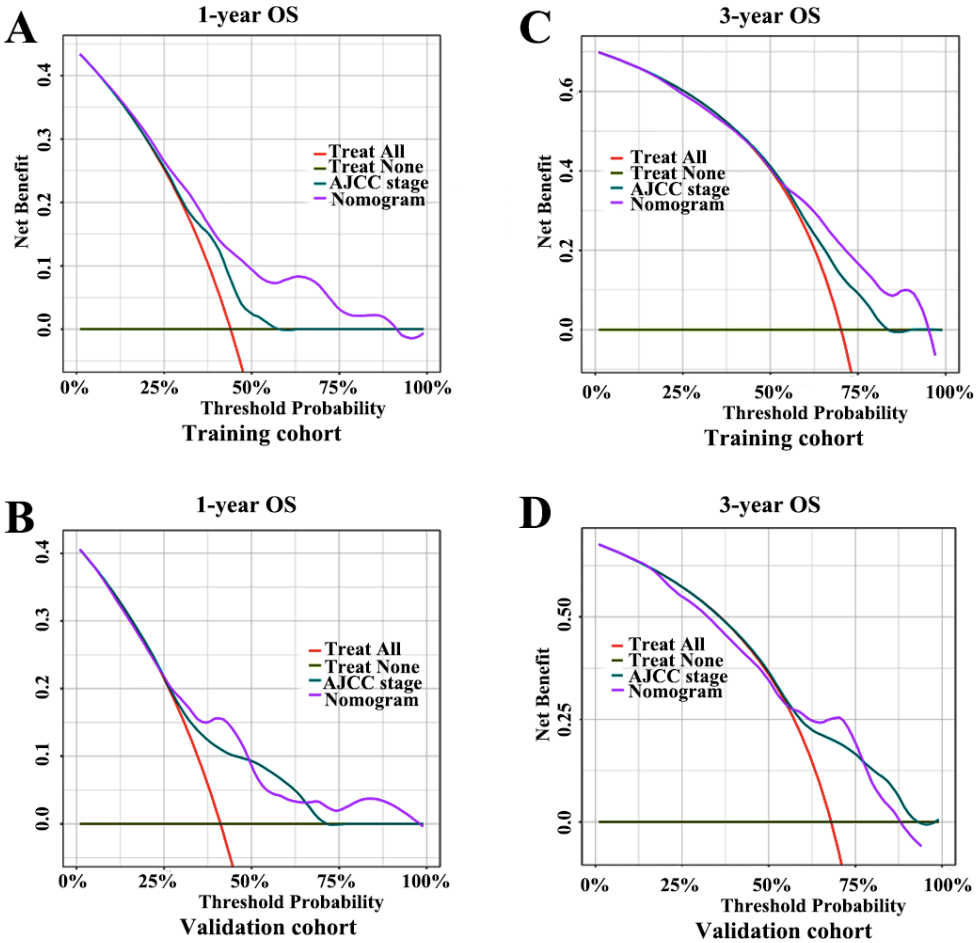

Figure S4 DCA of nomograms for predicting 1- and 3-year OS. (A) DCA of nomogram to predicting 1-year OS in the training cohort, (B) DCA of nomogram to predicting 1-year OS in the validation cohort, (C) DCA of nomogram to predicting 3-year OS in the training cohort, and (D) DCA of nomogram to predicting 3-year OS in the validation cohort. AJCC, American Joint Committee on Cancer; DCA, decision curve analyses; OS, overall survival.

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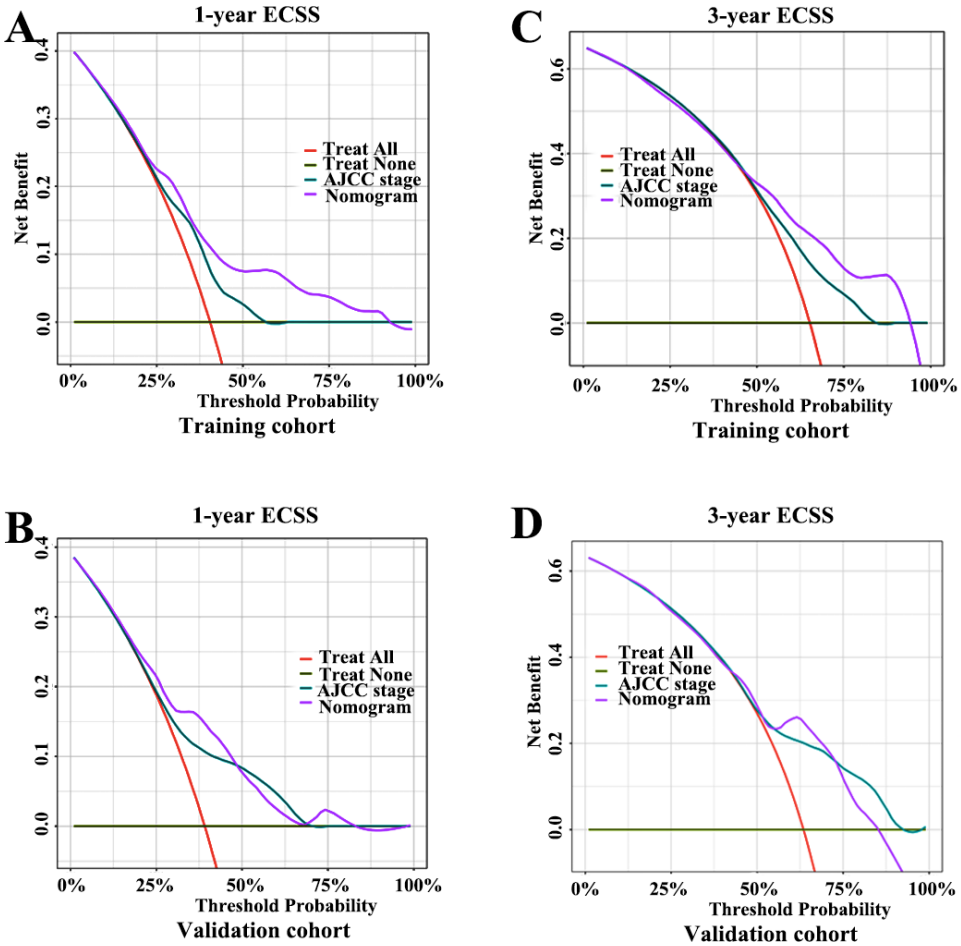

Figure S5 DCA of nomograms for predicting 1- and 3-year ECSS. (A) DCA of nomogram to predicting 1-year ECSS in the training cohort, (B) DCA of nomogram to predicting 1-year ECSS in the validation cohort, (C) DCA of nomogram to predicting 3-year ECSS in the training cohort, and (D) DCA of nomogram to predicting 3-year ECSS in the validation cohort. AJCC, American Joint Committee on Cancer; DCA, decision curve analyses; ECSS, esophageal cancer-specific survival.

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