Original Article

A predictive model for advanced esophageal cancer involving the lower third of the esophagus

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Background: Esophageal cancer (EC) is one of the most common malignant tumors worldwide, which has severely threatened human health. This study aims to evaluate the prognostic factors and predictors of survival in patients diagnosed with advanced lower third esophageal carcinoma (aLEC). Based on the Surveillance, Epidemiology, and End Results (SEER) database, we developed a model (nomogram) to provide accurate and individualized survival prediction for the patients who have lost the opportunity to undergo radical surgery.

Methods: Using SEER database, the basic information and Medicare data of patients diagnosed with aLEC from 2010 to 2015 were collected. The patients were randomly divided into the training and validation set according to an 8:2 ratio. Univariate and multivariate Cox analyses were used to investigate variables significantly correlated with disease-specific survival (DSS). A nomogram was constructed to predict the prognosis of EC patients. We used the area under the curve (AUC) of the receiver operating characteristic (ROC) curve for the evaluation of performance. Furthermore, calibration curves were used to evaluate the accuracy of the model. The clinical utility was also assessed via decision curve analysis (DCA). Differences in clinicopathological characteristics between T1NanyM1 and T2-4NanyM1 stages were evaluated using the Chi-squared test. Cox regression analysis was performed and Kaplan-Meier curves were plotted to evaluate the impact of T-stage, chemotherapy, and radiotherapy on the survival time of EC patients.

Results: Results of multivariate regression analysis demonstrated that histology type, T stage, and chemotherapy were independent prognostic factors for predicting survival time in patients with aLEC. Notably, the constructed nomogram suggested that patients with stage T2 or T3 had a higher survival rate at 6 months, 1 year, and 2 years compared with those with stage T1. DCAs showed that the predictive nomogram was clinically useful. There were fewer patients with stage T1NanyM1 receiving chemotherapy (P=0.004) or radiotherapy (P<0.001) than patients with stage T2-4NanyM1. Moreover, patients with stage T1NanyM1 who underwent chemotherapy had a better prognosis than those who did not [hazard ratio (HR) 3.15, 95% confidence interval (CI): 2.58–3.83; P<0.001]. For patients with stage T1NanyM1, radiotherapy did not improve outcomes (HR 0.98, 95% CI: 0.82–1.17; P=0.80).

Conclusions: A prognostic nomogram integrating three clinicopathological factors was constructed to predict survival in aLEC patients. Chemotherapy improves outcomes of patients with stage T1NanyM1 aLEC.

Keywords: Prognosis model; survival analysis; esophageal; esophageal squamous cell carcinoma (ESCC); Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

Esophageal cancer (EC) is one of the most common malignancies worldwide. According to the 2022 global cancer statistics report, EC ranked the seventh in mortality worldwide among malignant tumors (1). The timing and distribution pattern of tumor metastasis vary depending on anatomical locations of the primary tumor. The location of primary tumor also determines the treatment modality and cure rate. The incidence of adenocarcinoma at the distal esophagus and esophagogastric junction continues to rise (2). Jain *et al.* proposed that esophageal adenocarcinoma (EAC) was more common in the United States and some European countries and more often involved the distal esophagus (3). In addition, a study from India reported that esophageal squamous cell carcinoma (ESCC) often affected the distal third of the esophagus (4). Ai *et al.* believed that the lower esophagus was more likely to be the primary site in patients with liver metastases of EC than the upper esophagus (5). Therefore, further studies of EC are still needed.

The 5-year survival rate for EC patients worldwide is 15–20% (6). Infiltration and metastasis are one of the leading causes of death and poor prognosis in patients with EC. Despite advances in EC treatment over the past few decades, the clinical outcome for advanced EC remains very poor (7-9), with a median survival rate of only 8–10 months and 5-year relative survival rate of only 5% in EC patients with distant metastasis (10). The highly heterogeneous of advanced EC and the different treatment options lead to different survival outcomes (11).

At present, there are very limited studies on clinical prognostic factors and prognostic model in patients with advanced lower third esophageal carcinoma (aLEC). From a clinical practice perspective, the establishment of prognostic model and nomogram may help optimize individualized treatments and improve clinical outcomes. The Surveillance, Epidemiology, and End Results (SEER) database is a systematic population-based cancer database with one of the largest cohorts of EC patients. Therefore, it is meaningful to develop prognostic model of survival prediction specifically for patients with aLEC based on the SEER dataset.

Based on the SEER database, this study aimed to determine the clinical features associated with disease-specific survival (DSS) in patients with aLEC. These variables were used to construct a prognostic model to accurately predict survival. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1116/rc).

Highlight box

Key findings

- Histology, T stage, and chemotherapy were independent risk factors related to the prognosis of patients with advanced lower third esophageal carcinoma (aLEC).

What is known and what is new?

- The prognosis of patients diagnosed with aLEC is poor.
- Chemotherapy could improve the survival time of aLEC patients, which might serve as a reference for clinical application.

What is the implication, and what should change now?

- In this study, a prognostic nomogram integrating three clinicopathological factors was constructed to predict survival in aLEC patients. From a clinical practice perspective, the establishment of the prognostic model and nomogram may help optimize individualized treatments and improve clinical outcomes.

Methods

Data sources

We used the SEER*Stat (v 8.4.0) to extract data. Patients diagnosed with first primary malignant EC which was located in the lower third of the esophagus were included.

The collected information included sex, age, race, year of diagnosis, grade, the International Classification of Diseases for Oncology-3rd edition (ICD-O-3) Hist/behave, T stage (7th edition, American Joint Committee on Cancer), N stage, M stage, reason for no cancer-directed surgery, chemotherapy recode, radiation recode, diagnostic confirmation, SEER cause-specific death classification, survival months and patient ID. ICD-O-3 Hist/behave included EAC (8140/3, 8480/3, 8144/3, 8255/3, 8574/3, 8481/3, 8323/3, 8260/3, and 8211/3), ESCC (8070/3, 8071/3, 8074/3, and 8072/3), and other pathological types including adenosquamous carcinoma, non-small-cell carcinoma, signet ring cell carcinoma, carcinoma

undifferentiated, neuroendocrine carcinoma, NOS carcinoma, small cell carcinoma, large cell neuroendocrine carcinoma, carcinoma diffuse type, and pseudosarcomatous carcinoma (8560/3, 8046/3, 8490/3, 8020/3, 8246/3, 8010/3, 8041/3, 8013/3, 8145/3, and 8033/3). We applied reference number (11169-Nov2020) and obtained permission to access the SEER research data. No approval of the institutional review board was required as the SEER database contained no identifiers and was publicly available. Inclusion criteria were (I) patients with a site recode as esophagus, (II) first malignant primary indicator, (III) year of diagnosis from 2010 to 2015, (IV) M1 stage, and (V) no history of surgery. Exclusion criteria were: (I) incomplete information, and (II) survival time less than 1 month. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Construction of the nomogram

Patients were randomly divided into training and validation sets in an 8:2 ratio. The endpoint was DSS. Epidemiological and clinical data of the patients in the two sets were presented descriptively. Variables with P<0.05 in univariate analysis were included in multivariate analysis.

We constructed the nomogram according to the results of multivariate analysis to predict the DSS at 6 months, 1 year, and 2 years of patients with aLEC.

Model validation

The receiver operating characteristic (ROC) curves were plotted. The area under the ROC curve (AUC) was used in the training and validation sets to evaluate the predictive performance. The AUC values range from 0.50 to 1.00. The higher the AUC value, the better the prediction accuracy. In addition, calibration curves were analyzed by plotting the nomogram-predicted DSS and the actual probability of DSS. Internal validation of the model was performed via bootstrapping with 1,000 replicates. Decision curve analysis (DCA) was used to assess the net benefits for a range of threshold probabilities in both training and validation sets to estimate the clinical usefulness of the nomogram. The model with a higher net benefit at any threshold was considered the better model.

Survival analysis

Differences in clinicopathological characteristics between T1NanyM1 and T2-4NanyM1 stages were evaluated using the Chi-squared test. Survival analysis was performed on aLEC patient data to clarify the impact of T-stage, chemotherapy, and radiotherapy on the outcome. Survival curve differences were analyzed by Cox regression, and survival curves were plotted using the Kaplan-Meier method.

Statistical analysis

All analyses were performed using R software (version 4.0.5). Univariate and multivariate Cox regression analyses were used to evaluate independent prognostic factors. Further nomogram construction and calibration were also conducted. The R software packages used in this study were mainly the "foreign", "survival", "caret", "survminer", "rms", and "rmda" packages. Significance was assumed as P<0.05.

Results

Patient characteristics

This study involved in 1,546 patients with aLEC (*Figure 1*), which included 1,238 cases who were randomly assigned to the training set and 308 to the validation set in an 8:2 ratio. The general characteristics of all participants are shown in *Table 1*. For training set, there were 1,080 Males (87.24%). Patients <65 years accounted for 55.01% and the percentage of White patients was 90.71%. Most patients (62.6%) were determined as grade III and the most common histologic type was adenocarcinoma (79.89%). There were 437 (35.3%), 100 (8.08%), 417 (33.68%), and 284 (22.94%) patients with T stage of T1, T2, T3 and T4, and 278 (22.46%), 707 (57.11%), 159 (12.84%), and 94 (7.59%) patients with N stage of N0, N1, N2 and N3, respectively. There were 914 (73.83%) patients who received chemotherapy, and 583 (47.09%) patients who received radiotherapy.

Univariate and multivariate analyses

Univariate analysis on factors was conducted to identify the possible prognosis factors. As shown in *Figure 2*, the forest plot illustrates the hazard ratio (HR) and 95% confidence interval (CI) of the DSS. Based on the results of univariate analysis (*Table 2*), variables, including age, histology, T stage, and chemotherapy were considered as candidates for multivariate analyses.

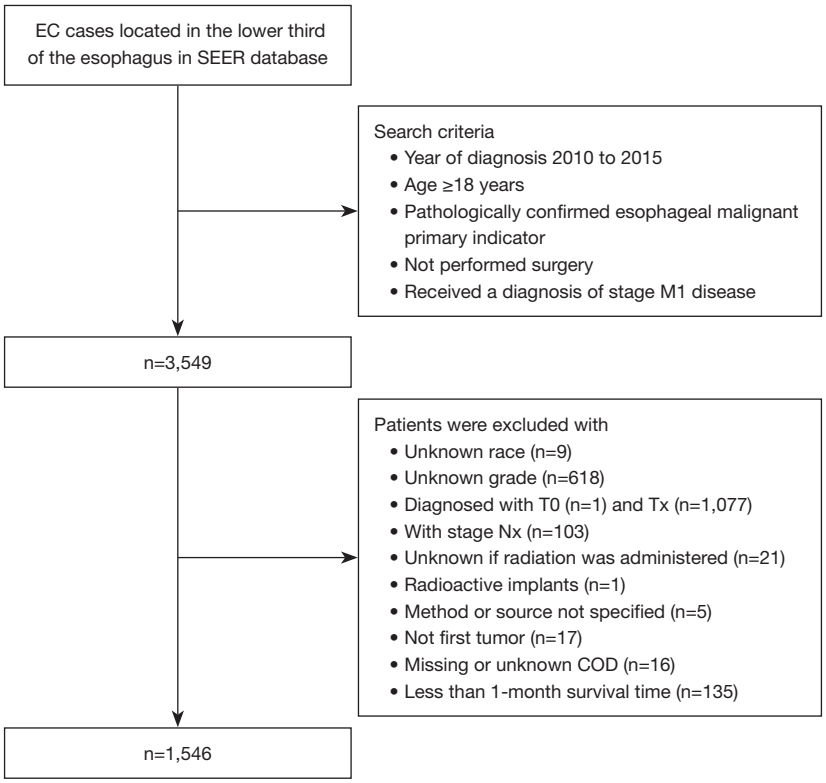

Figure 1 Flowchart of patient selection. EC, esophagus carcinoma; SEER, Surveillance, Epidemiology, and End Results; COD, cause of death.

Construction and validation of the nomogram

The results of multivariate analysis showed that histology, T stage, and chemotherapy were independent risk factors related to the prognosis of patients with aLEC (*Figure 2*). The variables were integrated to develop a prognostic nomogram for predicting 6-month, 1-year and 2-year survival of patients with aLEC (*Figure 3*).

ROC curve analysis was also used to assess the predictive capacity of the nomogram. As shown in *Figure 4*, the model had high AUC values. The AUCs for 6-month, 1-year, and 2-year DSS prediction in the training set were 0.742, 0.685, and 0.637, respectively. Similarly, in the validation set, the AUCs for 6-month, 1-year, and 2-year DSS prediction were 0.701, 0.679, and 0.752, respectively. The calibration curve shows that the 45° dashed line represents the ideal performance. This nomogram matched with the actual survival rates in both training and validation sets (*Figure 5*). Further, *Figure 6* presents the clinical utility of the model. These results demonstrated that the model combining clinicopathologic characteristics has high potential for clinical application.

General clinical characteristics of patients based on T-stage stratification

We found that patients with stage T1NanyM1 had poor survival. As the prognosis of patients with stage T1 showed specificities in the present study, we performed a T-stage stratified analysis to clarify the factors associated with the prognosis of aLEC. The differences in general clinical characteristics between patients with T1 stage and those with T2-4 stage are shown in *Table 3*. No significant differences were found between the two groups regarding sex, age, race, grade, and histology (P>0.05). However, the proportion of patients with stage N0M1 was significantly higher in patients with stage T1 than that in patients with stage T2-4 (P<0.001). This suggests that aLEC patients with stage T1 are more likely to have distant organ metastases without lymph node metastases. In addition, significantly fewer patients with stage T1NanyM1 aLEC received chemotherapy (P=0.004) or radiotherapy (P<0.001) than patients with stage T2-4NanyM1.

Table 1 Patient characteristics (n=1,546)

Variable	Training set (n=1,238)	Validation set (n=308)	P
Sex			0.64
Female	158 (12.76)	43 (13.96)	
Male	1,080 (87.24)	265 (86.04)	
Age			>0.99
<65 years	681 (55.01)	169 (54.87)	
≥65 years	557 (44.99)	139 (45.13)	
Race			0.45
Black	70 (5.65)	17 (5.52)	
White	1,123 (90.71)	275 (89.29)	
Other	45 (3.63)	16 (5.19)	
Year of diagnosis			0.49
2010	192 (15.51)	57 (18.51)	
2011	218 (17.61)	41 (13.31)	
2012	200 (16.16)	50 (16.23)	
2013	209 (16.88)	54 (17.53)	
2014	193 (15.59)	46 (14.94)	
2015	226 (18.26)	60 (19.48)	
Grade†			0.81
I	43 (3.47)	8 (2.60)	
II	397 (32.07)	105 (34.09)	
III	775 (62.6)	189 (61.36)	
IV	23 (1.86)	6 (1.95)	
Histology			0.29
EAC	989 (79.89)	241 (78.25)	
ESCC	143 (11.55)	32 (10.39)	
Other	106 (8.56)	35 (11.36)	
T stage			0.37
T1	437 (35.3)	107 (34.74)	
T2	100 (8.08)	20 (6.49)	
T3	417 (33.68)	97 (31.49)	
T4	284 (22.94)	84 (27.27)	
N stage			0.63
N0	278 (22.46)	68 (22.08)	
N1	707 (57.11)	181 (58.77)	
N2	159 (12.84)	42 (13.64)	
N3	94 (7.59)	17 (5.52)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Training set (n=1,238)	Validation set (n=308)	P
Chemotherapy			0.16
No	324 (26.17)	68 (22.08)	
Yes	914 (73.83)	240 (77.92)	
Radiotherapy			0.66
No	655 (52.91)	158 (51.3)	
Yes	583 (47.09)	150 (48.7)	

Data are presented as n (%). †, Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

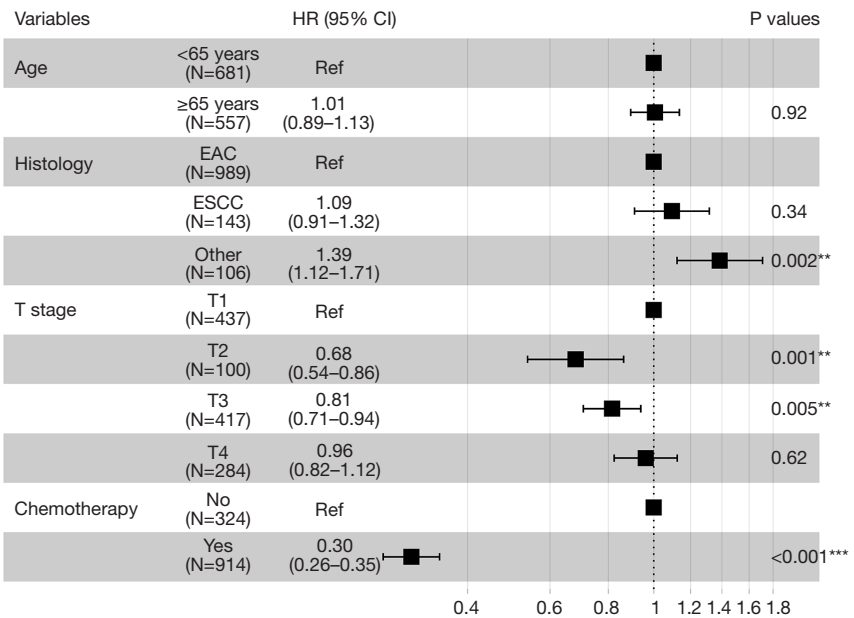

Figure 2 Forest plot presenting the result of multivariate analysis of different variables. **, P<0.01; ***, P<0.001. HR, hazard ratio; CI, confidence interval; Ref, reference; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

Kaplan-Meier survival analysis

As shown in *Figure 7A*, in patients with stage N0M1, T stage did not affect survival outcome (HR =0.97, 95% CI: 0.78–1.22; P=0.80). However, in patients with stage N1-3M1, patients with stage T1 survived significantly shorter in time than patients with T2-4 stage (*Figure 7B*, HR =0.78, 95% CI: 0.69–0.89; P<0.001). Survival of nonchemotherapy patients did not differ by T stage (*Figure 7C*, HR =0.82, 95% CI: 0.67–1.01; P=0.06). However, among metastatic patients who received chemotherapy, patients with stage T2-4 had better survival than those with stage T1 (*Figure 7D*, HR =0.87, 95% CI: 0.76–0.99; P=0.03). In addition, patients with stage T2-4 had a significantly better prognosis than patients with stage T1, with or without radiotherapy. Kaplan-Meier survival curves for non-radiotherapy patients (HR =0.85, 95% CI: 0.73–0.98; P=0.03) and patients treated with radiotherapy (HR =0.80, 95% CI: 0.68–0.95; P=0.01) are presented in *Figure 7E*,*7F*, respectively.

The effect of chemotherapy and radiotherapy on the prognosis of aLEC patients with stage T1NanyM1 is illustrated in *Figure 8*. Non-chemotherapy was significantly associated with poor survival of patients with stage T1 (*Figure 8A*, HR =3.15, 95% CI: 2.58–3.83; P<0.001).

Table 2 Univariate analysis for disease-specific survival

Variable	HR	95% CI	P
Sex			
Female		Ref	
Male	1.142	0.954–1.369	0.15
Age			
<65 years		Ref	
≥65 years	0.875	0.777–0.984	0.03
Race			
Black		Ref	
White	0.977	0.759–1.258	0.86
Other	0.933	0.63–1.38	0.73
Year of diagnosis			
2010		Ref	
2011	0.92	0.755–1.121	0.41
2012	0.944	0.769–1.158	0.58
2013	0.938	0.767–1.146	0.53
2014	0.977	0.795–1.2	0.82
2015	0.911	0.74–1.122	0.38
Grade†			
I		Ref	
II	1.023	0.729–1.435	0.90
III	1.228	0.882–1.71	0.22
IV	1.617	0.953–2.741	0.08
Histology			
EAC		Ref	
ESCC	1.231	1.026–1.478	0.03
Other	1.314	1.065–1.621	0.01
T stage			
T1		Ref	
T2	0.673	0.532–0.852	0.001
T3	0.779	0.676–0.898	0.001
T4	1.025	0.878–1.198	0.75
N stage			
N0		Ref	
N1	0.931	0.804–1.077	0.33
N2	0.906	0.738–1.114	0.35
N3	1.084	0.847–1.388	0.52
Chemotherapy			
No		Ref	
Yes	0.299	0.261–0.342	<0.001
Radiotherapy			
No		Ref	
Yes	0.921	0.819–1.035	0.17

†, Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. HR, hazard ratio; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

However, radiotherapy was found not to affect the outcome of patients with stage T1NanyM1 (*Figure 8B*, HR =0.98, 95% CI: 0.82–1.17; P=0.80).

Discussion

Timely detection and early surgery could significantly improve the clinical outcomes of patients with early-stage EC. In recent decades, continuous advancements have been made in surgical techniques. According to different pathological types, tumor locations and stages, the treatment strategy of each EC is varied (12). For example, Huscher *et al.* showed the feasibility, clinical utility, and safety of intrathoracic robotic-sewn esophageal anastomosis during Ivor Lewis esophagectomy for adenocarcinoma of the lower third of the esophagus, or cancer at the gastro-esophageal junction type I (Siewert classification) (13). Moreover, with the increasing use of immunotherapy in EC, surgical resection combined with neoadjuvant or adjuvant therapy has been proven to improve the outcome (14). However, the prognosis for advanced EC is still poor (1,12). Due to the high individual heterogeneity of different patients, their survival time varies widely (15). This study established a nomogram to predict the survival in patients with aLEC based on general demographic and clinicopathologic data. The predictors included in this nomogram model can be easily obtained from clinical practice, which represent a reference for early identification of high-risk groups.

Histology features are important predictor of outcome of patients diagnosed with EC. Xi *et al.* suggested that ESCC was associated with a substantially higher pathological complete remission (pCR) rate than EAC, and survival

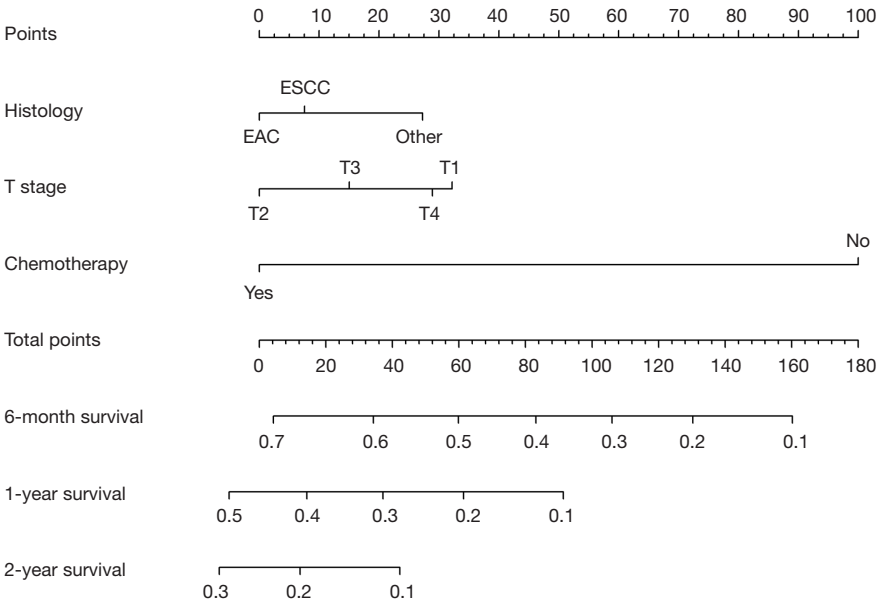

Figure 3 Nomogram predicting the outcome. Nomogram was used to predict the 6-month, 1-year, and 2-year DSS rates of patients with aLEC. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; DSS, disease-specific survival; aLEC, advanced lower third esophageal carcinoma.

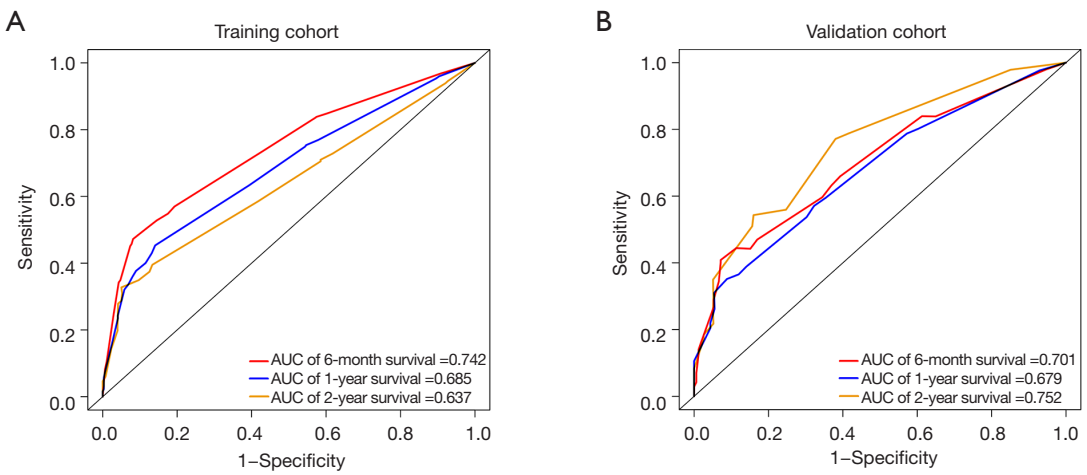

Figure 4 ROC curves of the nomogram. (A) The AUC values of time-dependent ROC curves in the nomogram predicting 6-month, 1-year, and 2-year DSS rates in the training set. (B) The AUC values of time-dependent ROC curves in the nomogram predicting 6-month, 1-year, and 2-year DSS rates in the validation set. AUC, area under the curve; ROC, receiver operating characteristic; DSS, disease-specific survival.

times and recurrence patterns significantly varied between these two histology types (16). Similarly, Saeed *et al.* proposed that the treatment regimen for EC patients should be based on histology type and tumor location (17). For patients with aLEC, individuals with EAC had a better clinical outcome than those with other pathological types. Esophageal wall is rich in lymphoid tissue, infiltration into the submucosa may lead to distant lymphatic metastases or extensive jumping metastases (18-20). In addition, Ludmir *et al.* reported that direct infiltration and metastasis can

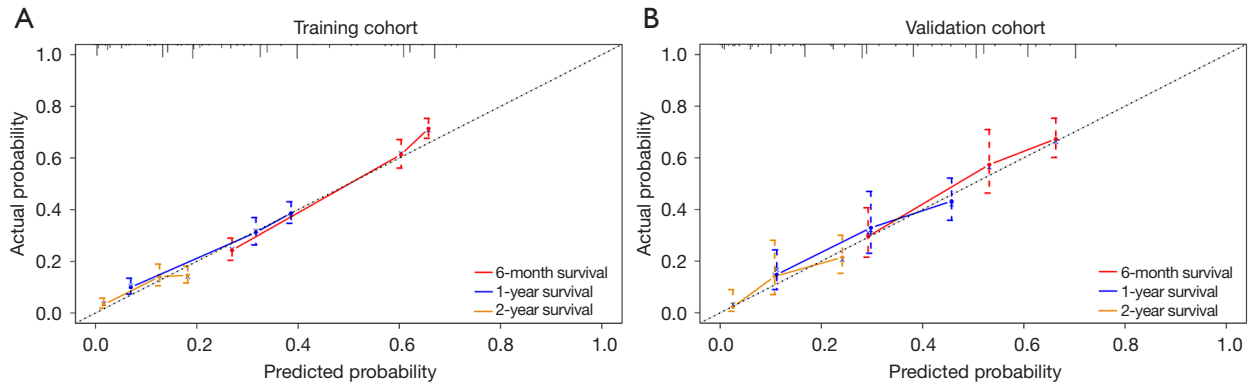

Figure 5 The calibration curve for predicting patients with aLEC at 6 months, 1 year, and 2 years. (A) The training set. (B) The validation set. aLEC, advanced lower third esophageal carcinoma.

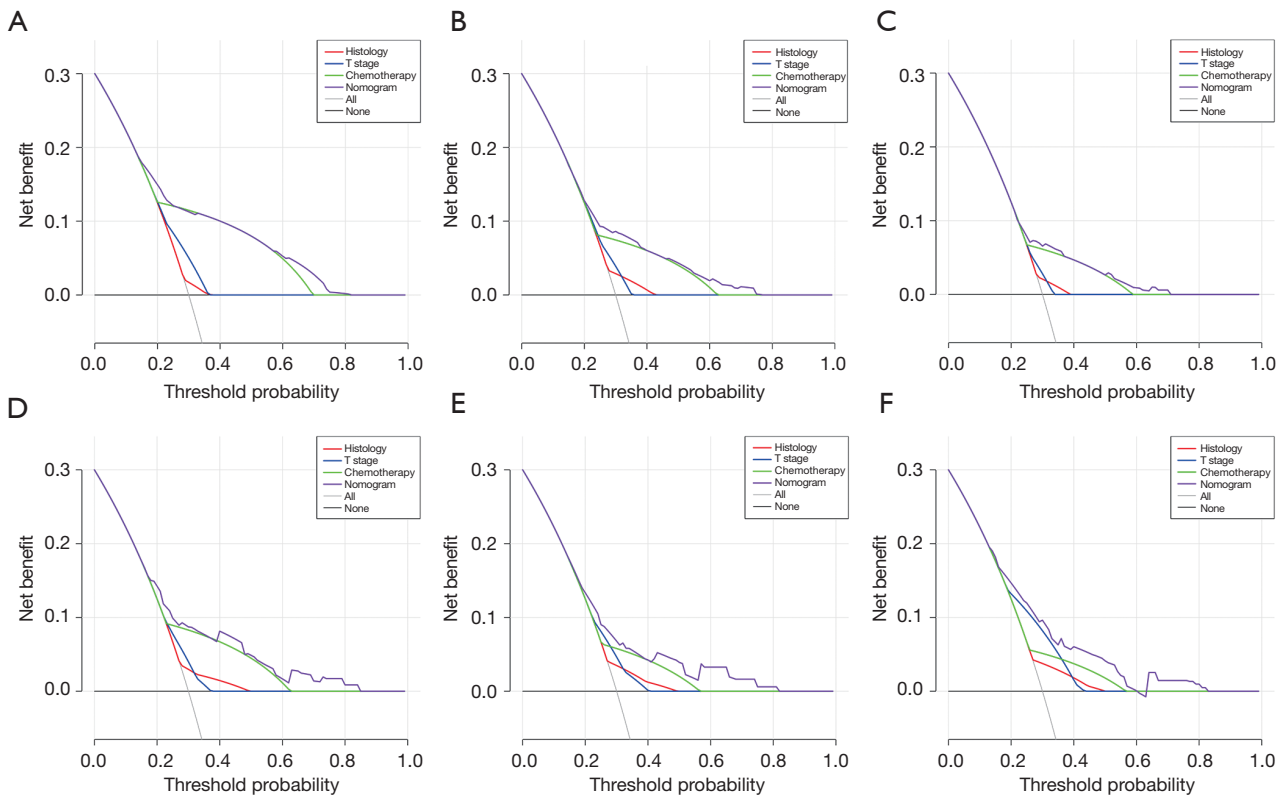

Figure 6 DCA of the nomogram. The 6-month (A), 1-year (B), and 2-year (C) DSS rates based on DCA of nomogram in the training set. The 6-month (D), 1-year (E), and 2-year (F) DSS rates based on DCA of nomogram in the validation set. DCA, decision curve analysis; DSS, disease-specific survival.

occur in the early stage of EC (21). Survival analysis is necessary for patients with EC at early T stage and distant metastases. Notably, the nomogram established in this study showed that among patients with aLEC, survival time was better in patients with stage T2/T3 than in patients with T1 disease, indicating relatively poor prognosis of patients with stage T1 aLEC.

Advanced EC is mainly treated with chemotherapy and

Table 3 Patient characteristics based on the stratification factor of stage T1

Variable	T1 (n=544)	T2–T4 (n=1,002)	P
Sex			0.97
Female	70	131	
Male	474	871	
Age			0.87
<65 years	297	553	
≥65 years	247	449	
Race			0.13
Black	24	63	
White	503	895	
Other	17	44	
Grade[†]			0.93
I	16	35	
II	180	322	
III	338	626	
IV	10	19	
Histology			0.76
EAC	429	801	
ESCC	66	109	
Other	49	92	
N stage			<0.001
N0	188	158	
N1-3	356	844	
Chemotherapy			0.004
No	162	230	
Yes	382	772	
Radiotherapy			<0.001
No	338	475	
Yes	206	527	

[†], Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

the best supportive care. Compared to the best supportive care, chemotherapy significantly prolongs survival time and improves the quality of life in patients with advanced EC. Chemotherapy plays an essential role in the treatment of advanced EC (22,23). However, EC patients often present feeding difficulties and poor nutrition, along with rapid disease progression. Therefore, chemotherapy should be carefully selected. For advanced EC patients suffering poor general condition, hemotherapy can temporarily inhibit patients' disease progression; however, it also triggers many adverse effects and reduce the patient's motivation for undertaking the treatment. Furthermore, Rajagopal *et al.* reported that chemotherapy did not confer a survival benefit in patients with advanced EC (24). It is necessary to evaluate the effect of chemotherapy on the survival time of advanced EC patients. In this study, we found that chemotherapy has a significant benefit on DSS in patients with aLEC.

The clinical staging of patients with malignant tumors is of great significance for prognosis evaluation and guidance of treatment. Tumor staging has great influence on the clinical decision-making process and the clinical outcome of patients (25). This study involved in 1,546 patients with aLEC. Multivariate Cox regression analysis suggested that histology, T stage, and chemotherapy were associated with DSS in patients with aLEC. The calibration curves showed good linearity. In addition, DCA demonstrated that the model resulted in optimal net benefit, suggesting that the nomogram has an excellent predictive value. Therefore, we believe that our nomogram can be used to optimize treatment regimens and follow-up management.

Primary esophageal lesions are usually less symptomatic in stage T1 than that in stage T2-4, which may lead the patients to seek medical attention much later. Previous studies have reported that patients with metastatic EC could still gain survival benefits from radiochemotherapy (26,27). The evidence on the current treatment status of EC patients with stage IV remains insufficient. The study showed that the proportion of patients with stage T1NanyM1 who received chemotherapy or radiotherapy was significantly lower than that of patients with stage T2-4NanyM1. This is consistent with adverse outcomes in patients with stage T1NanyM1. We also found no difference in survival time between non-chemotherapy patients with stage T1NanyM1 and those with stage T2-4NanyM1. Among patients who received chemotherapy, those with stage T2-4NanyM1 had a better prognosis. However, aLEC patients with stage T1NanyM1 still had a significant survival benefit from chemotherapy, which is consistent with the previously reported effect of chemotherapy on survival in patients with advanced EC (28,29).

Furthermore, we did not find a survival advantage for patients with aLEC who received radiotherapy. However,

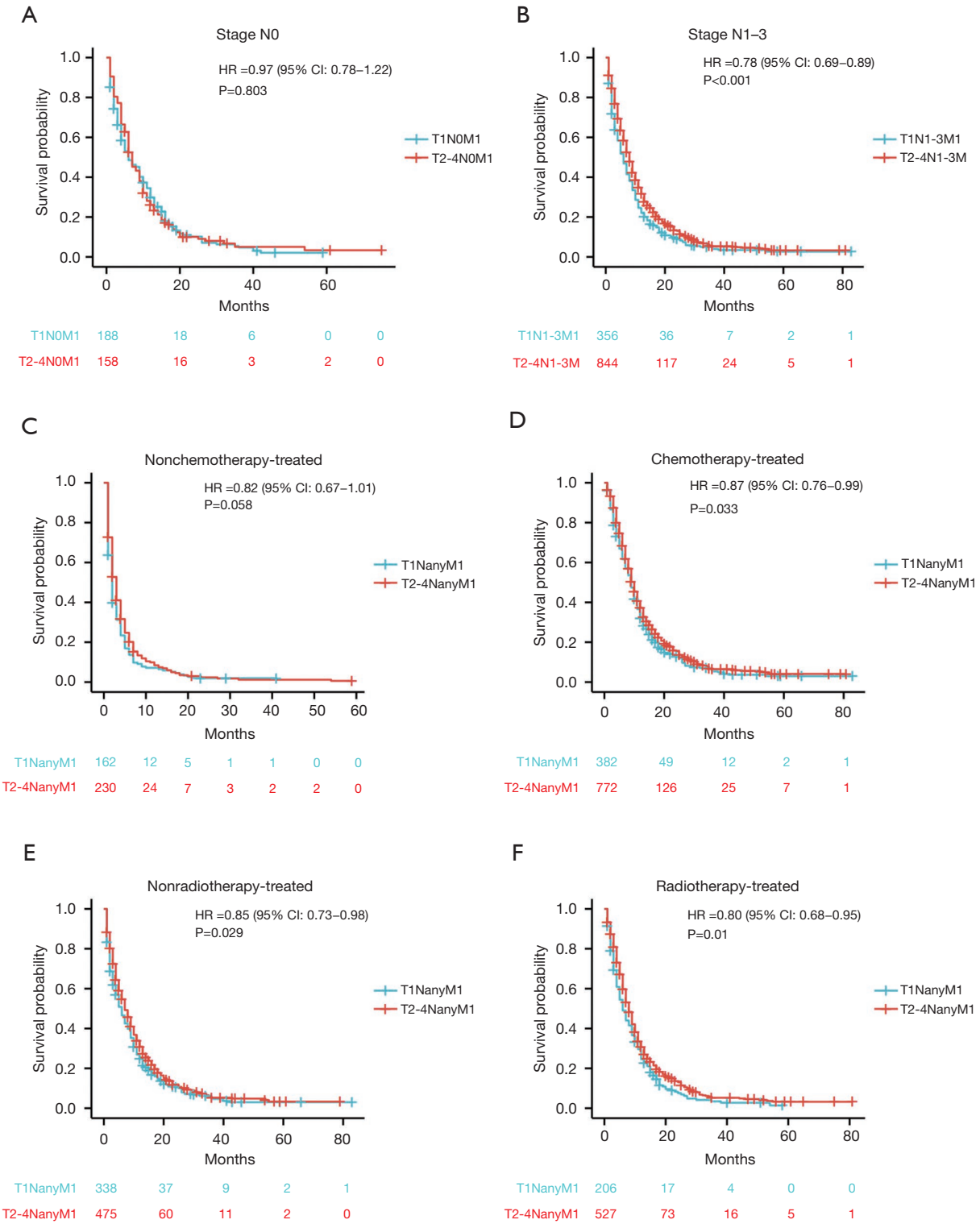

Figure 7 Disease-specific survival of patients with aLEC according to N stage (A,B), chemotherapy (C,D), and radiotherapy (E,F). HR, hazard ratio; CI, confidence interval; aLEC, advanced lower third esophageal carcinoma.

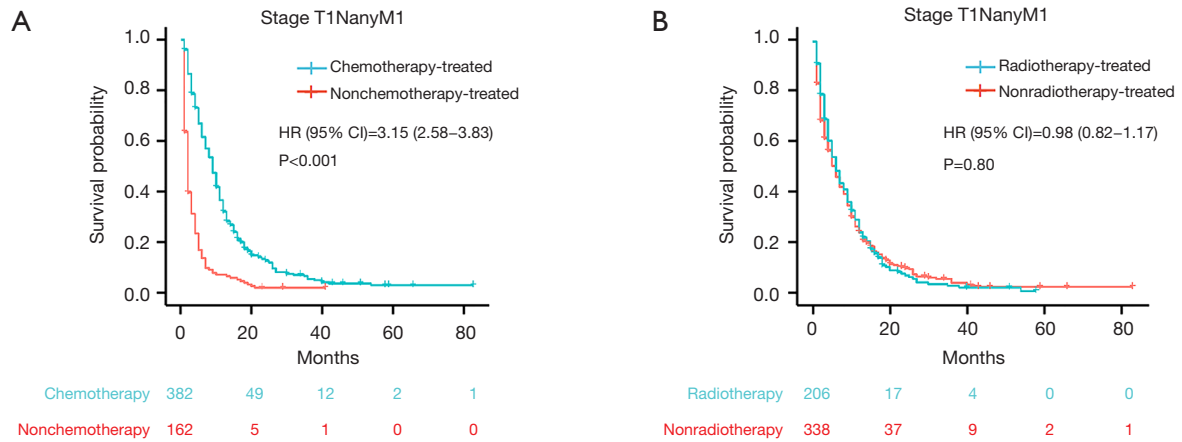

Figure 8 Disease-specific survival of aLEC patients with stage T1NanyM1. HR, hazard ratio; CI, confidence interval; aLEC, advanced lower third esophageal carcinoma.

Zhang *et al.* suggested that radiotherapy for patients with metastatic EC markedly improved prognosis (30). In contrast to present study, the study of Zhang only included patients with ESCC (30). Prospective randomized studies are still necessary.

Conclusions

In summary, three variables derived from the multivariate analysis were integrated into the nomogram construction, which was validated and showed good predictive power. Moreover, our results suggested that chemotherapy could improve survival time of aLEC patients, which might serve as a reference for clinical application. Nevertheless, there are some limitations in this study. Firstly, this was a retrospective study based on the SEER data, indicating the need for further external validation. Secondly, as chemotherapy regimens were not provided in the SEER database, evaluations of chemotherapy regimens on patient outcomes are still needed in the future.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1116/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1116/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).

References

1. Nierengarten MB. Global cancer statistics 2022: The

report offers a view on disparities in the incidence and mortality of cancer by sex and region worldwide and on the areas needing attention. Cancer 2024;130:2568.
2. O'Connor HJ. Forty years of Helicobacter pylori infection and changes in findings at esophagogastroduodenoscopy. Helicobacter 2023;28:e13026.
3. Jain S, Dhingra S. Pathology of esophageal cancer and Barrett's esophagus. Ann Cardiothorac Surg 2017;6:99-109.
4. Cherian JV, Sivaraman R, Muthusamy AK, et al. Carcinoma of the esophagus in Tamil Nadu (South India): 16-year trends from a tertiary center. J Gastrointestin Liver Dis 2007;16:245-9.
5. Ai D, Chen Y, Liu Q, et al. The effect of tumor locations of esophageal cancer on the metastasis to liver or lung. J Thorac Dis 2019;11:4205-10.
6. Lagergren J, Smyth E, Cunningham D, et al. Oesophageal cancer. Lancet 2017;390:2383-96.
7. Van Daele E, Scuderi V, Pape E, et al. Long-term survival after multimodality therapy including surgery for metastatic esophageal cancer. Acta Chir Belg 2018;118:227-32.
8. Blank S, Lordick F, Dobritz M, et al. A reliable risk score for stage IV esophagogastric cancer. Eur J Surg Oncol 2013;39:823-30.
9. Hu B, Zhu Y, Wu X. Comparison of prognostic factors of esophageal cancer between a Chinese cohort and the Surveillance, Epidemiology, and End Results (SEER) database: a retrospective cohort study. J Gastrointest Oncol 2022;13:527-38.
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
11. Zhou Y, Mo S, Cui H, et al. Immune-tumor interaction dictates spatially directed evolution of esophageal squamous cell carcinoma. Natl Sci Rev 2024;11:nwae150.
12. Deboever N, Jones CM, Yamashita K, et al. Advances in diagnosis and management of cancer of the esophagus. BMJ 2024;385:e074962.
13. Huscher CGS, Cobellis F, Lazzarin G. Intrathoracic Robotic-Sewn Anastomosis During Ivor Lewis Esophagectomy for Cancer: Back to Basics? J Gastrointest Surg 2023;27:1034-41.
14. Park D, Jeon WJ, Yang C, et al. Advancing Esophageal Cancer Treatment: Immunotherapy in Neoadjuvant and Adjuvant Settings. Cancers (Basel) 2024;16:318.
15. Brosda S, Aoude LG, Bonazzi VF, et al. Spatial intra-tumour heterogeneity and treatment-induced genomic evolution in oesophageal adenocarcinoma: implications for prognosis and therapy. Genome Med 2024;16:90.
16. Xi M, Yang Y, Zhang L, et al. Multi-institutional Analysis of Recurrence and Survival After Neoadjuvant Chemoradiotherapy of Esophageal Cancer: Impact of Histology on Recurrence Patterns and Outcomes. Ann Surg 2019;269:663-70.
17. Saeed SM, Naffouje S, Mehta R, et al. Impact of histology classification on pathologic treatment response and overall survival in distal esophageal cancer patients: a propensity matched analysis. Dis Esophagus 2021;34:doaa099.
18. Wang Y, Zhu L, Xia W, et al. Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. Cancer Manag Res 2018;10:6295-303.
19. Tang X, Zhou X, Li Y, et al. A Novel Nomogram and Risk Classification System Predicting the Cancer-Specific Survival of Patients with Initially Diagnosed Metastatic Esophageal Cancer: A SEER-Based Study. Ann Surg Oncol 2019;26:321-8.
20. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.
21. Ludmir EB, Robey B, Shelby E, et al. Skeletal muscle metastasis from signet ring cell esophageal adenocarcinoma. Transl Gastroenterol Hepatol 2016;1:37.
22. Sobajima J, Kumamoto K, Haga N, et al. Early evaluation of the apoptotic index ratio is useful in predicting the efficacy of chemoradiotherapy in esophageal squamous cell carcinoma. Oncol Lett 2012;3:287-92.
23. Creemers A, Ter Veer E, de Waal L, et al. Discordance in HER2 Status in Gastro-esophageal Adenocarcinomas: A Systematic Review and Meta-analysis. Sci Rep 2017;7:3135.
24. Rajagopal PS, Nipp RD, Selvaggi KJ. Chemotherapy for advanced cancers. Ann Palliat Med 2014;3:203-28.
25. Goense L, van Rossum PS, Kandioler D, et al. Stage-directed individualized therapy in esophageal cancer. Ann N Y Acad Sci 2016;1381:50-65.
26. Qiu B, Zhou Y, Lou M, et al. The Effect of the Appropriate Timing of Radiotherapy on Survival Benefit in Patients with Metastatic Esophageal Cancer Who Have Undergone Resection of Primary Site: A SEER Database Analysis. J Oncol 2022;2022:6086953.
27. Shao Y, Zhang M, Ye L, et al. Survival differences between chemotherapy and chemoradiotherapy in metastatic esophageal cancer: a propensity score-matched study based on the SEER database. Ann Palliat Med 2021;10:3826-35.
28. Midthun L, Kim S, Hendifar A, et al. Chemotherapy predictors and a time-dependent chemotherapy effect in metastatic esophageal cancer. World J Gastrointest Oncol

2022;14:511-24.
29. Huang J, Xu B, Liu Y, et al. Irinotecan plus S-1 versus S-1 in patients with previously treated recurrent or metastatic esophageal cancer (ESWN 01): a prospective randomized, multicenter, open-labeled phase 3 trial. Cancer Commun (Lond) 2019;39:16.
30. Zhang R, Jia M, Li P, et al. Radiotherapy improves the survival of patients with metastatic esophageal squamous cell carcinoma: a propensity score matched analysis of Surveillance, Epidemiology, and End Results database. Dis Esophagus 2019. doi: 10.1093/dote/doy074.

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