Comparisons of prognosis prediction accuracy between modified and unmodified versions of 8th edition ypTNM

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Background: The prognostic value of the existing 8th edition post-neoadjuvant treatment (ypTNM) appears to be limited, and necessary reassessment and modification should be carried out as needed. This study aimed to compare the prognosis prediction accuracy of modified and unmodified versions of the 8th edition ypTNM.

Methods: Esophageal cancer patients who had received neoadjuvant therapy from the Surveillance, Epidemiology, and End Results (SEER) database were included in this observational longitudinal study. The median follow-up time was 26 months. All-cause mortality was the outcome variable. Demographic and clinical variables were collected as covariates. Kaplan-Meier (log-rank test) and Cox proportional hazards models were conducted for developing modified ypTNM staging. The concordance index (C-index) was calculated to analyze the discriminative ability of modified ypTNM staging.

Results: Overall, 3,595 patients met inclusion criteria. The 8th edition staging was not able to significantly discriminate between patients with ypT1- and ypT2-, ypT3- and ypT4-, ypN2- and ypN3- disease, respectively. Using the modified staging, we found that patients with ypT0–2 [hazard ratio (HR) =1.232; 95% confidence interval (CI): 1.053–1.441] and ypT3–4 (HR =1.257; 95% CI: 1.136–1.390) with grade III + IV had a significant risk of death compared to those with grade I + II. As was the case for the ypN0 (HR =1.295; 95% CI: 1.073–1.562) group with middle and upper tumor locations compared to those with low tumor location. The modified staging possessed better homogeneity in terms of the chi-square likelihood ratio (143.443 *vs.* 102.044), Akaike information criterion (AIC) (32,683.716 *vs.* 32,719.115), and Schwarz's Bayesian criterion (SBC) (32,723.496 *vs.* 32,741.847), as well as better discriminatory ability (C-index of 0.577 *vs.* 0.560, P=0.045) compared to the 8th edition staging.

Conclusions: Although the modified ypTNM staging system we created by incorporating tumor grade and location to the original T and N displayed certain prognosis prediction accuracy compared with the 8th edition ypTNM staging, a larger sample size and prospective studies are needed to explore.

Keywords: Surveillance, Epidemiology, and End Results (SEER); esophageal cancer; ypTNM; grade; modified

Submitted Mar 07, 2022. Accepted for publication May 20, 2022.

doi: 10.21037/atm-22-2353

View this article at: https://dx.doi.org/10.21037/atm-22-2353

Introduction

Esophageal cancer ranks ninth in terms of incidence and sixth in terms of mortality among all malignancies worldwide (1,2). The complex anatomy of the mediastinum, coupled with high recurrence rates of esophageal cancer, leads to poor results in various traditional surgical interventions (3,4). It has been reported that preoperative chemoradiotherapy and chemotherapy could improve the prognosis of patients more than surgery alone, and neoadjuvant therapy has been used as the standard treatment for locally advanced esophageal cancer (5,6). For esophageal cancer, tumor staging after neoadjuvant therapy seems to be more predictive of the long-term prognosis of patients than the clinical stage before neoadjuvant therapy (7).

As the addition of neoadjuvant therapy has replaced simple esophagectomy and is associated with tumor down staging the pathological staging of advanced cancers has gradually lost its clinical significance (8). To help rectify this, the 8th edition of the post-neoadjuvant treatment staging (ypTNM) system was first proposed in the American Joint Committee on Cancer (AJCC) in 2017 (9). However, the prognostic power of the 8th ypTNM staging system remains unclear. To evaluate whether the pathologic staging system after neoadjuvant therapy distinguishes the survival of patients who had received radiotherapy (chemotherapy) followed by surgery for esophageal cancer, Yuan *et al.* supported the combination of ypT1 and ypT2 in the 8th edition of ypTNM staging system, and the modified staging has better performance than the 8th edition of ypTNM staging (10). Furthermore, ypTNM is not consistent with the pathological staging (pTNM) of patients receiving esophagectomy alone, and there is no equivalent staging between ypTisN0–3M0 and ypT0N0–3M0 in pTNM (11). In addition, the prognosis of early and middle-stage patients after neoadjuvant therapy is relatively worse, the 8th edition of ypTNM staging was not appropriate (11). A previous study found that the prognostic value of ypTN classification appears to be limited, and necessary reassessment and modification should be carried out as needed (12). Zhong *et al.* modified the ypTNM staging, developing a system that could more accurately assess the prognosis of patients with gastric cancer after neoadjuvant therapy compared with the AJCC 8th edition ypTNM staging (13). However, there are few studies on improving the ypTNM staging system for esophageal cancer.

In the 8th edition of pTNM staging, the pathological staging of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) is distinguishable, and the tumor location was added to the staging of ESCC. In addition, tumor grade is an independent predictor of total survival, which could improve the effect of ypTNM staging (10). It is important to improve the integration of 8th edition of ypTNM staging and to add some clinical variables to improve the prediction accuracy.

Thus, this study aimed to develop an improved ypTNM staging using T and N stages as well as tumor grade and location, and compare the prognosis prediction accuracy of modified and unmodified versions of the 8th edition ypTNM. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2353/rc).

Methods

Study design and population

The data of this observational longitudinal study were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18 Regs Research database (USA) from 2000 to 2015, which covers about 30% of the US population (14). This study was exempted from the Institutional Review Board approval because all data collected from SEER was de-identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The International Classification of Diseases for Oncology (ICD-O) tumor site codes C15.0 to C15.9 were used to identify esophageal cancer patients. The histological types were categorized into EAC (8140-8575) and ESCC (8440-8499). In this study, 92,534 patients were sampled. The inclusion criteria were as follows: (I) patients who definitively received radiotherapy before surgery, as it was not clear from the SEER data whether the chemotherapy time was before or after surgery; and (II) tumor location was the upper, middle, and lower one-third of esophagus. The exclusion criteria were as follows: (I) patients who did not receive radiotherapy before surgery; (II) patients with overlapping lesions of the esophagus and the thoracic esophagus because the pathological staging of the version at that time was uncertain for the definition of the tumor location; (III) pathologies other than ESCC or EAC, and distal metastases present at primary diagnosis; and (IV) patients with missing data.

Outcome variable

The primary outcome variable of this study was the all-

Table 1 AJCC 8th ypTNM staging for esophageal cancer after neoadjuvant therapy

T category	N category			
	N0	N1	N2	N3
T0 + T1 + T2	I	IIIA	IIIB	IVA
T3	II	IIIB	IIIB	IVA
T4a	IIIB	IVA	IVA	IVA
T4b	IVA	IVA	IVA	IVA

AJCC, American Joint Committee on Cancer.

Table 2 The modified ypTNM staging for esophageal cancer after neoadjuvant therapy

T category	Grade	N category			
		N0		N1	N2
		L	M + U	L + M + U	L + M + U
T0 + T1 + T2	I + II	IA	IIA	IIB	IIIA
	III + IV	IB	IIB	IIC	IIIB
T3 + T4	I + II	IB	IIB	IIC	IIIB
	III + IV	IIA	IIC	IIC	IV

L, M, and U were the lower, middle, and upper tumor locations, respectively.

cause mortality, which obtained from the SEER database records. The shortest follow-up time was 2 months and the longest follow-up time was 83 months.

The 8th edition of the AJCC ypTNM staging

The definitions for the T, N, and M stages were the primary tumor, regional lymph nodes, and distant metastasis, respectively. Specifically, cancer invading the lamina propria, muscularis mucosae, or submucosa was defined as T1; cancer invading the muscularis propria was defined as T2; cancer invading the adventitia was defined as T3; and cancer invading the local structures was defined as T4. Also, N was defined as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (metastases involving three to six nodes), and N3 (metastases involving seven or more nodes). Furthermore, M was categorized as M0 (no distant metastasis) and M1 (distant metastasis) (8).

Table 1 shows the detailed staging in the 8th edition was as follows: (I) under N0, T0–2 were combined into stage I, T3 into stage II, T4a into stage IIIB, and T4b into stage IVA; (II) under N1, T0–2 were merged into stage IIIA, T3 into stage IIIB, and T4a and T4b were in stage IVA; (III) under N2, T0–3 were combined into stage IIIB, T4a and T4b were in stage IVA; and (IV) the entire T category were in the stage IVA under N3 (*Tables 1,2*). As for the pathologic classification of patients, the ypT, and ypN categories were characterized according to the 8th ypTNM staging system. Specimens analyzed before 2017 were respectively reclassified under the 8th edition TNM staging system. The tumors were pathologically categorized as grade I (well-differentiated), grade II (moderately differentiated), grade III (poorly differentiated), or grade IV (undifferentiated/anaplastic).

Covariates

The following demographic and clinicopathologic were collected from the SEER database: year of diagnosis, age of diagnosis, sex, race, histologic type, and treatment strategies.

Statistical analysis

The characteristics of the study population were analyzed descriptively according to the number of cases and the composition ratio [n (%)]. Non-normal continuous variables were described as the median and interquartile range [M (Q1, Q2)]. Missing data were deleted. Overall survival (OS) was defined as the time between diagnosis and death due to any cause. Kaplan-Meier curves were constructed to analyze the OS and evaluate the staging systems, the log-rank tests were also utilized. Univariate and multivariate Cox regression models were used to analyze the influencing factors of death; the multivariate analyses for each staging system were adjusted for sex and radiation. The hazard ratio (HR) with 95% confidence interval (CI) was calculated.

The prognostic performance of both the modified and 8th edition ypTNM staging systems was compared in terms of homogeneity and discriminatory ability (13,15). Homogeneity was assessed according to the Chi-square likelihood ratio, and the Akaike information criterion (AIC) and Schwarz's Bayesian criterion (SBC) were used to compare the model fitting between the modified and 8th edition ypTNM staging (16,17). A higher Chi-square likelihood ratio and smaller AIC and SBC values indicated better homogeneity and greater prognostic value. Discriminatory ability was assessed using the concordance

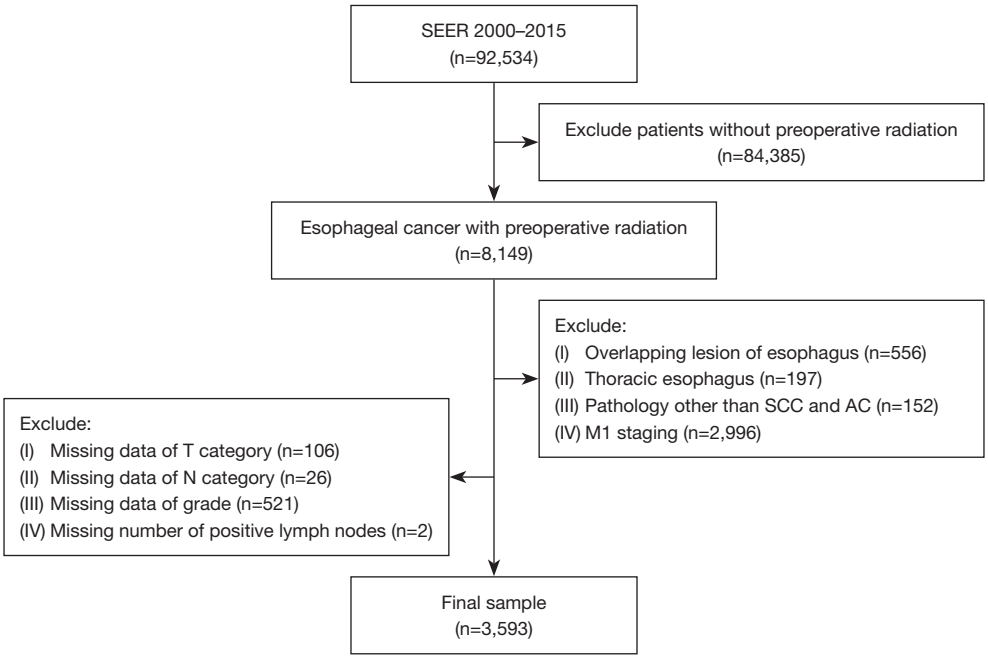

Figure 1 Systematic selection process flow chart. SEER, Surveillance, Epidemiology, and End Results; SCC, squamous cell carcinoma; AC, adenocarcinoma.

index (C-index) (18). R v.4.20 (R Foundation for Statistical Computing, Vienna, Austria) software was used to analyze the predictive value of ypTNM and the modified staging on death, and the Delong test was used to examine the C-index in terms of age, gender, race, and radiation sequence with surgery stratification. A C-index value of 1.0 indicated that the model could separate patients with different outcomes, while a C-index value of 0.5 indicated that the model was not random and had little practical utility. We conducted subgroup analyses to evaluate the predictive ability of the improved ypTNM staging in different sexes, races, ages, histologic types, and chemotherapies.

All statistical tests were two-sided, and $P<0.05$ was considered to indicate statistically significant differences. All statistical analysis was completed using SAS v.9.4 (SAS Institute, Cary, NC, USA) and R v.4.20 (R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Baseline characteristics

A total of 92,534 patients were sampled. We excluded patients who did not receive radiotherapy before surgery (n=84,385). Among those who received preoperative radiation, we used the upper, middle, and lower one-third to determine the tumor location, and excluded patients with overlapping lesions of the esophagus (n=556) and thoracic esophagus (n=197). Pathologies other than ESCC or EAC (n=152) and M1 staging (n=2,996) were also excluded from the analysis cohort. In addition, patients with missing data of T category (n=106), N category (n=26), grade (n=521), and number of positive lymph nodes (n=2) were excluded. A total of 3,593 patients comprised the final analytic sample (*Figure 1*). Table S1 demonstrates the sociodemographic and clinicopathologic characteristics of the included patients. In terms of the patients' races, the majority were white (91.43%), followed by black (4.87%), other races (3.59%), and unknown (0.11%). As for the gender distribution, males accounted for 84.44%, while females accounted for 15.56%. The median follow-up time was 26 months (range, 14–50 months).

Prognostic factors influencing survival in patients after neoadjuvant therapy

As shown in *Table 3*, the risk of death in males was 0.236 times higher (HR =1.236; 95% CI: 1.094–1.397) than that of females. In the 8th edition ypTNM staging, the risk

Table 3 Analysis of prognostic factors influencing survival in patients after neoadjuvant therapy

Variables	β	S.E	χ^2	P	HR	Lower	Upper
Age at diagnosis (years)							
20–29					Ref		
30–39	−0.020	0.471	0.002	0.967	0.980	0.389	2.470
40–49	−0.034	0.416	0.007	0.936	0.967	0.428	2.184
50–59	0.063	0.410	0.024	0.878	1.065	0.477	2.381
60–69	0.125	0.410	0.092	0.761	1.133	0.507	2.528
70–79	0.351	0.411	0.731	0.393	1.421	0.635	3.179
80–89	0.671	0.432	2.415	0.120	1.957	0.839	4.564
Sex							
Female					Ref		
Male	0.212	0.062	11.575	<0.001	1.236	1.094	1.397
Race							
Black					Ref		
Other	−0.067	0.148	0.205	0.651	0.935	0.700	1.249
Unknown	−1.199	1.003	1.430	0.232	0.301	0.042	2.152
White	−0.141	0.094	2.265	0.132	0.869	0.723	1.044
8th ypTNM							
Stage I					Ref		
Stage II	0.122	0.082	2.195	0.138	1.129	0.962	1.326
Stage IIIA	0.093	0.097	0.919	0.338	1.097	0.908	1.326
Stage IIIB	0.461	0.070	43.811	<0.001	1.585	1.383	1.817
Stage IVA	0.654	0.093	49.143	<0.001	1.923	1.602	2.309
Histologic type							
ESCC					Ref		
EAC	0.039	0.055	0.504	0.478	1.039	0.934	1.157
ypT category							
T1					Ref		
T0	1.205	1.002	1.446	0.229	3.336	0.468	23.777
T2	−0.004	0.080	0.002	0.960	0.996	0.851	1.166
T3	0.278	0.065	18.119	<0.001	1.320	1.162	1.501
T4	0.350	0.101	11.992	<0.001	1.419	1.164	1.729
ypN category							
N0					Ref		
N1	0.276	0.049	31.156	<0.001	1.317	1.196	1.451
N2	0.497	0.069	52.358	<0.001	1.643	1.436	1.880
N3	0.702	0.087	65.408	<0.001	2.019	1.703	2.393

Table 3 (*continued*)

Table 3 (*continued*)

Variables	β	S.E	χ^2	P	HR	Lower	Upper
Grade							
Grade I					Ref		
Grade II	0.109	0.103	1.113	0.291	1.115	0.911	1.365
Grade III	0.348	0.102	11.672	<0.001	1.416	1.160	1.730
Grade IV	0.077	0.219	0.125	0.724	1.081	0.703	1.660
Tumor location							
Lower thoracic					Ref		
Middle thoracic	0.072	0.064	1.250	0.263	1.075	0.947	1.219
Upper thoracic	0.224	0.154	2.099	0.147	1.250	0.924	1.692
Radiation sequence with surgery							
Radiation before and after surgery					Ref		
Radiation prior to surgery	−0.234	0.111	4.416	0.036	0.791	0.636	0.984
Chemotherapy							
No/unknown					Ref		
Yes	−0.322	0.166	3.770	0.052	0.725	0.524	1.003

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; S.E, standard error; HR, hazard ratio; Ref, reference.

of death was 0.585 times higher in stage IIIB (HR =1.585; 95% CI: 1.383–1.817) and 0.923 times in IVA (HR =1.923; 95% CI: 1.602–2.309) compared with those in stage I, respectively. Compared with ypT1 disease, ypT3 disease had a 0.320-fold increase in the risk of death (HR =1.320; 95% CI: 1.162–1.501), and ypT4 disease had a 0.419-fold increase (HR =1.419; 95% CI: 1.164–1.729). Furthermore, compared to ypN0 disease, the HRs for ypN1, N2, and N3 disease were 1.317 (95% CI: 1.196–1.451), 1.643 (95% CI: 1.436–1.880), and 2.019 (95% CI: 1.703–2.393), respectively. There were also significant differences observed between the HRs for grade I and grade III disease in the stratified Cox model [with grade I as the reference value: HR for grade III, 1.416 (95% CI: 1.160–1.730)], P<0.001.

The modified ypT- stage with grade proposed in this study

The Kaplan-Meier curves of both the 8th edition and the modified ypT- staging are shown in *Figure 2*. The 8th edition AJCC ypT- staging showed obvious overlapping between T1 and T2 disease, and between T3 and T4 disease (*Figure 2A*). However, a significant difference was identified in the survival curves for the different stages using the modified ypT- stage (T0 + T1 + T2, and T3 + T4) (*Figure 2B*).

In addition, no significant difference was observed between the HRs for grade II, grade III, and grade IV disease in patients with the ypT0–2 disease, using grade I as the reference (P>0.05; *Table 4*). As for patients with ypT3 and ypT4 disease, only grade III was statistically significant (HR =1.377; 95% CI: 1.070–1.772). After combining grade I + grade II and grade III + grade IV, the risk of death in patients with grade III + grade IV disease was significantly different compared to those with grade I + grade II disease in the ypT0–2 or ypT3–4 stages [(HR =1.232; 95% CI: 1.053–1.441) and (HR =1.257; 95% CI: 1.136–1.390), respectively].

The modified ypN- stage with tumor location proposed in this study

Using the 8th edition AJCC ypN- staging classification, the overlap between ypN2 and ypN3 disease was obvious, whereas differences were observed in the survival curves of different stages using the modified ypN- staging (N0, N1, and N2 + N3), as shown in *Figure 3*.

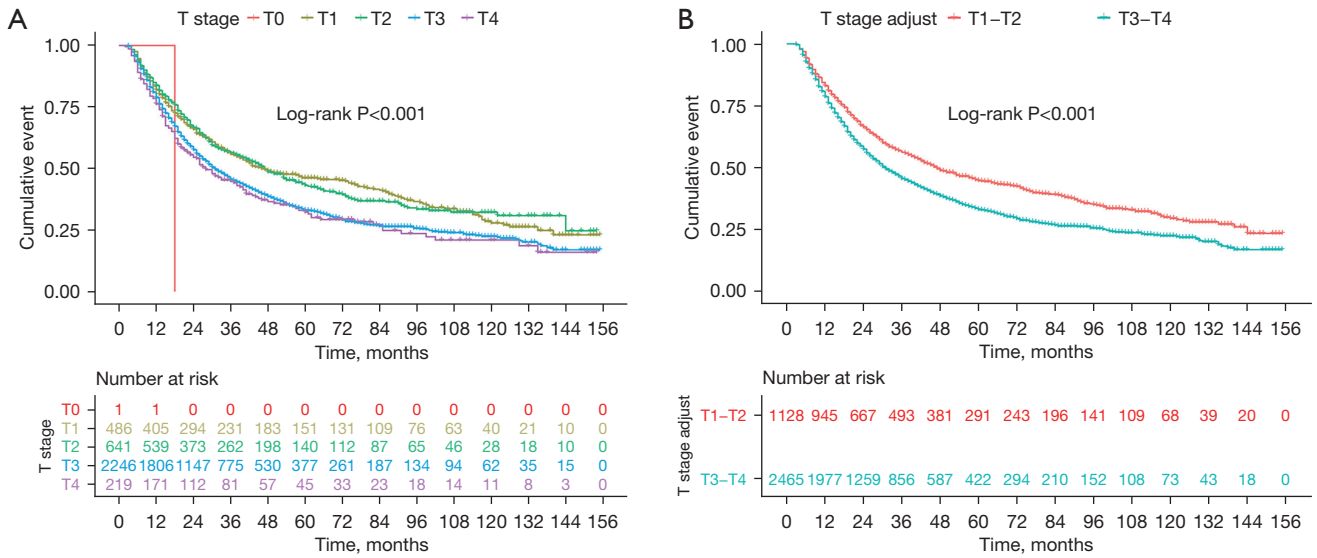

Figure 2 Survival analysis comparison of patients after neoadjuvant therapy between 8th edition AJCC ypT- staging and the modified ypT- staging. (A) ypT- stage of the 8th edition AJCC tumor staging system; (B) the modified ypT- staging method. AJCC, American Joint Committee on Cancer.

Table 4 Analysis of the 8th edition ypT- staging and the modified ypT- staging with grade using a Cox proportional hazards model

Grade	ypT- category					
	T0 + T1 + T2			T3 + T4		
	N	HR (95% CI)	P	N	HR (95% CI)	P
8th ypTNM						
I	76	Ref		119	Ref	
II	542	1.091 (0.784–1.519)	0.606	1,005	1.103 (0.854–1.425)	0.454
III	495	1.347 (0.968–1.875)	0.077	1,311	1.377 (1.070–1.772)	0.013
IV	15	0.857 (0.384–1.912)	0.705	30	1.172 (0.703–1.954)	0.544
Modified						
I + II	618	Ref		1,124	Ref	
III + IV	510	1.232 (1.053–1.441)	0.009	1,341	1.257 (1.136–1.390)	<0.001

HR, hazard ratio; CI, confidence interval; Ref, reference.

As shown in *Table 5*, the risk of death in patients with a middle tumor location in the ypN0 group was 0.239 times higher than those with lower tumor locations (HR =1.239; 95% CI: 1.011–1.518), and 0.638 times higher than those with upper locations (HR =1.638; 95% CI: 1.089–2.466). After combining the middle and upper groups, we still observed a 0.295-fold increased risk of death the middle + upper group compared to the lower group (HR =1.295; 95% CI: 1.073–1.562), which was statistically significant.

The modified ypTNM staging system

According to the results of the Cox analysis, the risk of death in the ypT3 + T4 (HR =1.331; 95% CI: 1.213–1.461), ypN1 (HR =1.317; 95% CI: 1.196–1.452), ypN2 + N3 (HR =1.757; 95% CI: 1.563–1.976) and grade III + IV (HR

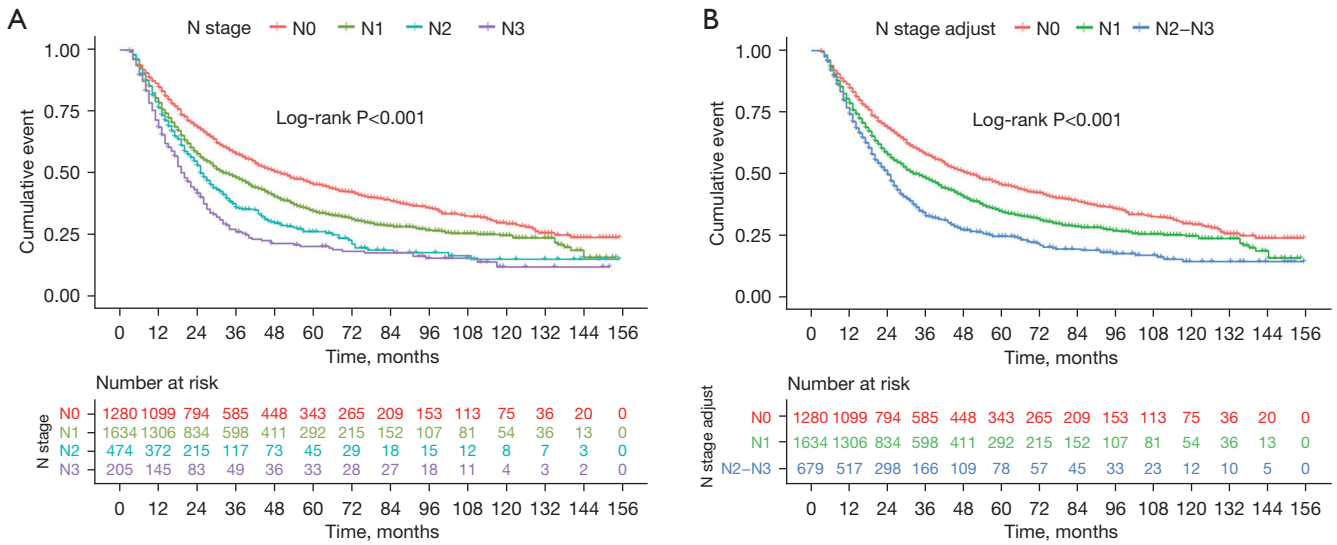

Figure 3 Survival analysis comparison of patients after neoadjuvant therapy between 8th edition AJCC ypN- staging and the modified ypN- staging. (A) ypN- staging of the 8th edition AJCC tumor staging system; (B) the modified ypN- staging method. AJCC, American Joint Committee on Cancer.

Table 5 Analysis of the 8th edition ypN- stage and the modified ypN- stage with tumor location using a Cox proportional hazards model

Tumor location	ypN category								
	N0			N1			N2 + N3		
	N	HR (95% CI)	P	N	HR (95% CI)	P	N	HR (95% CI)	P
8th ypTNM									
L	1,064	Ref		1,390	Ref		628	Ref	
M	182	1.239 (1.011–1.518)	0.039	217	1.058 (0.881–1.270)	0.547	46	1.064 (0.750–1.509)	0.728
U	34	1.638 (1.089–2.466)	0.018	27	0.929 (0.547–1.575)	0.783	5	3.318 (1.370–8.036)	0.008
Modified									
L	1,064	Ref		1,390	Ref		628	Ref	
M + U	216	1.295 (1.073–1.562)	0.007	244	1.045 (0.877–1.244)	0.625	51	1.165 (0.840–1.618)	0.360

L, M, and U were the lower, middle, and upper tumor locations, respectively. HR, hazard ratio; CI, confidence interval.

=1.277; 95% CI: 1.173–1.389) groups was significantly increased, compared with that of ypT0–2, ypN0, and grade I + II, respectively (*Table 6*).

Considering the previously described results of the modified ypT- stage with grade and ypN- stage with tumor location, a modified ypTNM staging classification was proposed (*Table 2*). The modified staging classification system maintained the T and N definitions of the 8th edition AJCC system, and the grade and tumor location were also considered.

Comparison of modified ypTNM staging with the 8th edition ypTNM staging

Using the modified ypTNM staging classification system, we observed a statistically significant increase in the calculated HRs with increasing disease stage in univariate Cox analysis (Table S2) and multivariate Cox analysis (after adjustment for sex and radiation) (*Table 7*). Specifically, the risk of death in stage II, III, and IV populations was significantly increased compared to those in stage I, P<0.001 (*Table 7*).

Table 6 Analysis of modified ypTNM staging with grade and tumor location using a Cox proportional hazards model

Variables	β	S.E	χ^2	P	HR	Lower	Upper
ypT category							
0+1+2					Ref		
3+4	0.286	0.048	36.254	<0.001	1.331	1.213	1.461
ypN category							
N0					Ref		
N1	0.276	0.049	31.214	<0.001	1.317	1.196	1.452
N2 + N3	0.564	0.060	88.870	<0.001	1.757	1.563	1.976
Grade							
I + II					Ref		
III + IV	0.244	0.043	32.017	<0.001	1.277	1.173	1.389
Tumor location							
L					Ref		
M + U	0.091	0.060	2.261	0.133	1.095	0.973	1.233

L, M, and U were the lower, middle, and upper tumor locations, respectively. S.E, standard error; HR, hazard ratio; Ref, reference.

Moreover, except for IIB and IIC, which exhibited no statistical significance, all other substages were significantly different compared to the IIA cohort: the HR of IA was 0.701 (95% CI: 0.566–0.872); IB was 0.821 (95% CI: 0.685–0.984); IIIA was 1.353 (95% CI: 1.151–1.591); IIIB was 1.408 (95% CI: 1.158–1.712); and IV was 1.684 (95% CI: 1.400–2.027). However, only the stage IIIB and IVA cohorts showed a significantly different risk of death compared to patients in stage II, with HRs of 1.392 (95% CI: 1.230–1.575) and 1.683 (95% CI: 1.415–2.002), respectively. In addition, the survival curves were well separated by stage using the modified classification (*Figure 4*).

The likelihood ratios, AIC, and SBC analysis were conducted to compare the prognostic performance of both the modified and 8th edition AJCC staging systems. In the modified substage, the results showed that the likelihood ratio test was χ^2=143.443 (P<0.001), AIC =32,683.716, and SBC =32,723.496. In the modified stage, the model with the likelihood ratio test was 102.571 (P<0.001), AIC was 32,716.588, and SBC was 32,733.637, indicating that the modified model was effective and well fitted overall. The likelihood ratio test of the 8th edition of staging was χ^2=102.044 (P<0.001), AIC =32,719.115, and SBC =32,741.847. Overall, the AIC and SBC values in the modified stage were both lower than the 8th edition stage, which indicated that the model fitting results of the modified sub-staging and staging system were better than those of the 8th edition stage, and the sub-staging system was better than those of the staging system.

In *Table 8*, the C-index of the modified ypTNM stage was 0.577, which was significantly higher than the 8th edition staging system (0.560) in all populations (P=0.045). Also, in the ≥65 years old cohort, the C-index of the modified stage (0.570) was higher than that of the 8th edition stage (0.544), and the difference was statistically significant (P=0.041). Moreover, the modified stage also showed a good predictive effect on mortality in the subgroup of patients who received chemotherapy as well as those who received radiation before surgery.

Discussion

Our study aimed to modify the existing ypTNM staging classification and further subdivide patients from five groups into eight groups, in order to obtain more accurate prognostic identification. The modified ypTNM staging classification displayed better homogeneity and discriminatory ability between different cohorts compared with the 8th edition AJCC staging systems.

According to the Kaplan-Meier curve and log-rank test, we found that ypT0–2 could be combined. The results of several previous studies were consistent with

Table 7 Multivariate analysis of the modified ypTNM and 8th edition ypTNM staging classifications

Variables	β	S.E	χ^2	P	HR	Lower	Upper
Modified stage							
I					Ref		
II	0.355	0.057	38.657	<0.001	1.427	1.276	1.596
III	0.553	0.083	44.288	<0.001	1.739	1.477	2.046
IV	0.771	0.082	89.409	<0.001	2.162	1.843	2.537
Modified substage							
IA	−0.354	0.110	10.283	0.001	0.701	0.566	0.872
IB	−0.198	0.092	4.577	0.032	0.821	0.685	0.984
IIA					Ref		
IIB	−0.171	0.105	2.650	0.104	0.843	0.686	1.035
IIC	0.072	0.083	0.743	0.389	1.074	0.913	1.265
IIIA	0.302	0.083	13.378	<0.001	1.353	1.151	1.591
IIIB	0.342	0.100	11.783	<0.001	1.408	1.158	1.712
IV	0.521	0.094	30.467	<0.001	1.684	1.400	2.027
8th ypTNM							
I	−0.120	0.082	2.152	0.142	0.887	0.755	1.041
II					Ref		
IIIA	−0.034	0.092	0.136	0.713	0.967	0.807	1.158
IIIB	0.331	0.063	27.504	<0.001	1.392	1.230	1.575
IVA	0.521	0.089	34.550	<0.001	1.683	1.415	2.002

S.E, standard error; HR, hazard ratio; Ref, reference.

our findings. Mehta *et al.* studied 243 patients with lower esophageal cancer who received neoadjuvant chemotherapy and found there was no prognostic difference between ypT0–3 categories (19). Similarly, the authors revealed that there was no difference in prognosis among ypT0, ypT1 and ypT2, and only ypT4 showed significantly poorer survival in a large single-center population (12). This may be attributable to the fact that tumors with a high proliferation rate respond well to neoadjuvant therapy. In this case, residual tumor cells are more likely to be invasive, which is related to a high risk of recurrence and poor prognosis. Furthermore, we observed a substantial difference in the survival curves between the different stages using the modified ypT- staging classification. In addition, previous studies have reported tumor grade as an important prognostic factor for patients undergoing esophageal cancer resection or neoadjuvant therapy plus surgery (20-22). We also simplified the grade classification, which represents the degree of tumor differentiation, and merged it with the ypT- category. We found that grade III + IV was significant in both ypT0–2 and ypT3–4 populations, using grade I + II as the reference.

Lymph node status after neoadjuvant therapy is also an important factor affecting prognosis in our study, and ypN2 and ypN3 were combined according to the survival curve. Indeed, it is generally believed that tumor differentiation and the numbers of positive or negative lymph nodes are independent prognostic factors (23,24). Pathological evaluation requires the removal of enough lymph nodes to evaluate the ypN category. Since the highest N classification (N3) is defined as metastases involving seven or more nodes, any resection should theoretically include at least seven resected lymph nodes for correct interpretation. The recommendation adopted by the AJCC was that at least 10

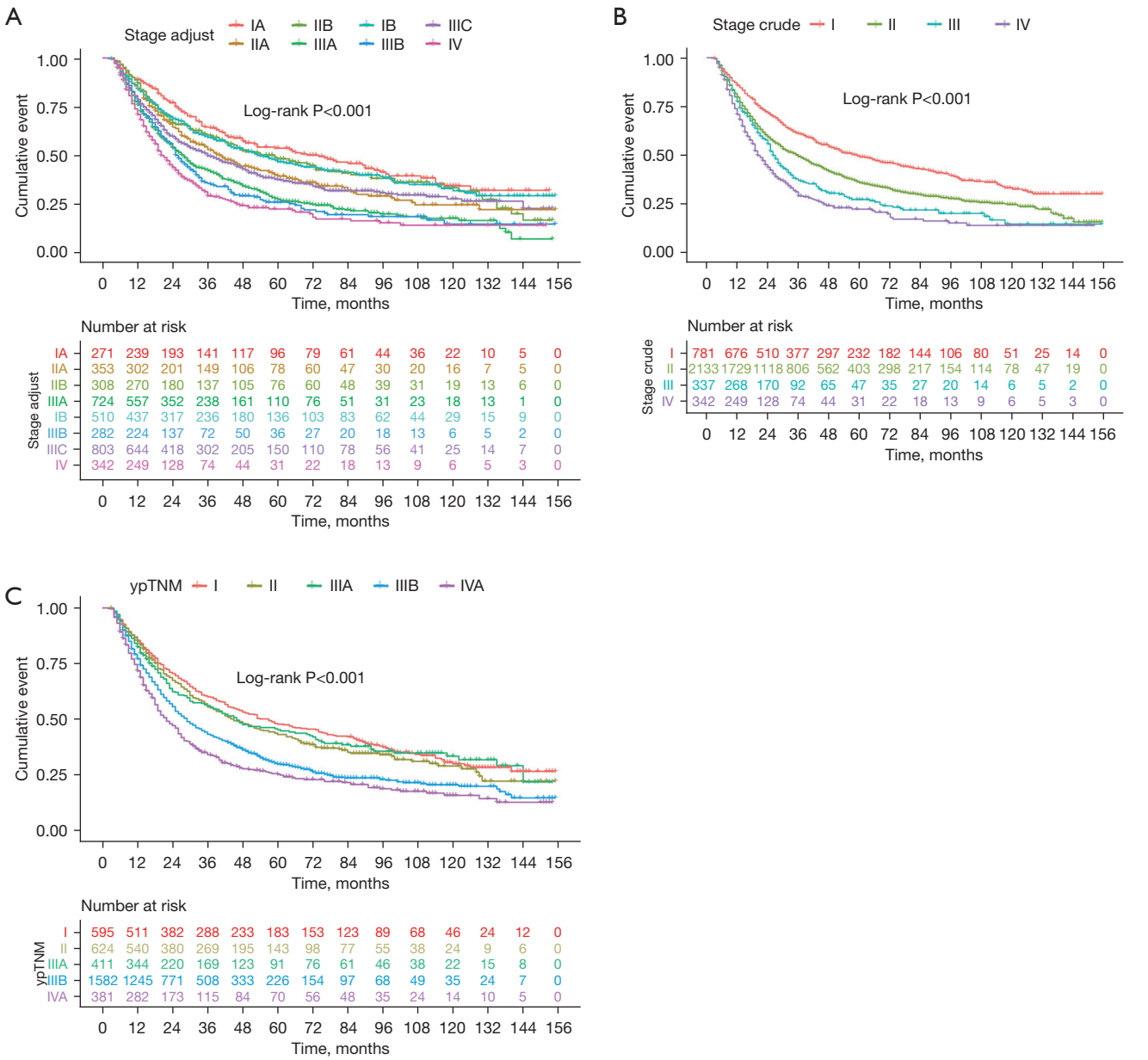

Figure 4 Kaplan-Meier curves of patients after neoadjuvant therapy. (A) The modified stage; (B) the modified substage; (C) the 8th edition AJCC tumor staging system. AJCC, American Joint Committee on Cancer.

lymph nodes should be removed for T1 cancer, at least 20 lymph nodes should be removed for T2 cancer, and at least 30 lymph nodes should be removed for T3 cancer (25). Persistent regional lymph node metastases (ypN1) predict poor survival, and resection of metastatic regional lymph nodes (ypN0) does not equate to cure. Survival is moderate both in patients with ypN0 disease confined to the esophageal wall as well as those with complete remission, regardless of ypT (26). Tumor location had an impact on survival only in patients with N0 disease, which may be due to insufficient lymph node resection, leading to a missed diagnosis of positive lymph nodes and the patient being incorrectly classified as ypN0. Currently, tumor location is considered to be significant for survival in patients with ypN0.

To our knowledge, few studies have improved the staging of patients with esophageal cancer after neoadjuvant

Table 8 C-index of the modified and 8th edition ypTNM staging classifications

Variables	8th ypTNM		Modified stage		Z	P
	C	S.E	C	S.E		
Total	0.560	0.006	0.577	0.006	2.003	0.045
Sex						
Male	0.558	0.007	0.576	0.007	1.818	0.069
Female	0.590	0.017	0.584	0.017	0.250	0.803
Race						
Black	0.621	0.027	0.624	0.028	0.077	0.939
Others	0.586	0.034	0.594	0.035	0.164	0.870
White	0.560	0.007	0.576	0.007	1.616	0.106
Radiation sequence with surgery						
Radiation before and after surgery	0.592	0.030	0.548	0.036	0.939	0.348
Radiation prior to surgery	0.562	0.006	0.579	0.006	2.003	0.045
Age (years)						
<65	0.581	0.008	0.588	0.009	0.581	0.561
≥65	0.544	0.009	0.570	0.009	2.043	0.041
Histologic type						
ESCC	0.554	0.015	0.560	0.015	0.283	0.777
EAC	0.566	0.007	0.583	0.007	1.717	0.086
Chemotherapy						
Yes	0.561	0.006	0.578	0.006	2.003	0.045
No	0.662	0.047	0.671	0.040	0.146	0.884

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; S.E, standard error.

treatment based on the 8th edition of ypTNM staging. A study has suggested that staging classification in ypTNM mixed with grade, histology, and location should be seen as a complex stratification (26). In this study, the modified ypTNM, included tumor grade and location, had smaller AIC and SBC values and a higher C-index than the 8th ypTNM stage, implying that the modified stage was superior in prognosis stratification and death prediction. Moreover, multivariate analysis of the modified stage revealed that as the tumor stage increased, the risk of death also increased in the improved staging. The survival analysis results showed that the curves had little overlap under the modified ypTNM staging, which indicated that it could more accurately represent the stage of esophageal cancer. Although the modified ypTNM staging system is a promising step towards a more accurate esophageal cancer staging classification after neoadjuvant therapy, there is still a need to develop innovative and more effective treatments for this devastating disease. It is worth noting that tumor response is a postoperative diagnosis, and there is currently a lack of available methods to accurately predict it.

The modified ypTNM staging system proposed in this study is superior to the 8th AJCC ypTNM staging system; however, there are some limitations that should be noted. First, the SEER database does not collect information about the time of chemotherapy, so patients that received neoadjuvant therapy included only those received preoperative radiotherapy. Among the excluded patients who did not receive radiotherapy before surgery, there may have been neoadjuvant patients who received preoperative chemotherapy. However, through the two indicators of surgery and radiotherapy in an exact time

sequence, it is ensured that the subjects included were all patients with neoadjuvant therapy, ensuring the applicability of the results and their comparability with the 8th edition staging. Second, in this study, the SEER database served as a retrospective cohort containing data from 2000 to 2015, with the staging system updated from the 6th to the 8th edition. As a result, the description and definition of different editions were inconsistent with the 8th edition, but all patients were consistent. Future research should focus on the impact of the latest classification of tumor grade and location on patient outcomes, and adjustments for staging should be made. Third, the sample size was limited, and the extrapolative ability was insufficient. The SEER cohort was primarily a white population from western hemisphere, and thus, it is not possible to assume that the staging system was generalizable in other populations, as the prevalence and treatment strategies of esophageal cancer differ between countries. Therefore, future studies should explore the improvement of staging and enhance the extrapolative ability through prospective, multi-center, cohort studies with large sample sizes.

Conclusions

In this study, we developed and verified a modified ypTNM staging of esophageal cancer after neoadjuvant therapy using SEER data. Although the modified ypTNM staging system displayed certain prognosis prediction accuracy compared with the 8th edition ypTNM staging, a larger sample size and prospective studies are needed to explore.

Acknowledgments

The authors appreciate the academic support from the AME Esophageal Cancer Collaborative Group.
Funding: This research was supported by the performance incentives guide special project of the Chongqing Scientific Research Institutes (No. cstc2019jxj1130005).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at available at https://atm.amegroups.com/article/view/10.21037/atm-22-2353/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2353/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). This study was exempted from the Institutional Review Board approval because all data collected from SEER was de-identified.

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(English Language Editor: A. Kassem)

Cite this article as: Jiang Y, Huang Y, Wang Z, Xu W, Xu J, Teng F, Yin Z, Flores RM, Hirahara N, Mitsos S, Wakefield CJ, Guo D, Yang R. Comparisons of prognosis prediction accuracy between modified and unmodified versions of 8th edition ypTNM. Ann Transl Med 2022;10(10):600. doi: 10.21037/atm-22-2353

Table S1 Sociodemographic and clinicopathologic characteristics of the study population

Variables	Total (n=3,593)	Alive (n=1,422)	Died (n=2,171)
Year of diagnosis, n (%)			
2004	206 (5.73)	38 (2.67)	168 (7.74)
2005	212 (5.90)	40 (2.81)	172 (7.92)
2006	232 (6.46)	51 (3.59)	181 (8.34)
2007	271 (7.54)	64 (4.50)	207 (9.53)
2008	239 (6.65)	57 (4.01)	182 (8.38)
2009	257 (7.15)	87 (6.12)	170 (7.83)
2010	296 (8.24)	87 (6.12)	209 (9.63)
2011	340 (9.46)	122 (8.58)	218 (10.04)
2012	348 (9.69)	148 (10.41)	200 (9.21)
2013	399 (11.10)	201 (14.14)	198 (9.12)
2014	389 (10.83)	233 (16.39)	156 (7.19)
2015	404 (11.24)	294 (20.68)	110 (5.07)
Age at diagnosis (years), n (%)			
20–29	12 (0.33)	6 (0.42)	6 (0.28)
30–39	35 (0.97)	17 (1.20)	18 (0.83)
40–49	292 (8.13)	129 (9.07)	163 (7.51)
50–59	983 (27.36)	394 (27.71)	589 (27.13)
60–69	1,471 (40.94)	604 (42.48)	867 (39.94)
70–79	730 (20.32)	252 (17.72)	478 (22.02)
80–89	70 (1.95)	20 (1.41)	50 (2.30)
Sex, n (%)			
Female	559 (15.56)	260 (18.28)	299 (13.77)
Male	3,034 (84.44)	1,162 (81.72)	1,872 (86.23)
Race, n (%)			
Black	175 (4.87)	54 (3.80)	121 (5.57)
Other	129 (3.59)	55 (3.87)	74 (3.41)
Unknown	4 (0.11)	3 (0.21)	1 (0.05)
White	3,285 (91.43)	1,310 (92.12)	1,975 (90.97)
8^{th} ypTNM, n (%)			
Stage I	470 (14.39)	204 (15.86)	266 (13.43)
Stage II	624 (19.10)	284 (22.08)	340 (17.16)
Stage IIIA	329 (10.07)	149 (11.59)	180 (9.09)
Stage IIIB	1,563 (47.84)	573 (44.56)	990 (49.97)
Stage IVA	281 (8.60)	76 (5.91)	205 (10.35)
Histologic type, n (%)			
ESCC	695 (19.34)	278 (19.55)	417 (19.21)
EAC	2,898 (80.66)	1,144 (80.45)	1,754 (80.79)
ypT category, n (%)			
T0	1 (0.03)	0 (0.00)	1 (0.05)
T1	486 (13.53)	201 (14.14)	285 (13.13)
T2	641 (17.84)	301 (21.17)	340 (15.66)
T3	2,246 (62.51)	851 (59.85)	1,395 (64.26)
T4	219 (6.10)	69 (4.85)	150 (6.91)
ypN category, n (%)			
N0	1,280 (35.62)	578 (40.65)	702 (32.34)
N1	1,634 (45.48)	638 (44.87)	996 (45.88)
N2	474 (13.19)	165 (11.60)	309 (14.23)
N3	205 (5.71)	41 (2.88)	164 (7.55)
Grade, n (%)			
Grade I	195 (5.43)	90 (6.33)	105 (4.84)
Grade II	1,547 (43.06)	673 (47.33)	874 (40.26)
Grade III	1,806 (50.26)	640 (45.01)	1,166 (53.71)
Grade IV	45 (1.25)	19 (1.34)	26 (1.20)
Tumor location, n (%)			
Lower thoracic	3,082 (85.78)	1,232 (86.64)	1,850 (85.21)
Middle thoracic	445 (12.39)	167 (11.74)	278 (12.81)
Upper thoracic	66 (1.84)	23 (1.62)	43 (1.98)
Radiation sequence with surgery, n (%)			
Radiation before and after surgery	127 (3.53)	43 (3.02)	84 (3.87)
Radiation prior to surgery	3,466 (96.47)	1,379 (96.98)	2,087 (96.13)
Chemotherapy, n (%)			
No/unknown	50 (1.39)	13 (0.91)	37 (1.70)
Yes	3,543 (98.61)	1,409 (99.09)	2,134 (98.30)
Follow-up time (months)			
M [Q_1, Q_3]	26 [14, 50]	45 [25, 80]	18 [10, 32]
Mean ± SD	37.56±33.04	55.87±32.29	25.60±23.09
Min	2	3	2
Max	155	155	144

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SD, standard deviation.

https://dx.doi.org/10.21037/atm-22-2353

Table S2 Univariate analysis of the modified ypTNM staging classification

Variables	β	S.E	χ^2	P	HR	Lower	Upper
Modified stage							
I					Ref		
II	0.353	0.057	38.098	<0.001	1.423	1.272	1.592
III	0.565	0.083	46.4564	<0.001	1.760	1.496	2.071
IV	0.777	0.082	90.751	<0.001	2.174	1.853	2.551
Modified substage							
IA	−0.355	0.110	10.349	0.001	0.701	0.565	0.871
IB	−0.198	0.092	4.576	0.032	0.821	0.685	0.984
IIA					Ref		
IIB	−0.184	0.105	3.089	0.079	0.832	0.678	1.021
IIC	0.067	0.083	0.638	0.424	1.069	0.908	1.258
IIIA	0.309	0.083	13.985	<0.001	1.362	1.158	1.602
IIIB	0.352	0.100	12.482	<0.001	1.422	1.170	1.729
IV	0.526	0.094	31.048	<0.001	1.693	1.407	2.037
8^{th} ypTNM							
I					Ref		
II	0.122	0.082	2.195	0.138	1.129	0.962	1.326
IIIA	0.093	0.097	0.919	0.338	1.097	0.908	1.326
IIIB	0.461	0.070	43.811	<0.001	1.585	1.383	1.817
IVA	0.654	0.093	49.143	<0.001	1.923	1.602	2.309

S.E, standard error; HR, hazard ratio; Ref, reference.

https://dx.doi.org/10.21037/atm-22-2353