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Gastrointestinal Cancer

Modified ypTNM Staging Classification for Gastric Cancer after Neoadjuvant Therapy: A Multi-Institutional Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gastric cancer • ypTNM staging • Neoadjuvant therapy • Modified • Validation

Abstract

Background. The benefits of neoadjuvant therapy for patients with locally advanced gastric cancer (GC) are increasingly recognized. The 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual first proposed ypTNM staging, but its accuracy is controversial. This study aims to develop a modified ypTNM staging.

Patients and Methods. Clinicopathological data of 1,791 patients who underwent curative-intent gastrectomy after neoadjuvant therapy in the Surveillance, Epidemiology, and End Results database, as the development cohort, were retrospectively analyzed. Modified ypTNM staging was established based on overall survival (OS). We compared the prognostic performance of the AJCC 8th edition ypTNM staging and the modified staging for patients after neoadjuvant therapy.

Results. In the development cohort, the 5-year OS for AJCC stages I, II, and III was 58.8%, 39.1%, and 21.6%, respectively, compared with 69.9%, 54.4%, 34.4%, 24.1%, and 13.6% for modified ypTNM stages IA, IB, II, IIIA, and IIIB. The modified staging had better discriminatory ability (C-index: 0.620 vs. 0.589, $p < .001$), predictive homogeneity (likelihood ratio chi-square: 140.71 vs. 218.66, $p < .001$), predictive accuracy (mean difference in Bayesian information criterion: 64.94; net reclassification index: 35.54%; integrated discrimination improvement index: 0.032; all $p < .001$), and model stability (time-dependent receiver operating characteristics curves) over AJCC. Decision curve analysis showed that the modified staging achieved a better net benefit than AJCC. In external validation ($n = 266$), the modified ypTNM staging had superior prognostic predictive power (all $p < .05$).

Conclusion. We have developed and validated a modified ypTNM staging through multicenter data that is superior to the AJCC 8th edition ypTNM staging, allowing more accurate assessment of the prognosis of patients with GC after neoadjuvant therapy. ***The Oncologist*** 2021;26:e99–e110

Implications for Practice: The 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual first proposed ypTNM staging, but its accuracy is controversial. Based on multi-institutional data, this study developed a modified ypTNM staging, which is superior to the AJCC 8th edition ypTNM staging, allowing more accurate assessment of the prognosis of patients with gastric cancer after neoadjuvant therapy.

Introduction

Globally, gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths [1]. GC is often diagnosed at an advanced stage in China, Europe, and the U.S. [2, 3]. Despite the

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development of radical surgery techniques and perioperative chemotherapy, the survival of patients with advanced GC is still poor. The 5-year overall survival (OS) is mostly less than 50% [4]. In recent years, surgeons in the East and West have gradually realized that patients with locally advanced GC can benefit from preoperative (neoadjuvant) treatment, and more and more patients receive neoadjuvant therapy [5–7]. How to effectively stratify the prognosis of these patients has become a hot topic of current research. Because there are no staging criteria specifically for patients who undergo surgical resection and are given neoadjuvant therapy before surgery, prognostic evaluation of such patients has used the American Joint Committee on Cancer (AJCC) pTNM staging system in the past [8], but this application has not been validated and has neglected the possible downstage effects of neoadjuvant therapy. The 8th edition of the AJCC manual, released in 2017, proposed the post-neoadjuvant treatment staging (ypTNM) system for the first time [9], filling the gap in clinical application.

The 8th edition of the AJCC manual first described the staging system for patients who receive neoadjuvant therapy, which is undoubtedly a major advancement in precision therapy and lays a solid foundation for patient evaluation after neoadjuvant treatment. However, although it meets the clinical needs to a certain extent, the current staging only divides patients with nonmetastatic GC after neoadjuvant therapy into three stages, stage I, stage II, and stage III, and it does not make a more detailed distinction, which is also the limitation of the ypTNM staging mentioned in the manual. In addition, a limited number of patients were available for this analysis (n = 683), with a median follow-up of only 23 months [10]. It is urgent to find a larger sample of patients with longer follow-up times to verify and recalibrate the ypTNM staging. Neoadjuvant therapy often affects the status of the primary tumor and lymph nodes; however, comparing the 8th edition of the AJCC ypTNM staging and the 7th edition of the AJCC pTNM staging (supplemental online Fig. 1), there was no difference in stages I–III between the two classifications. In other words, the AJCC 8th edition ypTNM staging is a simple integration of the AJCC 7th edition pTNM staging, which may not be very suitable for prognostic evaluation of patients after neoadjuvant therapy. Although mostly because of the lack of sufficient clinical data, a modified ypTNM staging system for patients with GC after neoadjuvant therapy is needed. Therefore, this study aims to establish a modified ypTNM staging through a large data sample from the U.S. and to validate the modified staging through data from China and Italy to accurately assess the prognosis of patients with GC after neoadjuvant therapy.

Materials and Methods

Population and Covariates

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18 Regs Research database (registration number 11994-Nov2018), which covers approximately 27.8% of the U.S. population (based on the 2010 census) [11]. Because of changes in coding (specifically the AJCC staging) and the requirement of at least 1 year of follow-up, data were extracted from the SEER database from 2004 to 2015. A value of 6 for the category "CS Lymph Nodes Eval" was used to select patients with GC who received neoadjuvant therapy before surgery in the SEER database, which meant the patient met criteria for AJCC y-pathologic (yp) staging. All the cases were restaged according to the criteria described in the AJCC cancer staging manual (8th edition).

The inclusion criteria were defined as follows: the presence of primary GC; no combined malignancy, preoperative chemotherapy, or preoperative radiotherapy; no distant metastasis; and complete ypT category and ypN category information. Exclusion criteria were defined as follows: histology showing a tumor type other than adenocarcinoma and remnant GC. The selection scheme of the SEER database is shown in supplemental online Figure 2. The remaining 1,791 patients who underwent curative-intent resection after neoadjuvant therapy were included as the development cohort in the present study.

Clinicopathological data were routinely collected. The tumor site was divided into four subsites: lower third (C16.3 and C16.4), upper third (C16.0 and C16.1), middle third (C16.2, C16.5, and C16.6), and overlapping (C16.8) [12]. The tumors were pathologically categorized as low grade (well and moderately differentiated), high grade (poorly differentiated and undifferentiated), or Gx (grade could not be evaluated). The histological types were categorized into general (8140–8389: adenomas and adenocarcinomas) and special (8440–8499: cystic, mucinous, and serous neoplasms). Tumor size was assessed on the basis of the largest diameter of resected specimens.

Multi-institutional data from the following centers that satisfied the aforementioned inclusion criteria were included in the validation analysis: Fujian Medical University Union Hospital (FMUUH) from 2000 to 2015 in China (n = 111), Qinghai University Affiliated Hospital (QUAH) from 2012 to 2014 in China (n = 58), and the International Study Group on Minimally Invasive Surgery for GC (IMIGASTRIC) between 2000 and 2014 in Italy (n = 97). The institutional review boards of all the participating institutions approved the study.

In the validation cohort we studied, the regimen of neoadjuvant chemotherapy included the selective use of fluorouracil, oxaliplatin, paclitaxel, and other drugs when necessary. The efficacy of neoadjuvant therapy was evaluated every two cycles of treatment using enhanced computed tomography and ultrasound endoscopy, and the therapy was prematurely terminated in cases of disease progression. In all resectable cases, elective gastrectomies were scheduled for 2 to 4 weeks after neoadjuvant therapy. Fluorouracil-based adjuvant chemotherapy was recommended for patients with advanced GC after surgery in the validation cohort.

The cause of death among the SEER cohorts was defined using the cause-of-death codes [13]. All patients from validation centers received standard postoperative follow-up, including visits every 3 to 6 months for the first 2 years, every 6 to 12 months from the third to the fifth year, and once per year thereafter. All the patients were observed until death or the final follow-up date of June 2019 in the validation cohort.

Table 1. Sociodemographic and clinicopathologic characteristics of the development and the validation cohort

Variable	Development cohort (*n* = 1,791), *n* (%)	Validation cohort (*n* = 266), *n* (%)	*p* value
Region			
U.S.	1,791 (100)		
China		169 (63.5)	
Italy		97 (36.5)	
Year of operation			
2004–2009	527 (29.4)	75 (28.2)	.681
2010–2015	1,264 (70.6)	191 (71.8)	
Age, years, mean ± SD	60.2 ± 11.5	59.4 ± 11.3	.315
Race			<.001
White	1,376 (76.8)	0 (0.0)	
Black	173 (9.7)	0 (0.0)	
Other[a]	238 (13.3)	169 (63.5)	
Unknown	4 (0.2)	97 (36.5)	
Sex			.438
Female	464 (25.9)	63 (23.7)	
Male	1,327 (74.1)	203 (76.3)	
Site			<.001
Upper	1,046 (58.4)	114 (42.9)	
Middle	312 (17.4)	93 (35.0)	
Lower	217 (12.1)	47 (17.7)	
Overlapping	131 (7.3)	12 (4.5)	
NOS	85 (4.7)	0 (0.0)	
Histological type			.009
General types	1,364 (76.2)	183 (68.8)	
Special types	427 (23.8)	83 (31.2)	
Size			<.001
≤2 cm	248 (13.8)	22 (8.3)	
>2 cm, ≤5 cm	669 (37.4)	112 (42.1)	
>5 cm	545 (30.4)	116 (43.6)	
Linitis plastica	37 (2.1)	6 (2.3)	
Unknown	292 (16.3)	10 (3.8)	
Surgical procedure			<.001
Partial gastrectomy	973 (54.3)	90 (33.8)	
Total gastrectomy	553 (30.9)	176 (66.2)	
Gastrectomy, NOS	265 (14.8)	0 (0.0)	
Grade			<.001
High	463 (25.9)	107 (40.2)	
Low	1,216 (67.9)	143 (53.8)	
Gx	112 (6.3)	16 (6.0)	
ypT category			.010
T1	153 (8.5)	23 (8.6)	
T2	222 (12.4)	52 (19.5)	
T3	727 (40.6)	87 (32.7)	
T4a	560 (31.3)	88 (33.1)	
T4b	129 (7.2)	16 (6.0)	

(continued)

Table 1. (continued)

Variable	Development cohort (*n* = 1,791), *n* (%)	Validation cohort (*n* = 266), *n* (%)	*p* value
ypN category			.001
N0	486 (27.1)	84 (31.6)	
N1	474 (26.5)	53 (19.9)	
N2	446 (24.9)	50 (18.8)	
N3	385 (21.5)	79 (29.7)	
LNs examined			<.001
Mean ± SD	19.8 ± 12.7	29.4 ± 12.8	
<15	690 (38.5)	21 (7.9)	
≥15	1,101 (61.5)	245 (92.1)	
ypTNM staging (AJCC 8th)			.614
I	227 (12.7)	39 (14.7)	
II	598 (33.4)	90 (33.8)	
III	966 (53.9)	137 (51.5)	
Modified ypTNM staging			.118
IA	93 (5.2)	17 (6.4)	
IB	265 (14.8)	45 (16.9)	
II	555 (31.0)	70 (26.3)	
IIIA	515 (28.8)	66 (24.8)	
IIIB	363 (20.3)	68 (25.6)	
Adjuvant radiotherapy			<.001
None	1,532 (85.5)	261 (98.1)	
Yes	259 (14.5)	5 (1.9)	
Adjuvant chemotherapy[b]			
None	NA	97 (36.5)	
Yes	NA	169 (63.5)	
Neoadjuvant radiotherapy			<.001
None	1,016 (56.7)	258 (96.6)	
Yes	775 (43.3)	9 (3.4)	
Neoadjuvant chemotherapy[b]			
None	NA	2 (0.8)	
Yes	NA	264 (99.2)	

Abbreviations: AJCC 8th, American Joint Committee on Cancer 8th edition; Gx, grade could not be evaluated; LN, lymph node; NA, not applicable; NOS, not otherwise specified.
[a]American Indian/Alaska Native, Asian/Pacific Islander.
[b]In the SEER database, category record "Chemotherapy recode (yes, no/unk)" does not distinguish between preoperative and postoperative chemotherapy in detail.

Statistical Analysis

Overall survival was defined as the time from surgery to death from any cause. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to determine significance. Variables associated with OS were selected using univariate and multivariate Cox regression models. To investigate which staging system was more suitable for prognostic assessment, a two-step multivariate analysis was performed [14]. In step 1 of multivariate analysis, all significantly important prognostic factors in univariate analysis were considered, except for the modified ypTNM staging system. In step 2 of multivariate analysis, the modified staging system was also considered, together with the AJCC 8th edition staging system and other significantly important prognostic factors in univariate analysis. In addition, we employed a univariate Cox analysis at later time points (time-dependent Cox analysis) to assess the prognostic system for survival among patients who were alive after a certain number of years [15].

The performance of a prognostic system has been shown to be related to discriminatory ability (greater differences in survival among patients in different stages within each system) and homogeneity (small differences in survival among patients in the same class within each system). Harrell's C-index was used to measure the discriminatory ability of different staging systems [16, 17]. The likelihood ratio chi-square score was calculated using Cox regression to measure homogeneity; a higher likelihood ratio chi-square

Table 2. The AJCC 8th edition ypTNM staging definitions and the modified ypTNM staging definitions for gastric cancer after neoadjuvant therapy, with cross-tabulation of stage distributions

Definitions for ypT, ypN	
ypT category (primary tumor)	
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T2	Tumor invades the muscularis propria
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
ypN category (regional lymph nodes)	
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in seven to 15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

ypTNM staging (AJCC 8th)

	N0	N1	N2	N3
T1	I	I	II	II
T2	I	II	II	III
T3	II	II	III	III
T4a	II	III	III	III
T4b	III	III	III	III

Modified ypTNM staging

	N0	N1	N2	N3
T1	IA	II	IIIA	IIIA
T2	IB	II	IIIA	IIIA
T3	IB	II	IIIA	IIIB
T4a	II	II	IIIA	IIIB
T4b	IIIA	IIIA	IIIA	IIIB

	Development cohort					Validation cohort				
Systems	**IA**	**IB**	**II**	**IIIA**	**IIIB**	**IA**	**IB**	**II**	**IIIA**	**IIIB**
I	93	92	42	0	0	17	19	3	0	0
II	0	173	364	61	0	0	26	50	14	0
III	0	0	149	454	363	0	0	17	52	68

Abbreviation: AJCC 8th, American Joint Committee on Cancer 8th edition.

score indicates better homogeneity [18]. The Akaike information criterion (AIC) within the Cox regression model was used to compare performance between two staging systems; smaller AIC values represent more optimistic prognostic stratification [19]. We then calculated the relative likelihood of two models using the formula exp([AIC(model A) − AIC(model B)]/2) [20]. The relative likelihood can be interpreted as a *p* value for the comparison of both AIC values. The Bayesian information criterion (BIC) was used to assess the overall prognostic performance of different prognostic systems via bootstrap-resampling analysis [21]. The BIC and 95% confidence intervals indicate significantly different predictive capability of two staging systems if the zero value is not included. Net reclassification index (NRI) [22] and integrated discrimination improvement (IDI) index [23] were used to quantify the improvement from the new staging system for prediction of the patient's survival. We also performed time-dependent receiver operating characteristics (ROC) analysis to assess the discriminatory power of the prognostic model for time-dependent disease outcomes [24]. Decision curve analysis was used to evaluate the clinical usefulness of the prediction models [25]. An internal validation procedure using 1,000 bootstraps was applied to different staging systems. External validation was performed using the data from the multi-institutional cohort.

All data were processed using SPSS 19.0 (SPSS Inc., Chicago, IL) and R software (version 3.5.3). The data are presented as means ± SD for the continuous variables and as a number for the categorical variables. The differences between the groups were calculated by using Fisher's exact test, the *t* test, or the chi-square test, as appropriate. All the tests were two-sided, with a significance level set to $p < .05$.

Results

Demographic and Clinicopathological Characteristics

The clinicopathological features of the development cohort (n = 1,791) and the validation cohort (n = 266) are shown in Table 1. The mean ages of the development and validation cohorts were 60.2 ± 11.5 and 59.4 ± 11.3, respectively (p = .315), and the mean number of lymph node (LN) dissections was 19.8 ± 12.7 and 29.4 ± 12.8, respectively (p < .001). The patients in the two groups were significantly different in race,

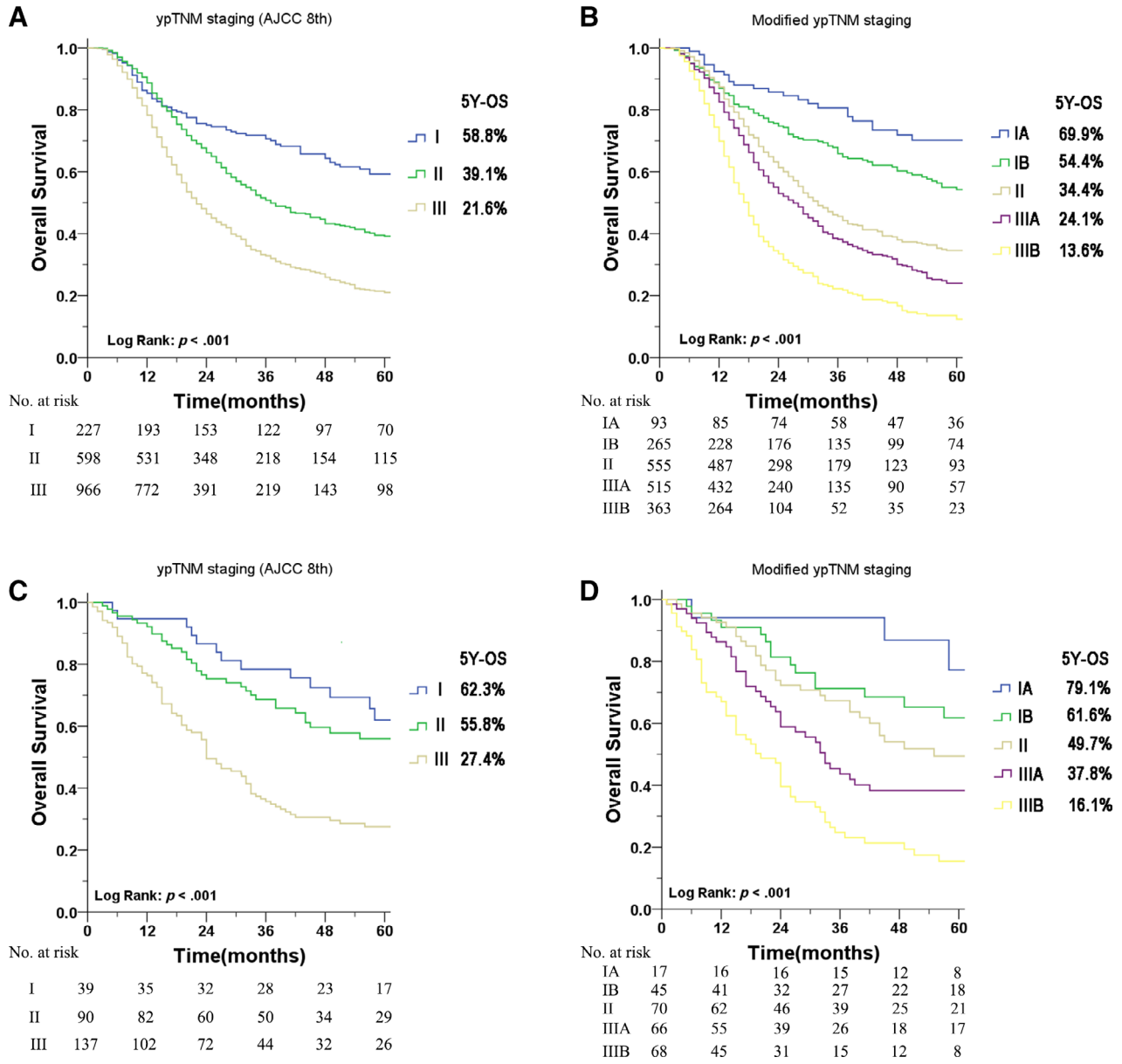

Figure 1. Kaplan-Meier survival curves of the different staging systems for patients after neoadjuvant therapy. **(A):** The AJCC 8th edition ypTNM staging system in the development cohort. **(B):** The modified ypTNM staging system in the development cohort. **(C):** The AJCC 8th edition ypTNM staging system in the validation cohort. **(D):** The modified ypTNM staging system in the validation cohort.
Abbreviations: AJCC 8th, American Joint Committee on Cancer 8th edition; OS, overall survival.

tumor site, histological type, grade, tumor size, surgical procedure, ypT category, and ypN category distribution (all $p < .05$). There was no significant difference in the distribution of sex or AJCC 8th edition ypTNM staging (both $p > .05$).

Development of a Modified Staging System

Supplemental online Table 1 shows the 5-year OS of each ypTNM subgroup in the development cohort. We found that the 5-year OS of ypT2N0M0 patients was higher than that of ypT1N1M0 patients belonging to AJCC 8th edition ypTNM stage I (54.9% vs. 42.4%), and the 5-year OS of patients with ypT3N0M0 was significantly higher than that of patients with ypT1N3M0 belonging to AJCC 8th edition ypTNM stage II (54.3% vs. 20.0%), whereas the 5-year OS of ypT4bN0M0 patients was also higher than that of ypT4bN3M0 patients belonging to the AJCC 8th edition ypTNM stage III (26.2% vs. 15.7%). Therefore, we reorganized each of the ypTNM subgroups with similar 5-year OS and established a modified ypTNM staging, which clearly identified five subgroups with different prognoses (Table 2). Table 2 also shows the changes in AJCC 8th edition ypTNM staging and modified ypTNM staging in the development and validation cohorts.

Survival of Two Staging Systems

The median follow-up time of the development cohort was 60.0 months (1–155 months), and death was observed in 1,097 (61.3%) patients. The median follow-up time was

Table 3. Two-step multivariate analysis of the prognostic factors for patients with gastric cancer after neoadjuvant therapy

Variables	Relative risk (95% CI)	*p value*
Development cohort		
Step 1		
Age	1.161 (1.075–1.253)	<.001
Race	0.987 (0.962–1.013)	.325
Site	1.001 (0.999–1.003)	.190
Histological type	1.300 (1.133–1.491)	<.001
Size	1.000 (0.998–1.001)	.696
Surgical procedure	1.169 (1.079–1.266)	<.001
Grade	0.998 (0.995–1.000)	.087
LN examined	0.751 (0.665–0.848)	<.001
ypTNM staging (AJCC 8th)	1.717 (1.561–1.888)	<.001
Step 2		
Age	1.164 (1.078–1.257)	<.001
Race	0.988 (0.960–1.016)	.388
Site	1.001 (0.999–1.002)	.355
Histological type	1.260 (1.098–1.446)	.001
Size	1.000 (0.998–1.001)	.850
Surgical procedure	1.14 (1.061–1.245)	.001
Grade	0.998 (0.995–1.000)	.106
LN examined	0.661 (0.583–0.749)	<.001
ypTNM staging (AJCC 8th)	1.018 (0.880–1.179)	.807
Modified ypTNM staging	1.540 (1.403–1.691)	<.001
Validation cohort		
Step 1		
Site	0.889 (0.725–1.089)	.255
Size	1.008 (1.000–1.016)	.047
Grade	1.001 (0.994–1.008)	.748
ypTNM staging (AJCC 8th)	1.892 (1.463–2.446)	<.001
Step 2		
Site	0.924 (0.755–1.131)	.445
Size	1.007 (0.999–1.015)	.080
Grade	1.002 (0.995–1.009)	.590
ypTNM staging (AJCC 8th)	0.965 (0.630–1.476)	.868
Modified ypTNM staging	1.636 (1.278–2.096)	<.001

Step 1, with consideration of all significantly important prognostic factors in univariate analysis except for the modified ypTNM stage; step 2, with consideration of all significantly important prognostic factors in univariate analysis, including the modified ypTNM stage.
Abbreviations: AJCC 8th, American Joint Committee on Cancer 8th edition; CI, confidence interval; LN, lymph node.

68.0 months (1–156 months) in the validation cohort, and 148 (55.6%) patients died during the follow-up. Figure 1 depicts the overall survival of the two staging systems. In the development cohort, the 5-year OS of the AJCC ypTNM stages I, II, and III were 58.8%, 39.1%, and 21.6% ($p < .001$). Applying the modified ypTNM staging, the 5-year OS was 69.9% for stage IA, 54.4% for stage IB, 34.4% for stage II, 24.1% for stage IIIA, and 13.6% for stage IIIB ($p < .001$). In the validation cohort, the 5-year OS of the AJCC ypTNM staging was 62.3% for stage I, 55.8% for stage II, and 27.4% for stage III ($p < .001$). The 5-year OS of the modified ypTNM staging was 79.1%, 61.6%, 49.7%, 37.8%, and 16.1% for IA, IB, II, IIIA, and IIIB, respectively ($p < .001$). According to the number of LN dissections (supplemental online Fig. 3), histological grade (supplemental online Fig. 4), and histological type (supplemental online Fig. 5), the modified ypTNM staging could separate the OS of each staged patient well (all $p < .001$).

Univariate and Multivariate Analysis

In the development cohort, univariate Cox regression analysis (supplemental online Table 2) showed that age, race, tumor size, histological type, tumor size, surgical procedure, histological grade, number of LN dissections, AJCC 8th edition ypTNM stage, and modified ypTNM stage were associated with OS (all $p < .05$). Then, a two-step multivariate Cox analysis was used to identify the independent prognostic factors of OS (Table 3). The multivariate analysis in the first step included all OS-related prognostic factors except the modified ypTNM stage, and the AJCC 8th edition ypTNM stage was an independent prognostic factor affecting OS ($p < .001$). The second-step multivariate analysis included all OS-related prognostic factors, including modified ypTNM stage. The results showed that modified ypTNM stage was an independent prognostic factor for OS ($p < .001$), whereas the AJCC 8th edition ypTNM stage disappeared ($p = .807$). Similar results were observed in the validation cohort. Univariate analysis revealed that tumor site, tumor size, histological grade, AJCC 8th edition ypTNM stage, and modified ypTNM stage were correlated with OS ($p < .05$). Multivariate analysis in the first step showed that the AJCC 8th edition ypTNM stage was an independent factor affecting OS ($p < .001$), whereas in the second-step multivariate analysis, the AJCC ypTNM stage ($p = .868$) was replaced by modified ypTNM stage ($p < .001$).

Time-dependent Cox analysis (supplemental online Table 3) showed that the modified ypTNM staging system could differentiate patients' prognoses over time among patients with GC after neoadjuvant therapy in both the development and validation cohorts.

Comparing the Prognostic Performance of the Two Staging Systems

Table 4 compares the prognostic predictive power of the two staging systems. In the development cohort (internal validation), the prognostic discriminating ability (C-index) of the modified ypTNM staging was better than that of the AJCC 8th edition system (0.620 vs. 0.589, $p < .001$). AIC analysis showed that the modified staging had a better goodness of fit than the AJCC staging (14,793.55 vs. 14,867.50, $p < .001$). The modified ypTNM staging had a better survival predictive homogeneity (higher likelihood ratio chi-square) compared with the AJCC ypTNM staging. BIC was used to compare the prognostic performance of the different staging systems. It accurately considered the number of parameters included in the staging system. The results showed that the modified ypTNM staging had a significant advantage over the AJCC ypTNM staging (mean difference in BIC:

Table 4. Comparison of the prognostic performance of the AJCC 8th edition ypTNM staging system and the modified ypTNM staging system

Variable	ypTNM staging (AJCC 8th)	Modified ypTNM staging	*p* value
Development cohort (internal validation)			
Harrell's C-index[a]	0.589 (0.572–0.605)	0.620 (0.602–0.638)	<.001
AIC[b]	14,867.50	14,793.55	<.001
Likelihood ratio chi-square[c]	140.71	218.66	<.001
Mean difference in BIC (95% CI)[d]	64.94 (25.55–96.46)		
NRI (95% CI)	35.54% (14.04%–43.12%)		<.001
IDI (95% CI)	0.032 (0.012–0.053)		.002
Validation cohort (external validation)			
Harrell's C-index[a]	0.631 (0.591–0.671)	0.668 (0.625–0.712)	.014
AIC[b]	1,461.06	1,443.6	<.001
Likelihood ratio chi-square[c]	28.75	45.15	<.001
Mean difference in BIC (95% CI)[d]	17.50 (1.98–32.88)		
NRI (95% CI)[e]	44.26% (10.00%–66.18%)		<.001
IDI (95% CI)[e]	0.048 (0.000–0.086)		.048

Abbreviations: AIC, Akaike information criterion; AJCC 8th, American Joint Committee on Cancer 8th edition; BIC, Bayesian information criteria; CI, confidence interval; IDI, integrated discrimination improvement index; NRI, net reclassification index.
[a]A higher Harrell's C-index indicates higher discriminative ability.
[b]Smaller AIC values indicate better optimistic prognostic stratification.
[c]A higher likelihood ratio chi-square score indicates better homogeneity.
[d]The BIC was used to assess the overall prognostic performance of different prognostic systems via bootstrap-resampling analysis.
[e]NRI and IDI quantify the improvement by the new staging system in predicting the patient's 5-year survival.

64.94). With the NRI or the IDI index, the survival prediction performance of the modified ypTNM staging was improved compared with the AJCC 8th edition staging (NRI: 35.54%, $p < .001$; IDI: 0.032, $p < .001$). Similarly, in external validation, the modified ypTNM staging was superior to the AJCC ypTNM staging in various indicators, reflecting the prognostic predictive power of the staging system (all $p < .05$).

The stratified analysis showed that the prognostic performance of the modified ypTNM staging was higher than that of the AJCC ypTNM staging in the development cohort, regardless of whether the number of LNs was adequate (supplemental online Table 4). We also performed a stratified analysis based on the histological grade (supplemental online Table 5) and the histological type (supplemental online Table 6). The results showed that in the development cohort, regardless of grade and histological type, the prognostic performance of the modified ypTNM staging was better than that of the AJCC ypTNM staging. In the external validation cohort, although the number of patients was limited, regardless of grade and histological type, the prognostic performance of the modified ypTNM staging showed a trend toward superiority of the AJCC ypTNM staging.

Time-Dependent ROC Curves and Decision Curve Analysis

Time-dependent ROC curves were used to compare the continuity trends of hazard ratios across systems. As shown in Figure 2A and B, the modified ypTNM staging was superior to the AJCC ypTNM staging over time in both the development and validation cohorts. We also used the decision curve to intuitively evaluate and compare the clinical applicability of the staging systems (Fig. 2C, D). The results showed that the modified staging could achieve better net benefits at the same probability threshold compared with the AJCC staging in both groups. According to the number of LN dissections (supplemental online Fig. 6), histological grade (supplemental online Fig. 7), and histological type (supplemental online Fig. 8), stratified analysis indicated that the modified staging was superior to the AJCC ypTNM staging in both the decision curve and the time-dependent ROC curve.

Discussion

GC is still a major global health problem, although with the popularity of upper gastrointestinal endoscopy screening, most patients with GC are diagnosed at an advanced stage [2, 26]. In recent years, based on clinical research on neoadjuvant therapy for GC [7, 27–29], preoperative therapy for GC has been increasingly recommended by Eastern and Western scholars. The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines also emphasize that neoadjuvant therapy can be used as a routine recommended treatment for patients with locally advanced GC [30, 31]. In contrast to the previous application of pTNM directly to the prognostic evaluation of patients with GC after receiving neoadjuvant therapy, the 8th edition of the AJCC manual provided the first standard for prognostic evaluation after neoadjuvant chemotherapy, and the ypTNM staging came into being. However, because of the limited number of cases included in the analysis of the AJCC manual, patients with nonmetastatic GC were only divided into three stages, I, II, and III, and our results showed that the 5-year OSs of patients in the same AJCC

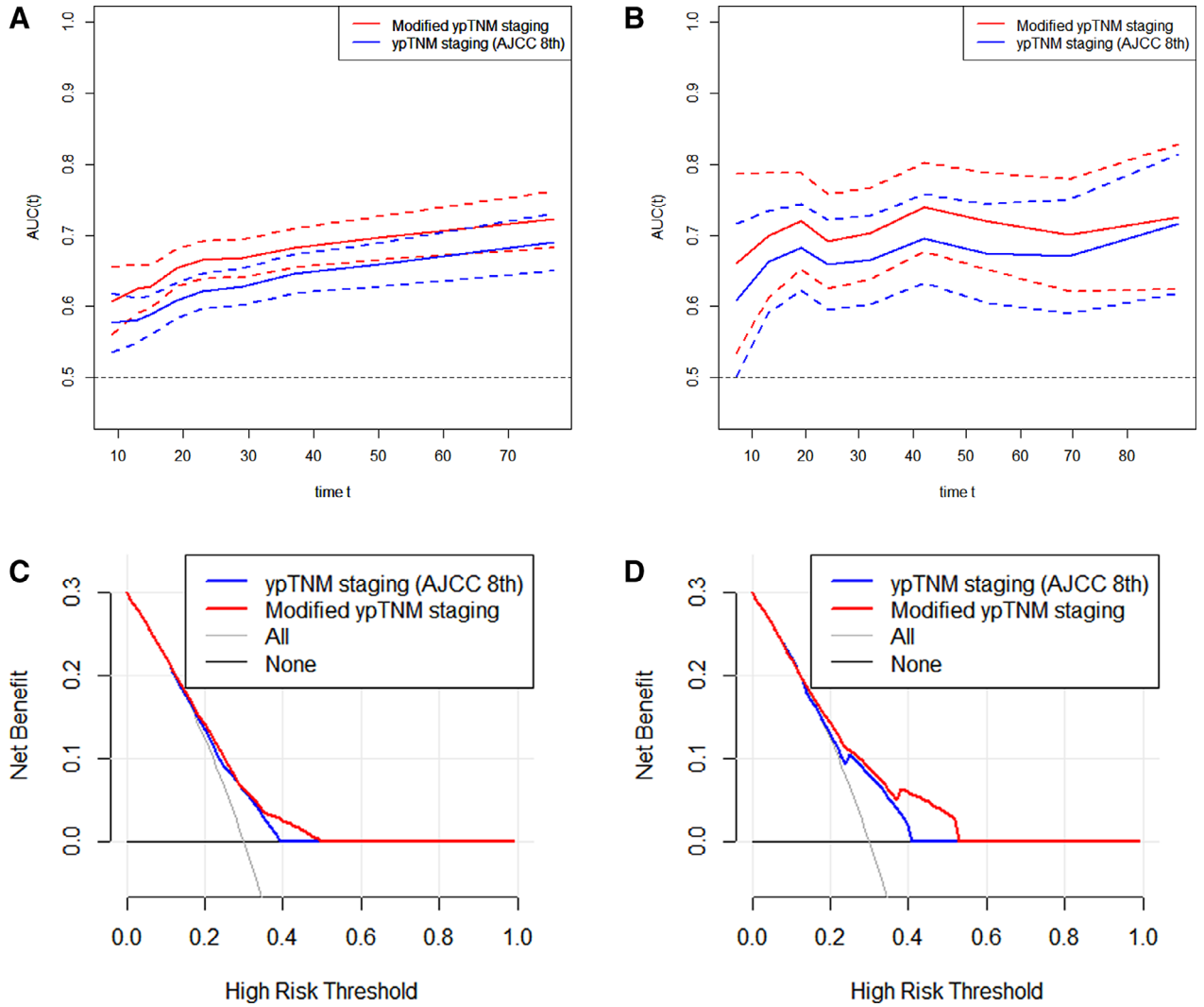

Figure 2. Comparison of the clinical usefulness of the AJCC 8th edition ypTNM staging system and the modified ypTNM staging system. Time-dependent receiver operating characteristics (ROC) curves for the AJCC 8th edition ypTNM staging system and the modified ypTNM staging system in the development cohort **(A)** and the validation cohort **(B)**. The *x*-axis represents the years after surgery, and the *y*-axis represents the estimated area under the ROC curve for survival at the time of interest. Decision curve analysis for overall survival after surgery in the development cohort **(C)** and the validation cohort **(D)**. The *y*-axis measures the net benefit.

Abbreviations: AJCC 8th, American Joint Committee on Cancer 8th edition; AUC, area under the curve.

8th edition stage could be very different. More detailed staging is the direction of the next edition of AJCC ypTNM staging. Our study confirmed the worth of the modification of the existing ypTNM staging and the more detailed classification of patients into five groups, which achieved more accurate prognostic discrimination. A detailed distinction between the prognosis of patients after surgery will facilitate postoperative adjuvant treatment options and follow-up surveillance. Moreover, time-dependent Cox regression showed that the modified ypTNM staging system differentiated the patients' prognoses well, with prolonged postoperative survival time. This modified ypTNM staging will help doctors provide patients with longer-term, more accurate counseling.

We used a variety of prognostic model evaluation indicators to compare the modified ypTNM staging system and the AJCC 8th edition ypTNM staging system in 1,791 patients who had undergone surgery after neoadjuvant chemotherapy from the SEER database. The discriminatory ability, predictive homogeneity, predictive accuracy, and model stability of the modified staging were superior to those of the AJCC 8th edition staging. At the same time, the two-step Cox regression analysis further indicated that the modified staging was significantly better than the AJCC 8th edition staging in evaluating the OS. Retrospective analysis showed that ≥15 LN dissections had a positive effect on the survival of patients with GC [32, 33]. The current guidelines also recommend ≥15 LN dissection for a more accurate staging [30, 34]. Our stratified analysis showed that the modified ypTNM staging was superior to the AJCC 8th edition ypTNM staging, regardless of whether the number of LN dissections was more than 15, which showed the stability of the modified staging. The study also used a validation cohort from China and Italy (mean LN examined: 29.4; D2

LN dissections: 94.0%) to confirm that the modified staging could still be used to evaluate the prognosis of patients after neoadjuvant therapy in Asian and European populations better than the existing AJCC ypTNM staging.

Previous studies have shown that different histological grades and histological types may have different responses to neoadjuvant therapy [35, 36]. Therefore, according to different histological grades and histological types, further stratified analysis was carried out. Our results show that the prognostic predictive performance of modified staging was still superior to the that of existing AJCC ypTNM staging for patients with well differentiated or poorly differentiated tumors, common adenocarcinomas, or special type adenocarcinomas, such as signet-ring cell carcinoma.

To maintain consistency in postoperative pathological judgment, ypT and ypN categories were defined with reference to pT and pN categories. A closer look at the AJCC TNM staging reveals that the 8th edition of the AJCC ypTNM staging is identical to the 7th edition of the AJCC pTNM staging in the broad classification. However, neoadjuvant therapy often has a downstaging effect on patients with cancer. Different patients have different therapeutic sensitivities to neoadjuvant therapy. Cancers that respond poorly to neoadjuvant therapy often exhibit stronger tumor invasion and metastatic ability [37]. We used a large sample of data to reorganize subgroups with similar 5-year survival rates to establish the new staging. In the modified staging, we found that the ypN category had a greater weighted effect on the prognosis of patients with GC receiving neoadjuvant therapy than ypT category. Further survival analysis under the ypT category and ypN category confirmed these findings (supplemental online Table 7; supplemental online Fig. 9). This may reflect that the primary tumor and metastatic LN respond differently to neoadjuvant therapy. Previous studies have also shown that LN status is more likely to affect the prognosis of patients receiving neoadjuvant therapy than the primary tumor state [38]. Our proposal has a quite different structure, suggesting stronger significance of the ypN category than the ypT category. Our modified staging allows us to assess the prognosis of patients receiving neoadjuvant therapy based on the response of the tumor to treatment, to a certain extent, and can provide a reference for future management and postoperative adjuvant treatment options for these patients.

The 5-year OS of patients between 2005–2009 and 2010–2015 in the development cohort was 33.6% and 31.1%, respectively (supplemental online Fig. 10). There was no significant difference between the two groups (p = .654). We also analyzed the OS of patients in the validation cohort according to the year of operation. The results showed that there was no significant difference between the two groups in 5-year OS (47.1% vs. 39.7%, p = .538). At the same time, we analyzed the OS of different centers in the validation cohort (supplemental online Fig. 11) and found that the 5-year OSs of FMUUH, IMIGASTRIC, and QUAH were 39.9%, 47.1%, and 39.6% respectively, and there was no significant statistical difference among the three groups (p = .596). The results of the univariate analysis showed that different years of operation or different centers are not independent prognostic factors of OS. We believe that although the patterns of neoadjuvant therapy are different in different periods, and with the progress of medical treatment, the neoadjuvant therapy has been continuously optimized, but the main factors that affect the prognosis may be ypT category and ypN category. The effect of the optimization of neoadjuvant treatment mode on the improvement of prognosis may be more reflected in its more obvious effect of downstaging. The modified ypTNM staging we established is based on the ypT category and ypN category, so it is more applicable and may be suitable for patients with GC who receive different neoadjuvant treatment schemes. We look forward to further validation of the modified ypTNM staging in the future through prospective studies of different neoadjuvant therapies.

The AJCC 8th edition ypTNM staging did not include patients with pathological complete response (ypCR) in the staging system. Because SEER did not describe ypCR or depth of invasion in detail, to ensure the reliability of staging, our modified ypTNM staging did not include patients with ypCR. In addition, although five patients in the validation cohort reached ypCR, their 5-year OS was 80.0%, which was similar to that of patients with stage IA. Because of the small number of patients, we did not include ypCR in the modified staging. A larger-sample analysis is still needed to further explore the prognosis of patients with ypCR and the best strategy for treating patients with ypCR. Previous studies have shown that the pathologic tumor response may affect the prognosis of patients with GC after neoadjuvant therapy [39]. However, studies such as the MAGIC trials have shown that the degree of tumor regression is not an independent prognostic factor [38]. This study is the largest study on the staging of patients with GC after neoadjuvant therapy. The SEER database provides a large amount of data from the U.S. population. Compared with data from one or two large centers, the SEER database can better reflect the overall prognosis of patients with GC receiving neoadjuvant therapy. The results are more universal and practical. However, the SEER database did not record the frequency of neoadjuvant therapy; we cannot know how many cycles of chemotherapy a given patient received, what regimen was given, etc., so we were unable to conduct further stratified analysis. There is no denying that the SEER data set may not be able to evaluate the ypN category very accurately, as fewer than 15 LNs were examined in 38.5% of the cases. The purpose of this study was to develop and validate a modified ypTNM staging, and the results showed that the modified staging was better than the AJCC 8th edition staging in both the development and validation cohorts. Supplemental online Table 1 also shows the 5-year OS of each ypTNM subgroup in the validation cohort. However, we found that because of the limited number of cases in the validation cohort, there were not enough cases in each ypTNM subgroup. In the validation cohort, one of two patients with ypT1N2M0 disease and one of two patients with ypT4bN1M0 disease were censored. Therefore, the 5-year OS of ypT1N2M0 and ypT4bN1M0 was not calculated. There may be some selection biases. AJCC TNM staging should be international, reflecting as many expert facilities as possible worldwide. The data used for AJCC 8th edition TNM staging was international, yet there were gaps

and limitations as well. Future iterations need to overcome limitations from individual databases like SEER that have only a selected cohort of patients. We look forward to further validation of this modified staging through global big data sets in the future, especially data from East Asia.

Conclusion

We have developed and validated a modified ypTNM staging through global multicenter data that is superior to the AJCC 8th edition ypTNM staging, allowing for a more accurate assessment of the prognosis of patients with GC after neoadjuvant therapy. It may provide a reference for the next edition of the AJCC ypTNM staging.

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Disclosures

The authors indicated no financial relationships.

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