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Is the AJCC TNM staging system still appropriate for gastric cancer patients survival after 5 years?

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ABSTRACT

Purpose: The aim of this study was to evaluate the prognostic value of the eighth AJCC TNM staging classification for patients with gastric cancer who had already survived for 5 years.

Patients and methods: Patients who underwent radical gastrectomy at a large eastern center were considered. The prognostic value of staging systems were assessed and compared. Additional external validation was performed using a dataset from the Surveillance, Epidemiology, and End Result (SEER) database.

Results: The 5-year overall survival (OS) rate for patients in the training set was 59.4%. With the prolongation of the survival time after surgery, the 5-year OS improved significantly ($P < 0.05$). However, there were no significant differences in survival curves among patients who have survived 5 years after surgery. The AUC and $\chi 2$ of the eighth AJCC classification for predicting of 5-year OS decreased gradually after surgery and appeared stable after 5 years. For patients who survived 5 years after surgery, we constructed a new TNM staging system (nTNM) according to the survival curves of T stage and N stage. A 2-step multivariate analysis showed that nTNM, age and sex were independent prognostic factors. The nTNM demonstrated superior prognostic stratification, with higher c-statistic and likelihood ratio chi-square scores and lower AIC values than those of the AJCC classification. Similar results were observed in the external validation set.

Conclusion: The nTNM predicted an additional survival more accurately than did the AJCC classification for patients who have survived 5 years after surgery; this may guide decisions regarding surveillance.

Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide [1]. In recent years, with the development of social economy and medical treatment, gastric cancer has been diagnosed earlier. In addition, the multimodal treatments for gastric cancer, especially new chemotherapeutic and biologic compounds, led to dramatically improve the patients' survival. More gastric cancer patients obtain longer-term survival. Accurate staging is critical for predicting the prognosis of malignant tumors, clinical decision making and determining surveillance strategy. The American Joint Committee on Cancer (AJCC) tumor-lymph node-metastasis (TNM) classification is currently the most important prognostic indicator for gastric cancer [2]; it is based on pathological and survival data after surgery (gradually based on 5-year overall survival). However,

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the risk of death changes over time, and survival probability for patients who already have survived for several years may change with respect to the probability predicted immediately after surgery [3]. Whether the AJCC classification can still provide a valid assessment of long-term prognosis in patients who have survived a specified period of time after surgery has not yet been reported. Therefore, the purpose of this study was to evaluate the changes in long-term prognosis and the prognostic value of the AJCC staging system for GC patients with prolongation of survival time after surgery to provide a more accurate staging system for patients who survive a long time after surgery.

Patients and methods

Study population

We retrospectively assessed all patients with resectable GC who were treated between January 1997 and December 2013 at Fujian Medical University Union Hospital (FMUUH). The inclusion criteria were defined as follows: (1) the presence of primary gastric cancer, (2) no distant metastasis, (3) R0 resection (no residual macroscopic or microscopic tumor), and (4) records of all relevant values. The following exclusion criteria were applied: (1) neoadjuvant chemotherapy, (2) histological identification of a tumor type other than adenocarcinoma or incomplete histopathological data, and (4) death within 1 month. Finally, 4556 patients were included in the study as the development cohort. Additional external validation was performed using a dataset from the Surveillance, Epidemiology, and End Results (SEER) database. Patients greater than 18 years of age in the SEER database with gastric cancer (ICD-*O*-3 code within the range of 8000–8152, 8154–8231, 8243–8245, 8250–8576, 8940–8950, and 8980–8990) who underwent gastrectomy between 1997 and 2010 were eligible for this study. According to the same inclusion and exclusion criteria, 5138 patients who survived more than 5 years after surgery were included as a validation cohort. Survival duration was measured from the time of surgery to either the last date that survival information was collected or the confirmed date of death. All patients were observed until death or the final follow-up date (FMUUH: December 2017, SEER: December 2013). The median follow-up for the two data sets was 105.0 months (FMUUH) and 120 months (SEER). All staging data within the database were updated and coded to conform with the 8th edition of the AJCC TNM staging system [2]. At FMUUH, adjuvant chemotherapy using 5-fluorouracil (5-FU)-based regimens was recommended to the majority of patients with advanced gastric cancer [3,4].

Statistical methods

Statistical analyses were performed using SPSS statistical software (version 18.0, SPSS Inc, Chicago, IL) and STATA version 12.0 (StataCorp, College Station, TX). The Kaplan-Meier method was used to estimate time-dependent survival probabilities. Evaluation of the monotonicity, distinctiveness, and homogeneity of the survival curves were conducted to judge staging adequacy. The prognostic abilities of the 8th AJCC classification for patients with gastric cancer who had already survived for a specified period of time after surgery were assessed by calculating the estimated area under the curve (AUC) and the likelihood ratio chi-square test. The log-rank test was used for statistical comparisons of the survival curves. A 2-step multivariate analysis was performed to investigate the validity of the new TNM system [5]. In the 1st step of the multivariate analysis, all significant factors in the univariate analysis were included as well as the 8th edition TNM system; the new TNM system was excluded. In the 2nd step of the multivariate analysis, the new TNM system was also included. The relative discriminatory abilities of the various TNM staging systems were assessed using the likelihood ratio chi-square test, the linear trend chi-square test, the Akaike information criteria (AIC) and Harrell's concordance index (c-statistic). A higher likelihood ratio chi-square score meant better homogeneity; a higher linear trend chi-square score showed better discriminatory ability and monotonicity; smaller AIC values represented better optimistic prognostic stratification [6]. A high c-statistic indicated better discriminatory ability [7,8]. Significant differences were assumed at P values less than 0.05 in a two-tailed test.

Results

Clinicopathological characteristics

A total of 4556 patients were included in the development cohort (Supplemental Table 1). Of these patients, 3463 (76.0%) were male and 1093 (24.0%) were female. The mean patient age at the time of surgery was 59.5 years. Based on the primary site of gastric cancer, 1866 (41.0%), 745 (16.4%), 1317 (28.9%) and 628 (13.8%) had tumors located at lower-third (L), middle-third (M), upper-third (U) and two or more positions of the stomach, respectively. In terms of surgery, 2020 (44.3%) patients underwent subtotal gastrectomy, and 41.8% received adjuvant chemotherapy after surgery. The average number of received lymph nodes was 29 and the average number of metastatic lymph nodes was 7. The majority of histological types were moderately or poorly differentiated tumors. According to the TNM staging system, 990 (21.7%), 823 (18.1%), and 2743 (60.2%) of the patients had stage I, II, and III disease, respectively (Supplemental Table 1).

Comparison of overall survival rate after surgery for GC

The median follow-up period was 105.0 (range, 1-277) months in the development cohort. The 5-year OS rates for patients after surgery and for those who had already survived 1–10 years after surgery were 59.2%, 66.6%, 74.7%, 80.8%, 84.9%, 87.5%, 89.4%, 87.3%, 86.0%, 84.2%, and 86.2%, respectively (Table 1). The 5-year OS rates at baseline to survival 4 years after surgery increased gradually and statistically ($P < 0.05$, Supplemental Fig. 1, Table 1). However, the 5-year OS rates of patients who survived 5 years–10 years after surgery tended to be stable, and no statistical significance was evident ($P > 0.05$, Supplemental Fig. 1, Table 1).

The prognostic value of the 8th AJCC classification

Fig. 1 shows the predictive performance of the 8th AJCC classification for predicting the 5-year OS of patients who survived each year after surgery. The AUCs and $\chi 2$ values of the 8th AJCC classification for predicting 5-year OS decreased gradually from surgery to survival 4 years after surgery and tended to remain stable and significantly lower than baseline at 5 or more years after surgery (Fig. 1A and B). For patients who survived 5 years after surgery, the survival curves of stage I and II were similar ($P > 0.05$, Fig. 2A) and were worse than those of the stage III patients according to the 8th AJCC classification ($P < 0.05$). This indicates that prognostic value of the 8th AJCC classification for the prediction of an additional survival of patients who survived more than 5 years after surgery decreased significantly.

Construction of an optimal staging system for patients at 5 years after surgery

The 5-year survival rates of patients at survival 5 years after

Table 1
Comparison of the overall survival at each year after surgery.

Time after surgery	OS (%)	P-0*	P-1*	P-2*	P-3*	P-4*	P-5*	P-6*	P-7*	P-8*	P-9*	P-10*
Baseline	59.2		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
1 year	66.6	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2 year	74.7	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
3 year	80.8	<0.001	<0.001	<0.001		0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.036
4 year	84.9	<0.001	<0.001	<0.001	<0.001		0.010	<0.001	0.009	0.010	0.075	0.227
5 year	87.5	<0.001	<0.001	<0.001	<0.001	0.010		0.245	0.561	0.345	0.558	0.830
6 year	89.4	<0.001	<0.001	<0.001	<0.001	<0.001	0.245		0.630	0.977	0.826	0.759
7 year	87.3	<0.001	<0.001	<0.001	<0.001	0.009	0.561	0.630		0.665	0.892	0.920
8 year	86.0	<0.001	<0.001	<0.001	<0.001	0.010	0.345	0.977	0.665		0.851	0.716
9 year	84.2	<0.001	<0.001	<0.001	0.003	0.075	0.558	0.826	0.892	0.851		0.869
10 year	86.2	<0.001	<0.001	0.001	0.036	0.227	0.830	0.759	0.920	0.716	0.869	

*P: Comparison of 5-year overall survival (OS) rate among patients who had survived a certain period of time following radical gastrectomy.
P-0: Compared the 5-year OS of patients after surgery.
P-1: Compared the 5-year OS of patients who have survived 1 year.
P-2: Compared the 5-year OS of patients who have survived 2 years.
P-3: Compared the 5-year OS of patients who have survived 3 years.
P-4: Compared the 5-year OS of patients who have survived 4 years.
P-5: Compared the 5-year OS of patients who have survived 5 years.
P-6: Compared the 5-year OS of patients who have survived 6 years.
P-7: Compared the 5-year OS of patients who have survived 7 years.
P-8: Compared the 5-year OS of patients who have survived 8 years.
P-9: Compared the 5-year OS of patients who have survived 9 years.
P-10: Compared the 5-year OS of patients who have survived 10 years.

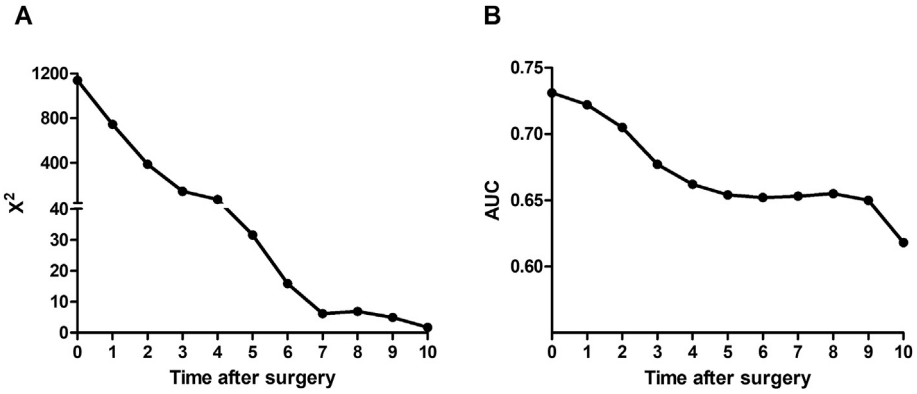

Fig. 1. A. The Chi-square value of the 8th AJCC staging system for prediction of overall survival at each year after surgery. B. The AUC value of the 8th AJCC staging system for prediction of overall survival at each year after surgery.

surgery according to the pT and pN categories are shown in Fig. 2B and C. No significant difference in survival could be observed among patients in stage T1, T2, and T3 ($P > 0.05$). The survival curves of T4a and T4b were similar ($P > 0.05$) and were significantly worse than those of T1, T2, and T3 ($P < 0.05$, Fig. 2B). Moreover, the prognosis of patients in stage N0 was significantly better than that of patients in N+ stage. However, the survival curves of stage N1, N2, and N3a were similar ($P > 0.05$) and were significantly better than those of N3b ($P < 0.05$, Fig. 2C).

According to these results, we divided T stages into two subgroups (T1-3 and T4a-4b), and we divided N stage into three subgroups as follows: N0, N1-3a and N3b stage. Furthermore, based on the new T stage and N stage, we generated six subgroups. We found that there was no significant difference in survival among patients with T1-3N0, T1-3N1-3a and T4N0 stage tumors ($P > 0.05$). The 5-year OS rates of patients in T1-3N3b, T4N1-3a and T4N3b were comparable ($P > 0.05$) but were worse than those of patients in T1-3N0, T1-3N1-3a and T4N0 ($P < 0.05$, Fig. 3A).

Therefore, we combined the T1-3N0, T1-3N1-3a and T4N0 into Stage I, and combined T1-3N3b, T4N1-3a and T4N3b into Stage II to simplify and establish a new TNM staging system (nTNM, Fig. 4). The 5-year OS rates of Stage I at 5 years after surgery was significantly better than those of Stage II (93.2% vs. 80.1%, $P < 0.05$, Fig. 3B).

Prognosis analysis

Univariate analyses suggested that age, gender, ASA score, tumor location, size, 8th AJCC classification and nTNM were associated with long-term overall survival of patients who have survived 5 years after surgery (all $P < 0.05$, Table 2). In the 1st step of the multivariate analysis, age, sex and 8th edition TNM system were confirmed to be independent prognostic factors (all $P < 0.05$, Table 2). When the nTNM was included in the 2nd step of the multivariate analysis, only nTNM remained significant ($P < 0.05$), and the 8th AJCC classification was no longer significant ($P = 0.222$, Table 2).

Prognostic performance of the nTNM

In the training set, the nTNM system demonstrated better optimistic prognostic stratification (smaller AIC value, 1748.74 vs 1751.57), better homogeneity (higher $\chi 2$ score, 36.31 vs 29.01), and better discriminatory ability (higher Harrell's C-index, 0.638 vs

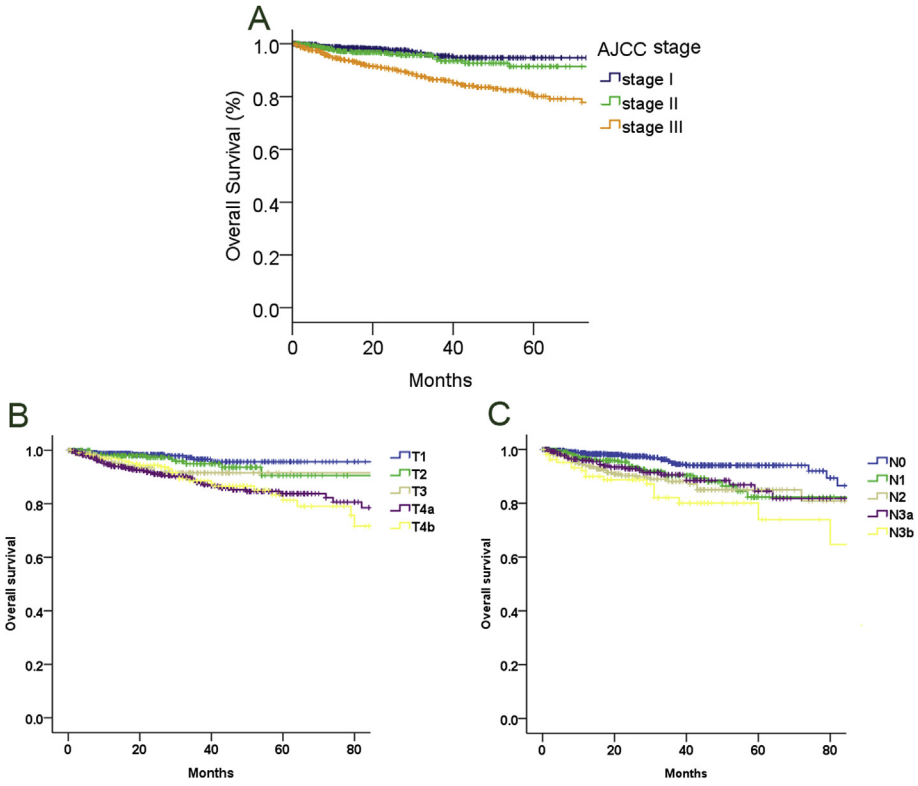

Fig. 2. Comparison of survival curves according to the 8th AJCC (A) TNM staging system, (B) T staging systems and (C) N staging systems at the 5th year after surgery.

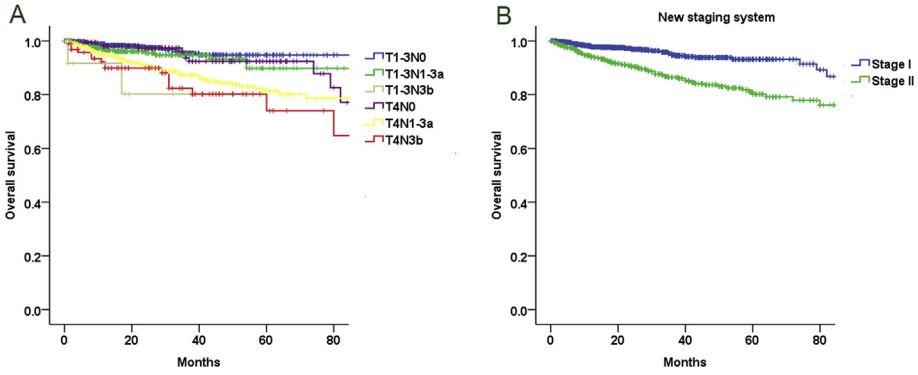

Fig. 3. A. Kaplan–Meier analysis for OS after 5 years according to recombination of T stage and N stage. B. The survival curves of the new staging system (nTNM).

nTNM	N0	N1-3a	N3b
T1-3	I	I	II
T4	I	II	II

Fig. 4. The definition of the new staging system (nTNM).

0.634) than did the 8th staging system (Table 3).

In the validation set, the nTNM stage also exhibited a smaller AIC value (35039.68 vs 35044.35) and higher $\chi 2$ score (13.26 vs 8.60) and Harrell's c-index (0.531 vs 0.521, Table 3), further confirming that the nTNM was simpler and gave better prognostic stratification than did the 8th AJCC classification for patients who survived 5 years after gastrectomy.

Discussion

In recent years, the standard surgical approach and several adjuvant therapy patterns suggested for the treatment of gastric cancer led to improved survival rates; the 5-year survival rates for patients with gastric cancer has exceeded 50% [9–12]. The AJCC TNM classification is important for assessing prognosis and determining appropriate treatment options for patients with gastric cancer; the 8th edition of the AJCC TNM classification system was published in 2016 [2]. For patients with gastric cancer, most recurrences or deaths occurred during the first 2 years after surgery, and the recurrence rate gradually decreased thereafter [13]. Thus,

Table 2
Two-step multivariable Cox proportional hazards analysis for overall survival at the 5th year after surgery.

Clinicopathologic Characteristics	Univariate Analysis	P	Multivariate analysis 1	P	Multivariate analysis 2	P
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age	1.964(1.389–2.776)	<0.001	1.869(1.322–2.644)	<0.001	1.945(1.375–2.751)	<0.001
Gender	0.549(0.338–0.893)	0.016	0.579(0.355–0.942)	<0.001	0.585(0.360–0.953)	0.031
ASA score	1.374(1.063–1.777)	0.015		0.111		0.119
Type of gastrectomy	0.786(0.572–1.078)	0.135				
Adjuvant chemotherapy	1.212(0.842–1.743)	0.301				
LNs resected	1.117(0.695–1.793)	0.648				
Tumor site	1.196(1.024–1.396)	0.024		0.571		0.610
Tumor size	1.541(1.086–2.188)	0.015		0.522		0.580
Histological type	1.231(0.787–1.924)	0.363				
AJCC 8th	1.885(1.481–2.398)	<0.001	1.873(1.471–2.386)	<0.001		0.222
nTNM				N/A	2.878(2.004–4.132)	<0.001

Note: Multivariate analysis 1, with consideration of all significantly important prognostic factors in univariate analysis except for the new staging system. Multivariate analysis 2, with consideration of all significantly important prognostic factors in univariate analysis including the new staging system.

Table 3
Comparison of the performance of the 8th AJCC staging system and new staging system for overall survival after 5 years' survival in a training and validation cohort.

	TNM system	C-index	AIC	$\chi 2$ (p value)
Training Set	AJCC 8th	0.634	1751.57	29.01(<0.001)
	nTNM	0.638	1748.74	36.31(<0.001)
Validation Set	AJCC 8th	0.521	35044.35	8.60(<0.001)
	nTNM	0.531	35039.68	13.26(<0.001)

the long-term survival of patients who have already survived for a specified period of time may change. For a variety of cancers, the survival probability of patients who have survived for a period was better than that at the time of surgery [14–16]. However, the AJCC TNM classification is based on 5-year overall survival rates post-operative [2]. When patients survive for a certain period of time, such as 5 years after surgery, whether the AJCC TNM classification still accurately predicts the prognosis of GC has not been reported. In our study, from baseline to survival 4 years after operative, the 5-year OS rate increased significantly from 59.4% to 93%. For those who survived 5 years or more, the 5-year OS rate did not improve significantly. Furthermore, the prognostic value of the 8th AJCC classification gradually decreased over time and tended to remain stable for patients who survived 5 years or more after surgery, indicating that for those patients who survived 5 years or more, the prognostic efficacy of the 8th AJCC classification became weakened. Nowadays, there were rare studies focused on the assessment of long-term prognosis in patients who have survived a specified period of time after surgery. Therefore, accurate prediction of prognosis for patients who survive a long time after surgery is crucial to develop follow-up plans.

Since the first edition of the AJCC Cancer Staging Manual was published in 1977, the T and N categories remain the most important indicators for patients' prognosis, which are consistent with our findings. Therefore, in order to maintain a good consistency between the new staging system and the 8th edition TNM staging system, and to facilitate clinical promotion and application, we did not introduce other new prognostic factors in this study. However, with the prolongation of survival time after surgery, it remained unclear as to whether the cut-off points of the two categories were applicable. We found that the survival curves of T1, T2 and T3 stage for patients who survived 5 years after surgery were similar and were significantly lower than that of T4 stage. Similarly, the prognosis of patients in N0 stage was better than that of patients in N1/N2/N3a stage, but the prognosis of patients in N3b stage was the worst. Thus, based on the survival analysis, we redivided the T and N stages and combined them. According to the survival curve of the recombination, we divided patients into Stage I and Stage II to develop the nTNM. Kaplan-Meier curves showed that the 5-year OS rates differed significantly according to the nTNM. To investigate the long-term prognostic factors for GC, 2-step multivariate analysis was performed. The 8th AJCC classification was confirmed as an independent factor for GC. When the nTNM was included in the 2nd step of the analysis, it became one of the independent predictors, whereas the influence of the 8th TNM system became insignificant. Furthermore, we showed that the nTNM gave better homogeneity, discriminatory ability and monotonicity of the gradients than did the 8th AJCC classifications. These results indicated that nTNM was superior to the 8th TNM system for patients who survived for 5 years after surgery. However, before considering whether to use a clinical prediction model, it is essential that its predictive performance is empirically evaluated in datasets that were not used to develop the model, notwithstanding potential lower predictive accuracy in an external validation set [17–19]. Moreover, the UICC/AJCC staging system is the worldwide used staging system. It is more stringent external validation involves a dataset from another country than external validation involves using a dataset from a different institution or a validation set from the same institution based on a data-splitting method [20]. On the other hand, because the gastric cancer in Asian patients may differ biologically from gastric cancer in Americans or Europeans [21–23], the prognostic value of the new TNM classification should also be evaluated in a Western-based population. Therefore, in the current study, the additional external validation was performed using an American dataset from the National Cancer Institute's SEER database. And we obtained similar results in the SEER database, indicating that the nTNM has better prognostic value for patients who survived 5 years after gastrectomy.

Our study has certain limitations. First, as a retrospective study, it may have been subject to selection bias. Second, the adjuvant therapy information in the SEER dataset was unclear, possibly affecting the prognosis. Despite these limitations, based on large Eastern and Western datasets, to the best of our knowledge this study was the first to find that the 8th AJCC staging system could not accurately predict the OS of GC patients who survived 5 years after gastrectomy. By restaging the T stage and N stage, we propose an nTNM that predicts the an additional survival patients who survive more than 5 years after gastrectomy more accurately; this is beneficial for postoperative follow-up planning for patients who survive more than 5 years after surgery. For patients in Stage I, tumor recurrence and metastasis are rare at 5 years after surgery, and we recommend that these patients be followed-up every two years. However, the 5-year OS rates for patients in Stage II who

survived 5 years was 80.1%, indicating that there remains a risk of tumor recurrence. Thus, it is still recommended that these patients should be followed-up once a year.

Author contributions

Lin JX, Lin JP, Zheng CH, Huang CM and Li P conceived of the study, analyzed the data, and drafted the manuscript; Tu RH, Li P, Xie JW, Wang JB, and Li P helped revise the manuscript critically for important intellectual content; Lu J, Chen QY, Cao LL, and Lin M helped collect data and design the study.

Conflict of interest

There are no conflicts of interest or financial ties to disclose from any of author.

Human rights statement and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.002.

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