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Research Paper

Proposal for a New TNM Stage based on the 7th and 8th American Joint Committee on Cancer pTNM Staging Classification for Gastric Cancer

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Abstract

Background: The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for gastric cancer incorporated several new changes. We aimed to assess the comparative prognostic values of the 7th and 8th AJCC pTNM staging systems in patients with gastric cancer (GC), and accordingly, to put forward a refined staging classification.

Methods: The SEER database was queried to identify GC patients between 2004 and 2009. GC patients from Sun Yat-sen University Cancer Center (SYSUCC) were used as external validation data. The Kaplan-Meier method and Cox proportional hazards regression models were used to analyze cause-specific survival (CSS). The prognostic performance of different staging schemes was assessed using the concordance index (c-index), Akaike's information criterion (AIC), and likelihood ratio χ^2 test.

Results: In the SEER cohort, stage migration occurred in 8.74% of patients. Survival analysis showed that it was better to treat T4bN0M0 + T4aN2M0 as stage IIIB and T4bN3bM0 as stage IV. Based on this, we established a new staging system which exhibited a superior c-index (0.7501) to the 7th and 8th AJCC staging systems (0.7498 and 0.7500, respectively). The new staging system also outperformed the 7th and 8th AJCC staging systems in terms of AIC and the likelihood ratio χ^2 test. The predictive superiority of the new staging system remained valid in the SYSUCC database.

Conclusions: We demonstrated that some stage modifications in the 8th AJCC pathologic staging were unnecessary. Therefore we established a new staging system, which was superior to the 7th and 8th staging systems.

Key words: Gastric Cancer; Prognosis; SEER; TNM staging classification

Introduction

Gastric cancer (GC) is the second most common cause of cancer-related deaths worldwide [1]. In 2015, more than 679,000 incident cases were estimated in China, and it was estimated to cause 498,000 deaths [2]. Until now the prognosis for GC patients remains poor. Accurate staging system is therefore essential to guide treatment and predict prognosis [3, 4].

The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system that we are now using is the 7th edition. The 8th Edition Cancer Staging System will be taken into implementation on January 1, 2018.

Several important changes were incorporated into the 8th edition staging system of GC. The 8th classifications provide more comprehensive tools, including cTNM, ypTNM and pTNM for stage grouping of GC patients under different situation [5]. cTNM and ypTNM are new proposed and need to be validated in clinical practice. Though there is no change to the definition of pT, pN and pM classification, pN3a and pN3b are treated different in the final pTNM classification. The changes only happen on stage II and stage III, especially stage III. In detail, T1N3bM0 and T2N3bM0 are upstaged from stage IIB, IIIA in the 7th edition to stage IIIB in the 8th edition. T3N3bM0 is upstaged from stage IIIB in the 7th edition to stage IIIC in the 8th edition. T4bN0M0 and T4aN2M0 are downstaged from IIIB in the 7th edition to IIIA in the 8th edition. Moreover, T4aN3aM0 and T4bN2M0 tumors are downstaged from IIIC in the 7th edition to IIIB in the 8th edition.

Changes made to the TNM classification are based on survival analyses from National Cancer Database NCDB (U.S.) and Shizuoka Cancer Center (Japan) dataset. However, it remains unclear whether these changes are necessary or not. Lu J et al. compare the 7th and 8th editions of the AJCC TNM classification for stage III GC patients in China and found that the 8th TNM edition may not provide significantly better accuracy in predicting prognosis of stage III GC patients [6, 7].

We sought to evaluate the discriminative ability of the AJCC 8th edition staging system and to study the impact of stage shift on stratification of survival using the Surveillance, Epidemiology, and End Results (SEER) database and a Chinese institutional cohort. Based on this analysis, we made some modification and put forward a new staging classification, aiming to better predict the prognosis.

Methods

Database

The SEER database is the largest publicly available cancer dataset. The exact dataset we used for this analysis was SEER Program (www.seer.cancer.gov) Research Data (1973-2014) based on the November 2016 submission, "Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (1973-2014 varying)". The study population was based on the SEER cancer registry. Inclusion criteria were: 1) adults (aged 18 years or older) patients; 2) gastric adenocarcinoma (also including mucinous adenocarcinoma and signet ring cell carcinoma) from 2004 to 2009; 3) with clear record of TNM 7th stage. Exclusion criteria were: 1) patients without follow-up records (survival time code of 0 months); 2) patients without TNM stage. Patients were staged using the 7th and 8th editions of the AJCC TNM staging systems. Because SEER is public-use data, institutional review board approval and informed consent was waived.

Another cohort from the Sun Yat-sen University Cancer Center (SYSUCC) was used as external validation data. It included all the gastric adenocarcinoma cancer patients who received therapy and had full record of follow-up in SYSUCC during 2001 and 2012 (Supplementary table 1). The study protocol for the Chinese cohort was approved by the independent Ethics Committees at SYSUCC.

A new TNM stage classification

Based on our analysis, we suggested setting up a new TNM staging system. In this new system, both T4aN2M0 and T4bN0M0 were classified as IIIB. Moreover, since there was no significant survival difference between patients with T4bN3bM0 and with stage IV. We restaged T4bN3bM0 as stage IV (Supplementary table 2).

Statistical Methods

The primary endpoint of this study was 5-year cause specific survival (CSS). Survival function estimation and comparison among different variables were performed using Kaplan–Meier estimates and the log-rank test. The multivariate Cox proportional hazard model was used to evaluate the hazard ratio (HR) and the 95 % CI for all the known prognostic factors, including location, race/ethnicity, histology, grade, TNM stage, grade and therapy (Surgery with or without radiotherapy). The discriminatory ability of the staging schemes was measured using the concordance index (C-index) [8] and the Akaike's information criterion (AIC). The prognostic homogeneity of the staging schemes was assessed using the Likelihood ratio χ^2 test. The higher the C-index and the likelihood ratio χ^2 value, or the lower the AIC value, the better performance of the staging scheme. We used the Intercooled Stata 13.0 (Stata Corporation, College Station, TX) and R software v. 3.2.3 (http://www.r-project.org) for analysis. Statistical significance was set at two-sided $P < 0.05$.

Results

Patient Demographics in SEER database

The study identified 18,125 gastric adenocarcinoma patients from SEER database (Table

1). Of these patients, 11,357 (62.66%) were male and 6,768 (37.34%) were female. The median age of the whole group was 66 years old. The patient distribution from 2004 to 2009 was balanced. Over two thirds of patients were Caucasian and about 15% of the patients were Asian. Most of the patients had poorly differentiated tumors and 23% of the patients had signet ring cell carcinoma. The most common tumor sites were cardia (27.54%) and antrum (21.51%). About 40% of the patients did not receive surgery. The surgery methods included palliative resection and radical resection. About half of the patients (47.81%) were diagnosed with metastatic diseases.

Table 1. Clinicopathologic factors and survival of the gastric cancer patients using the SEER dataset

Factor	Number (%)	Median OS (months)	5-year survival rate (%)	*P* value
Age				
<66	8689 (47.94)	14	27.00 (26.04-27.98)	
>65	9436 (52.06)	13	27.88 (26.92-28.85)	0.4428
Sex				
Female	6768 (37.34)	13	27.55 (26.43-28.67)	
Male	11357 (62.66)	14	27.33 (26.47-28.20)	0.5400
Year of diagnosis				
2004	3119 (17.21)	13	26.56 (24.94-28.20)	
2005	2950 (16.28)	13	26.39 (24.72-28.09)	
2006	3028 (16.71)	13	27.89 (26.22-29.58)	
2007	3056 (16.86)	14	26.68 (25.03-28.35)	
2008	2976 (16.42)	15	28.85 (27.14-30.58)	
2009	2996 (16.53)	14	28.17 (26.49-29.87)	0.2837
Ethnicity				
Caucasian	12603 (69.53)	12	25.09 (24.29-25.89)	
African American	2379 (13.13)	12	26.59 (24.73-28.48)	
Asian	2783 (15.35)	26	39.26 (37.35-41.16)	
Others	360 (1.98)	9	21.12 (16.70-25.89)	<0.001
Grade				
Well differentiated	572 (3.16)	110	56.82 (52.50-60.90)	
Moderately differentiated	4053 (22.36)	25	39.01 (37.43-40.59)	
Poorly differentiated	10900 (60.14)	13	24.35 (23.50-25.21)	
Undifferentiated	357 (1.97)	12	22.07 (17.73-26.73)	
Unknown	2243 (12.38)	6	14.32 (12.81-15.90)	<0.001
Location				
Cardia	4992 (27.54)	14	24.03 (22.80-25.28)	
Fundus	653 (3.60)	10	22.64 (19.35-26.11)	
Body	1613 (8.90)	13	29.89 (27.56-32.25)	
Antrum	3898 (21.51)	21	36.04 (34.45-37.63)	
Pylorus	620 (3.42)	19	32.47 (28.65-36.35)	
Lesser curvature	1584 (8.74)	29	41.18 (38.61-43.72)	
Greater curvature	736 (4.06)	18	32.23 (28.68-35.82)	
Overlapping lesion	1489 (8.22)	8	16.03 (14.09-18.07)	
NOS	2540 (14.01)	6	15.90 (14.40-17.46)	<0.001
Histology				
Adenocarcinoma	13454 (74.23)	14	29.18 (28.37-29.99)	
Mucinous adenocarcinoma	493 (2.72)	16	28.40 (24.28-32.66)	
Signet ring cell carcinoma	4178 (23.05)	11	21.58 (20.27-22.92)	<0.001
Surgery				
Yes	10833 (60.04)	37	43.56 (42.58-44.54)	
No	7210 (39.96)	4	2.24 (1.88-2.66)	<0.001
T stage				
T1	3539 (19.53)	88	51.99 (50.27-53.68)	
T2	1546 (8.53)	80	52.95 (50.28-55.54)	
T3	4157 (22.94)	24	33.11 (31.60-34.62)	
T4a	2947 (16.26)	16	20.75 (19.21-22.33)	
T4b	2681 (14.79)	6	7.43 (6.39-8.57)	
Tx	3255 (17.96)	3	1.95 (1.45-2.56)	<0.001
N stage				
N0	4147 (22.88)	NR	69.58 (68.10-71.02)	
N1	2038 (11.24)	31	39.93 (37.68-42.17)	
N2	1938 (10.69)	23	29.93 (27.78-32.11)	
N3a	1890 (10.43)	16	17.77 (15.96-19.67)	
N3b	1032 (5.69)	10	8.53 (6.81-10.49)	
Nx	7080 (39.06)	4	2.04 (1.69-2.45)	<0.001
M stage				
M0	9460 (52.19)	54	48.71 (47.65-49.76)	
M1	8665 (47.81)	5	3.17 (2.77-3.60)	<0.001
TNM 7th stage				
IA	1781 (9.83)	NR	85.45 (83.65-87.07)	
IB	907 (5.00)	NR	72.82 (69.63-75.73)	
IIA	1305 (7.20)	NR	60.41 (57.57-63.13)	
IIB	1311 (7.23)	48	46.62 (43.74-49.45)	
IIIA	1219 (6.73)	29	34.54 (31.72-37.37)	
IIIB	1716 (9.47)	19	23.66 (21.54-25.85)	
IIIC	1221 (6.74)	14	13.87 (11.85-16.05)	
IV	8665 (47.81)	5	3.17 (2.77-3.60)	<0.001
TNM 8th stage				
IA	1781 (9.83)	NR	85.45 (83.65-87.07)	
IB	907 (5.00)	NR	72.82 (69.63-75.73)	
IIA	1305 (7.20)	NR	60.41 (57.57-63.13)	
IIB	1296 (7.15)	48	46.62 (43.74-49.45)	
IIIA	1829 (10.09)	26	32.17 (29.91-34.46)	
IIIB	1547 (8.54)	18	21.63 (19.47-23.86)	
IIIC	795 (4.39)	12	9.53 (7.45-11.9)	
IV	8665 (47.81)	5	3.17 (2.77-3.60)	<0.001
New TNM stage				
IA	1781 (9.83)	NR	85.45 (83.65-87.07)	
IB	907 (5.00)	NR	72.82 (69.63-75.73)	
IIA	1305 (7.20)	NR	60.41 (57.57-63.13)	
IIB	1296 (7.15)	48	46.62 (43.74-49.45)	
IIIA	1192 (6.58)	26	31.62 (29.26-34.00)	
IIIB	2184 (12.05)	19	22.88 (20.77-25.05)	
IIIC	688 (3.80)	12	9.53 (7.45-11.9)	
IV	8772 (48.40)	5	3.17 (2.77-3.60)	<0.001

The average number of dissected lymph nodes was 10.45 ± 14.86 (mean ± SD) (median 6). The mean number of metastatic nodes was 6.54 ± 15.05 (median 2).

There were 2922 patients with N3 tumors including 1890 N3a (64.68%) and 1032 N3b (35.32%).

Stage Migration

Among the 18,125 gastric cancer patients, 16,540 (91.26%) of them have same stage in these 2 TNM classification systems including stage IA, IB, IIA and IV (Table 2). Stage migration only happened in 8.74% of GC patients, including 1.56% (282/18125) of patients migrating to a higher tier (the stage in the AJCC 8th system was higher than the stage in the 7th system) and 7.19% (1303/18125) migrating to a lower tier (the stage in the AJCC 8th system was lower than the stage in the 7th system). Only 15 (0.08%) patients were upstaged from stage IIB to stage IIIB and these patients were stage T1N3bM0. All the rest changes happened on stage III, including 27 patients (T2N3bM0) from stage IIIA to stage IIIB, 240 patients (T3N3bM0) from stage IIIB to stage IIIC, 477

(T4aN2M0) and 160 (T4bN0M0) from stage IIIB to stage IIIA, 515 (T4aN3aM0) and 151 (T4bN2M0) patients from stage IIIC to stage IIIB.

Table 2. Distribution of patients in the 7th and the 8th AJCC TNM staging system

		AJCC TNM 8th stage								Sum
		IA	IB	IIA	IIB	IIIA	IIIB	IIIC	IV	
AJCC TNM 7th stage	IA	1781	0	0	0	0	0	0	0	1781
	IB	0	907	0	0	0	0	0	0	907
	IIA	0	0	1305	0	0	0	0	0	1305
	IIB	0	0	0	1296	0	15	0	0	1311
	IIIA	0	0	0	0	1192	27	0	0	1219
	IIIB	0	0	0	0	637	839	240	0	1716
	IIIC	0	0	0	0	0	666	555	0	1221
	IV	0	0	0	0	0	0	0	8665	8665
Sum		1781	907	1305	1296	1829	1547	795	8665	

Is the stage migration necessary?

To better understand the stage migration in the 8th edition of TNM classification, we compared the 5-year CSS between patients from two adjacent groups (Figure 1, supplementary table 3). We found that patients with stage IIIA had significantly better survival than patients with stage T4bN0M0 + T4aN2M0, *P*=0.0005. While there was no significant survival difference between patients with stage IIIB and stage T4bN0M0 + T4aN2M0, *P*=0.1705. Therefore it was better to treat T4bN0M0 + T4aN2M0 as stage IIIB as they were in the AJCC TNM 7th edition. Patients with stage T4aN3aM0 + T4bN2M0 did have a better prognosis than patients with stage IIIC and there was no significant survival difference between patients with stage T4aN3aM0 + T4bN2M0 and stage IIIB. It is reasonable to change T4aN3aM0 + T4bN2M0 from stage IIIC to stage IIIB as in the 8th edition. Patients with stage T3N3bM0 had a significantly better prognosis than stage IIIC and significantly worse prognosis than stage IIIB. Furthermore, we compared the survival among patients with stage T3N3bM0, T4aN3bM0, T4bN3aM0, T4bN3bM0 and TxNxM1 (Figure 3). We found that there was no significant difference among patients with stage T3N3bM0, T4aN3bM0 and T4bN3aM0, *P*=0.3041 and no survival difference between patients with stage T4bN3bM0 and TxNxM1, *P*=0.0551.

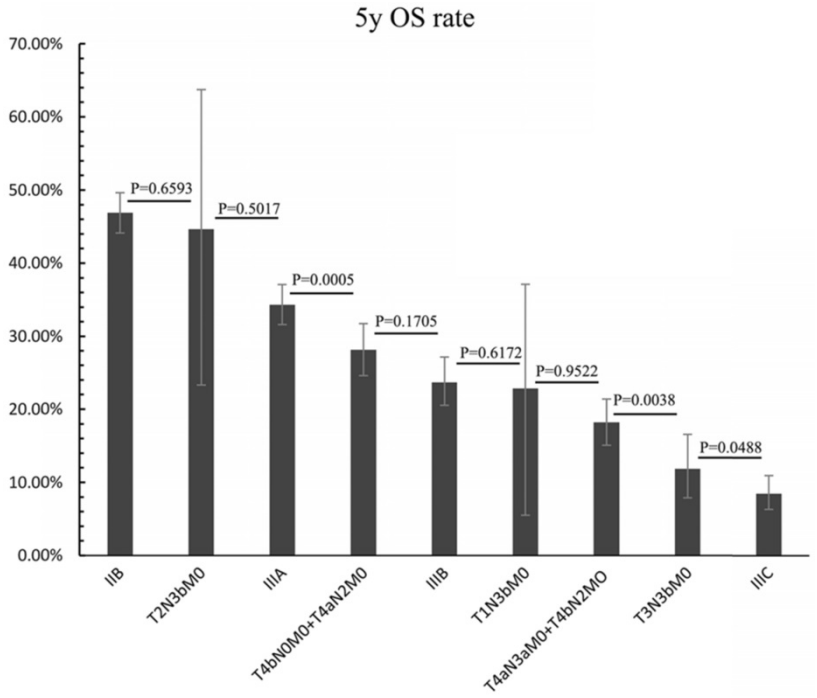

Figure 1. 5-year cause specific survival between patients from two adjacent groups.

Survival analysis

The mean follow-up for the entire SEER cohort was 28.59 months. The overall 5-year CSS for the whole group of patients was 27.42% (95% CI: 26.73%-28.10%), with median survival of 13.0 months. Figure 2 showed the survival curve of patients according to the TNM 7th edition (2A), TNM 8th edition (2B) and the new TNM stage (2C). The median survival for patients with stage IA to stage IIA was not reached yet. The median survival for patients with stage IIB and stage IV remained the same in all the three TNM stage systems. The median survival for patients with stage from IIIA to IIIC was 29 months, 19 months and 14 months in the TNM 7th edition, 26 months, 18 months and 12 months in the TNM 8th edition and 26 months, 19 months and 12 months in the new TNM stage systems (Table 1).

The univariated analysis showed that ethnicity, tumor grade, location, histology subtype, surgery, TNM stage were all significantly related to the CSS (Table 1). Multivariated analysis for factors that had significant correlation with CSS showed that ethnicity, tumor grade, location, surgery and TNM stage were all independent prognostic factors. The performance of the 7th, 8th and the new staging system were assessed by the C-index, AIC and likelihood ratio $\chi 2$ value (Table 3). The new staging system had the highest C-index, likelihood ratio $\chi 2$ value and lowest AIC which suggested that the new staging system was best in predicting the prognosis.

Validation using GC patients from SYSUCC

In order to validate the value of the new staging system, we compared the three staging classification in Chinese

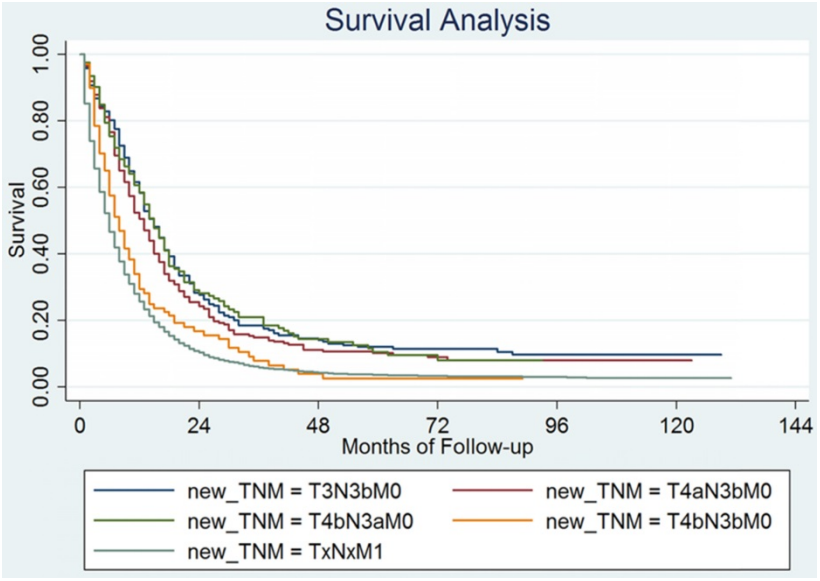

Figure 2. Survival curve of patients according to the TNM 7th edition (A), TNM 8th edition (B) and the new TNM stage (C).

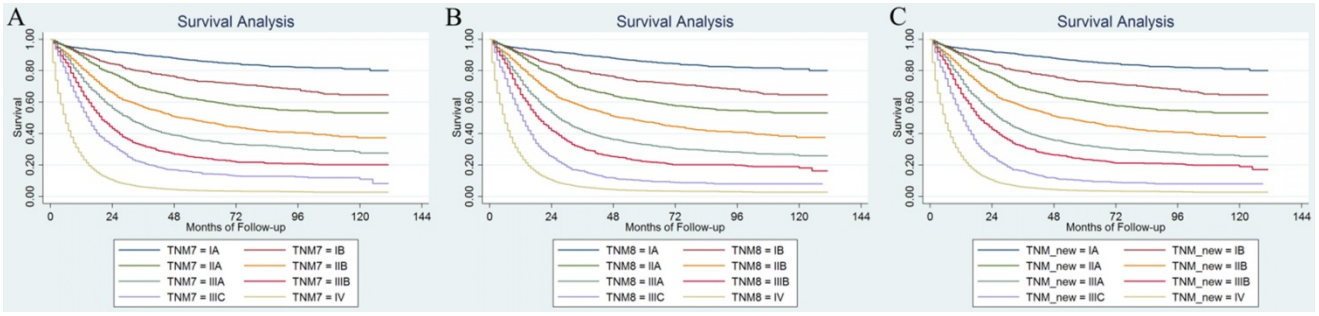

Figure 3. Survival comparison among patients with stage T3N3bM0, T4aN3bM0, T4bN3aM0, T4bN3bM0 and TxNxM1.

GC patients from SYSUCC and we also found that the new staging system was best with the highest C-index as well as likelihood ratio $\chi 2$ value and lowest AIC (Table 3).

Table 3. Comparison of the prognostic performance among the 7th, 8th and new AJCC TNM staging system

		Concordance indices		AIC	Likelihood ratio $\chi 2$
		C-index	Bootstrap 95% CI		
SEER database	7th TNM	0.7498	0.7446-0.7552	175219.9	8023.37
	8th TNM	0.7500	0.7447-0.7553	175180	8063.33
	New TNM	0.7501	0.7448-0.7554	175156.9	8086.39
SYSUCC database	7th TNM	0.7599	0.7429-0.7769	13438.99	751.55
	8th TNM	0.7576	0.7406-0.7746	13452.43	738.11
	New TNM	0.7608	0.7438-0.7778	13434.47	756.08

Discussion

Accurate staging is essential to guide treatment and predict prognosis. In order to ensure that the cancer care community has the necessary infrastructure in place for documenting the 8th Edition stage, the AJCC Executive Committee made the decision to delay the implementation of the 8th Edition Cancer Staging System to January 1, 2018. New to the 8th edition of the AJCC Cancer Staging Manual for epithelial cancers of the esophagus and esophagogastric junction are separate, temporally related cancer classifications: 1) before treatment decision (clinical); 2) after esophagectomy alone (pathologic); and 3) after preoperative therapy followed by gastrectomy (post-neoadjuvant pathologic). The addition of clinical and post neoadjuvant pathologic stage groupings needed to be validated in the clinical practise. Here, in our present study, we analysed the change to the pathologic TNM classification.

Compared to the change from 6th edition to 7th edition, the 8th pTNM edition only made small changes. In the pTNM 8th edition, pN3a and pN3b were treated differently in the final pTNM classification [5]. Stage migration only happened in 8.74% of GC patients. Basically, the main change happened in stage III patients. Only 15 (0.08%) patients were from stage IIB and they were upstaged to stage IIIB. In the TNM 8th edition, the percentage of stage IIIA increased, while stage IIIB and IIIC decreased. Though the 8th staging system had higher c-index than the 7th edition, the difference was not

significant. Lu J et al. evaluated the prognostic value of the AJCC TNM 8th classification in comparison with the 7th edition for stage III GC patients in China [6] and they found that the 8th TNM edition was more accurate in predicting stage III gastric cancer patients' prognosis than the 7th edition. However the C-index of 7th and 8th staging systems in Lu's research had no big difference. Similar results were reported in other malignancy diseases [9-14].

To analyse whether these were changes necessary, we compared the survival between patients from two adjacent groups. There was no significant difference between stage T1N3bM0 and stage IIIB, so it was reasonable to change stage T1N3bM0 from stage IIB to stage IIIC. However, there were only 15 patients in the category T1N3bM0 and 27 patients in the category T2N3bM0. The changes in these two categories did not affect a great number of patients. We found that patients with stage T4bN0M0+T4aN2M0 had no significant survival difference with stage IIIB, but worse survival than stage IIIA. Therefore it is better to treat T4bN0M0 + T4aN2M0 as stage IIIB as they were in the AJCC TNM 7th edition. Patients with stage T4aN3aM0 + T4bN2M0 had a better prognosis than patients with stage IIIC and no survival difference with stage IIIB. So it is reasonable to change T4aN3aM0 + T4bN2M0 from stage IIIC to stage IIIB. Patients with stage T3N3bM0 had a significantly better prognosis than stage IIIC and significantly worse prognosis than stage IIIB. Stage IIIC included T4aN3bM0, T4bN3aM0 and T4bN3bM0. Further analysis showed that there was no survival difference among patients with stage T3N3bM0, T4aN3bM0 and T4bN3aM0. Moreover patients with stage T4bN3bM0 had similar survival with stage IV patients. Based on this analysis, we established a new staging system. We restaged T4bN0M0 + T4aN2M0 as stage IIIB, T4bN3bM0 as stage IV in the new staging system. We found that the new staging system was best in predicting the prognosis with the SEER database. Moreover, the prognostic superiority of the new staging system was validated in Chinese GC patients.

From 6th to 7th edition, several studies showed that 7th edition TNM system performed better than the 6th edition in several aspects, including our previous study [4, 15, 16]. Though the 8th TNM staging classification seemed better than the 7th, we found that there were several unnecessary stage modifications in the 8th edition. By avoiding these unnecessary stage modifications and introducing more reasonable stage regrouping, we put forward a new staging classification which was better than both the 7th and 8th staging systems in predicting the prognosis. However, we need to realize that the value of TNM staging classification in predicting patients' prognosis has reached a plateau, because the newly proposed TNM staging showed only numerically but not statistically significantly improved C-index. To better predict patients' prognosis, other variables should be taken into consideration, such as histological and molecule phenotypes [17, 18]. It might be worthwhile to combine TNM classification system with molecular phenotypes [19-21].

The strength of this study included that we not only used the data from SEER, but also include dataset from our own hospital. Moreover, we put forward some modifications to the 8th TNM staging system, trying to make it better. Potential limitations of our study should be taken into consideration. Unmeasured factors in SEER database, such as chemotherapy and tumor biology might play roles in patient outcome. We did not put these factors into the cox regression analysis.

In conclusion, we demonstrated that it was more reasonable to treat T4bN0M0 + T4aN2M0 as stage IIIB. Furthermore we found that patients with stage T4bN3bM0 had similar survival with stage IV patients. Accordingly, we established a new staging system, which outperformed the 7th and 8th staging systems. However, the value of TNM staging classification in predicting patients' prognosis has reached a plateau.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v09p3570s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24:2137-50.
2. Chen W, Zheng R, Zeng H, Zhang S. The updated incidences and mortalities of major cancers in China, 2011. Chin J Cancer. 2015;34:502-7.
3. Qiu MZ, Qiu HJ, Wang ZQ, Ren C, Wang DS, Zhang DS, et al. The tumor-log odds of positive lymph nodes-metastasis staging system, a promising new staging system for gastric cancer after D2 resection in China. PLoS One. 2012;7:e31736.
4. Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, et al. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol. 2011;18:1869-76.
5. Ajani JA IH, Sano T, et al. Stomach. In: Amin MB, editor. AJCC Cancer Staging Manual.8th ed, New York: Springer-Verlag. 2016.
6. Lu J, Zheng CH, Cao LL, Li P, Xie JW, Wang JB, et al. Comparison of the 7th and 8th editions of the American joint committee on cancer TNM classification for patients with stage III gastric cancer. Oncotarget. 2017;8:83555-62.
7. Lu J, Zheng CH, Cao LL, Ling SW, Li P, Xie JW, et al. Validation of the American Joint Commission on Cancer (8th edition) changes for patients with stage III gastric cancer: survival analysis of a large series from a Specialized Eastern Center. Cancer Med. 2017;6:2179-87.
8. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-87.
9. Spolverato G, Bagante F, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, et al. Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma. J Surg Oncol. 2017;115:696-703.
10. Zivanovic O, Leitao MM, Iasonos A, Jacks LM, Zhou Q, Abu-Rustum NR, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the international Federation of gynecology and obstetrics and american joint committee on cancer staging systems. J Clin Oncol. 2009;27:2066-72.
11. Kim M, Kim WG, Oh HS, Park S, Kwon H, Song DE, et al. Comparison of the 7th and 8th Editions of the AJCC/UICC TNM Staging System for Differentiated Thyroid Cancer. Thyroid. 2017;27:773-7.
12. Meurgey A, Girard N, Merveilleux du Vignaux C, Maury JM, Tronc F, Thivolet-Bejui F, et al. Assessment of the ITMIG statement on the WHO histological classification and of the 8th TNM staging of thymic epithelial tumors, of a series of 188 thymic epithelial tumors. J Thorac Oncol. 2017;12:1571-81.
13. Yang L, Wang S, Zhou Y, Lai S, Xiao G, Gazdar A, et al. Evaluation of the 7th and 8th editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort. Oncotarget. 2017;8:66784-95.
14. Zhang D, Zheng Y, Wang Z, Huang Q, Cao X, Wang F, et al. Comparison of the 7th and proposed 8th editions of the AJCC/UICC TNM staging system for esophageal squamous cell carcinoma underwent radical surgery. Eur J Surg Oncol. 2017;43:1949-55.
15. Wang W, Sun XW, Li CF, Lv L, Li YF, Chen YB, et al. Comparison of the 6th and 7th editions of the UICC TNM staging system for gastric cancer: results of a Chinese single-institution study of 1,503 patients. Ann Surg Oncol. 2011;18:1060-7.
16. Wang W, Xu DZ, Li YF, Guan YX, Sun XW, Chen YB, et al. Tumor-ratio-metastasis staging system as an alternative to the 7th edition UICC TNM system in gastric cancer after D2 resection--results of a single-institution study of 1343 Chinese patients. Ann Oncol. 2011;22:2049-56.
17. Salazar R, Roepman P, Capella G, Moreno V, Simon I, Dreezen C, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. J Clin Oncol. 2011;29:17-24.
18. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202-9.
19. Cao Y, Liu H, Zhang H, Lin C, Li R, Wu S, et al. CXC chemokine receptor 1 predicts postoperative prognosis and chemotherapeutic benefits for TNM II and III resectable gastric cancer patients. Oncotarget. 2017;8:20328-39.
20. Pan YM, Wang CG, Zhu M, Xing R, Cui JT, Li WM, et al. STAT3 signaling drives EZH2 transcriptional activation and mediates poor prognosis in gastric cancer. Mol Cancer. 2016;15:79.
21. Wang W, Seeruttun SR, Fang C, Chen J, Li Y, Liu Z, et al. Prognostic Significance of Carcinoembryonic Antigen Staining in Cancer Tissues of Gastric Cancer Patients. Ann Surg Oncol. 2016;23:1244-51.