Superiority of the 8th edition of the TNM staging system for predicting overall survival in gastric cancer: Comparative analysis of the 7th and 8th editions in a monoinstitutional cohort

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Abstract. The present study was performed to evaluate the predictive capacity of the 8th edition vs. the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for overall survival (OS) of patients with gastric cancer. Data of eligible patients with gastric cancer in our institution between June 2004 and June 2014 were retrospectively reviewed. A total of 1,506 patients were followed up to July 2016, among whom 1,484 patients with complete stage information were included in the TNM staging analysis. A total of 339 (22.8%) patients presented stage migration, including 325 (21.9%) migrating to a lower tier and 14 (0.9%) to a higher tier. All patients with stage migration to a lower tier were in stage III, including 177 (54.5%) patients migrating from stage IIIB to IIIA, and 148 (45.5%) from stage IIIC to IIIB. Patients migrating from IIIB to IIIA yielded a median OS time and 5-year OS rate closer to those remaining in stage IIIA. Similarly, patients migrating from IIIC to IIIB yielded a median OS time and 5-year OS rate closer to those remaining in stage IIIB. The 7th edition of the staging system exhibited prognostic discrepancy in discriminating stage IIIA from IIIB on survival curves, which was improved in the 8th edition. The 8th edition had a better predictive capability of survival, as evidenced by a smaller value of -2log likelihood in the Cox proportional regression model (7th edition 4738.859 vs. 8th edition 4736.683). Therefore, the present study demonstrated that the 8th edition of the AJCC TNM staging system is superior to the 7th edition in predicting the OS of patients with gastric cancer.

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Abbreviations: AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis; OS, overall survival; MLNC, metastatic lymph node count; CEA, carcinoembryonic antigen; CA, cancer antigen; HR, hazard ratio

Key words: gastric cancer, American Joint Committee on Cancer, tumor-node-metastasis classification, 8th edition, survival

Introduction

Gastric cancer is one of the major causes of cancer-related mortality worldwide (1). The prognosis of gastric cancer varies by ethnicity, geographical region and disease severity at diagnosis. The tumor-node-metastasis (TNM) staging system has been validated as an effective tool for predicting the prognosis of malignant tumors, including gastric cancer (2). The first TNM classification for gastric cancer was published in the 2nd edition of the TNM Classification of Malignant Tumors in 1974 (3). Although some parts of the TNM staging system of gastric cancer remain controversial, with constant modifications it has become generally accepted and used to guide the management of gastric cancer worldwide.

The latest (8th) edition of the TNM classification was published in 2016 and replaced the 7th edition with several adopted modifications. In the 7th edition, the N3 category [metastatic lymph node count (MLNC) ≥7] had been subdivided into N3a (MLNC 7-15) and N3b (MLNC ≥16), but failed to incorporate this distinction into the final TNM staging (4). In the 8th edition, the N3 category is subdivided into N3a and N3b in the final pathological staging. Specifically, through this new classification, the T1N3bM0 of stage IIB was moved to IIIB, the T2N3bM0 of stage IIIA was moved to IIIB, the T3N3bM0 of stage IIIB was moved to IIIC, and the T4aN3aM0 of stage IIIC was moved to IIIB. Other modifications include T4 stage migrations, specifically T4bN0M0 and T4aN2M0 of stage IIIB moving to IIIA, and T4bN2M0 of IIIC moving to IIIB.

However, the necessity of these modifications remains unclear. In the present study, efforts were made to assess the prognostic significance of the 8th edition of the AJCC TNM staging system for gastric cancer. The aims were to: i) Evaluate the prognostic discrepancies in the presence or absence of the N3 category subdivision; ii) investigate the

suitability of stage migrations, namely two subcategories (T4bN0M0 and T4aN2M0) moving from stage IIIB to IIIA and another subcategory (T4bN2M0) from stage IIIC to IIIB; and iii) compare the predictive ability of the 7th vs. the 8th staging system regarding overall survival (OS).

Patients and methods

Patients. The medical records of 1,525 patients with biopsy-confirmed gastric cancer at the Department of General Surgery of Nanfang Hospital (Guangzhou, China) between June 2004 and June 2014 were retrospectively reviewed from a prospectively collected database (5). Of the 1,525 patients, 19 were excluded, including 10 patients with carcinoma *in situ*, 5 patients with synchronous malignancies (1 with prostate cancer, 1 with Hodgkin's lymphoma, 1 with colon cancer, 1 with bladder cancer and 1 with nasopharyngeal cancer), 3 patients who died of postoperative complications, and 1 patient aged <18 years. Finally, 1,506 eligible patients were included in the subsequent analysis. The study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University. Written informed consent was obtained from all patients prior to entering their information into the database.

Surgical resection with a curative intent was performed for stage I-III patients and attempted for those with peritoneal metastasis, if allowed by preoperative assessment and intraoperative observation. Personalized adjuvant chemotherapy regimens were prescribed for patients, mainly using capecitabine, oxaliplatin, leucovorin and irinotecan. For patients with T3-T4 lesions or lymph node metastases, adjuvant chemotherapy was generally recommended. In this analyzed cohort, 656 (62.1%) received adjuvant chemotherapy, whereas no patients received radiotherapy or chemotherapy as neoadjuvant treatment.

Methods. The patient demographic and clinicopathological data were analyzed, including gender (male or female), age (<60 or ≥60 years), history of abdominal surgery (yes or no), classification of comorbidities (0, 1 or ≥2), Eastern Cooperative Oncology Group performance status (0, 1 or ≥2), primary tumor size (≤5 or >5 cm), level of serum carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 (normal or elevated), type of gastrectomy (subtotal or total), resection extent (radical or palliative), differentiation degree (high/moderate or poor/signet-ring cell carcinoma) and positive resection margin (yes or no). Tumor classification was determined according to the 7th and 8th editions of the AJCC TNM staging system (referred to as 7th TNM and 8th TNM, respectively). For those patients with distant metastasis who were not considered eligible for surgical treatment, the pathological stage and T and N status were unavailable.

Statistical analysis. The aim of the present study was to evaluate whether the 8th TNM classification was superior to the 7th TNM classification in the prognostic prediction of patient OS. The OS time was defined as the duration from the date of surgery (or date of first diagnosis for those patients who did not undergo surgery) to the date of death or the last follow-up visit. The 5-year OS rate and median OS time were calculated, and survival curves were estimated using the Kaplan-Meier method. As mentioned above, the main modification in the 8th TNM staging system was the incorporation of N3 subdivisions (N3a and N3b) into the final pathological staging, which contributed to the shift of the final TNM classification. The discriminatory ability and monotonicity of gradient assessments were measured with the linear trend χ^2 test of survival curves. Among the four aforementioned groups with migration, three groups (T3N3bM0, T2N3bM0 and T1N3bM0) included only a small number of patients, and the survival outcomes could not be statistically assessed. Since another group (T4aN3aM0) was a subgroup of the T4 stage, it was integrated with the other three T4 subgroups (T4bN0M0, T4aN2M0 and T4bN2M0) for analysis. The presence of the stage migration phenomenon mainly occurred in stage III, namely T4bN0M0 and T4aN2M0 of stage IIIB in the 7th TNM migrating to stage IIIA in the 8th TNM, and T4aN3aM0 and T4bN2M0 of stage IIIC in the 7th TNM migrating to stage IIIB in the 8th TNM. To investigate the suitability of these stage migrations, survival comparison was performed between patients with stage migration and those remaining in the same stage category according to both editions. The log-rank test and hazard ratio (HR) were used during analysis of univariate risk factors. Variables associated with OS were included in a multivariable Cox proportional regression model to identify independent risk factors of OS in the two staging systems. Variables highly related to others were excluded from the final model. Finally, two Cox regression models were built based on the 7th and 8th TNM to compare their prognostic prediction abilities. The variables in the two models were identical, except for TNM classification; in other words, the model based on the 8th TNM was constructed by replacing the 7th TNM stage by the 8th TNM stage. The statistics, -2log likelihood of the Cox regression model, were calculated to compare the predictive efficacy of the two models. A smaller value indicated a better model for predicting outcome.

For the majority of the patients, the postoperative follow-up was assessed at 3-month intervals for the first 2 years, 6-month intervals for the next 3 years, and annually thereafter until the endpoints were reached. Physical examination, serum tumor biomarker levels, chest X-ray, abdominal ultrasonography, gastroendoscopy and positron emission tomography/computed tomography were selected for accurate assessment at each follow-up. The last follow-up was performed in July 2016.

All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 (two-tailed) was considered to indicate statistically significant differences.

Results

Demographic and clinicopathological characteristics of the patients. Of the 1,506 patients included, 1,018 (67.6%) were male and 488 (32.4%) were female. The mean age of the entire cohort was 55.6 years (range, 19-90 years). The cohort was followed up for a mean duration of 44.1 months (range, 1-145 months). The demographic characteristics, pathological characteristics and clinical outcomes of the patients are summarized in Table I. The total number of dissected lymph nodes was 32,439, with a mean ± standard deviation of

Table I. Demographics and univariate survival analysis results of the studied gastric cancer patients.

Variables	No. (%)	(95% CI)			Log-rank P-value
		5-year OS rate,%	Median OS time, months	Hazard ratio	
Sex	1,506				0.434
Male	1,018 (67.6)	47.4 (44.1-50.7)	55.0 (43.7-66.3)	0.943 (0.812-1.094)	
Female	488 (32.4)	44.7 (39.8-49.6)	48.0 (37.3-58.7)	(Reference)	
Age (years)	1,506				<0.001
<60	908 (60.3)	49.9 (46.4-53.4)	60.0 (40.9-79.1)	(Reference)	
≥60	598 (39.7)	41.3 (36.8-45.8)	38.0 (29.1-46.9)	1.306 (1.133-1.505)	
Abdominal surgery history	1,506				0.596
Yes	153 (10.2)	45.3 (36.5-54.1)	49.0 (20.9-77.1)	1.064 (0.844-1.341)	
No	1,353 (89.8)	46.7 (43.8-49.6)	54.0 (46.3-61.7)	(Reference)	
Classification of comorbidities	1,506				0.003
0	1,149 (76.3)	47.2 (44.1-50.3)	54.0 (44.2-63.8)	(Reference)	
1	269 (17.9)	48.3 (41.2-55.4)	56.0 (37.9-74.1)	0.957 (0.791-1.159)	
≥2	88 (5.8)	28.8 (16.6-41.0)	30.0 (15.2-44.8)	1.559 (1.188-2.407)	
ECOG PS	1,056				0.461
0	985 (65.4)	82.6 (0.018)	139.0 (128.1-149.9)	(Reference)	
1	350 (23.2)	79.7 (0.038)	84.4 (68.2-100.7)	1.274 (0.978-1.506)	
≥2	171 (11.4)	64.3 (0.111)	75.9 (72.7-78.9)	1.296 (0.934-1.625)	
Primary tumor size (cm)	1,344				<0.001
≤5	955 (71.1)	57.3 (53.8-60.8)	104.0 (98.5-109.5)	(Reference)	
>5	389 (28.9)	33.6 (28.3-38.9)	30.0 (25.6-34.4)	1.925 (1.642-2.257)	
Serum CEA	989				<0.001
Normal	832 (84.1)	48.1 (44.6-51.6)	56.0 (44.3-67.7)	(Reference)	
Elevated	157 (15.9)	29.0 (21.4-36.6)	22.0 (15.2-28.8)	1.726 (1.400-2.127)	
Serum CA 19-9	960				<0.001
Normal	769 (80.1)	49.2 (45.5-52.9)	57.0 (42.4-71.6)	(Reference)	
Elevated	191 (19.9)	28.5 (21.6-35.4)	20.0 (16.3-23.7)	1.903 (1.566-2.313)	
Gastrectomy type	1,363				<0.001
Subtotal	968 (71.0)	57.5 (54.2-60.8)	99.0 (94.8-103.2)	(Reference)	
Total	395 (29.0)	34.0 (28.5-39.5)	32.0 (26.8-37.2)	1.932 (1.644-2.271)	
Resection extent	1,363				<0.001
Radical	1075 (78.9)	61.1 (57.8-64.4)	Not reached	(Reference)	
Palliative	288 (21.1)	13.9 (9.6-18.2)	14.0 (12.2-15.8)	4.531 (3.849-5.332)	
Differentiation	1,375				<0.001
High/moderate	281 (18.7)	61.7 (55.4-68.0)	Not reached	(Reference)	
Poor/signet-ring cell	1,094 (79.6)	44.2 (40.9-47.5)	48.0 (40.7-55.3)	1.746 (1.413-2.158)	
Positive resection margin	1,363				<0.001
No	1321 (96.9)	52.3 (49.4-55.2)	68.0 (53.4-82.6)	(Reference)	
Yes	42 (3.1)	8.9 (0.0-19.1)	12.0 (8.9-15.1)	3.708 (2.632-5.223)	
Pathological T stage	1,500				<0.001
T1	200 (13.3)	92.6 (88.7-96.5)	Not reached	(Reference)	
T2	118 (7.9)	74.7 (66.3-83.1)	Not reached	2.616 (1.485-4.606)	
T3	73 (4.9)	60.9 (48.6-73.2)	Not reached	5.268 (2.938-9.446)	
T4a	833 (55.5)	43.7 (40.0-47.4)	48.0 (40.7-55.3)	7.235 (4.623-11.323)	
T4b	276 (18.4)	9.2 (5.1-13.3)	13.0 (10.8-15.2)	22.236 (14.060-35.168)	
Pathological N stage	1,363				<0.001
N0	473 (34.7)	77.5 (73.4-81.6)	Not reached	(Reference)	
N1	237 (17.4)	55.7 (48.6-62.8)	Not reached	2.196 (1.665-2.896)	
N2	287 (21.1)	42.2 (36.1-48.3)	47.0 (33.2-60.8)	3.340 (2.612-4.271)	
N3a	244 (17.9)	24.3 (18.4-30.2)	24.0 (19.4-28.6)	5.526 (4.336-7.044)	
N3b	122 (9.0)	17.4 (9.0-25.8)	18.0 (13.9-22.1)	7.133 (5.381-9.455)	

Table I. Continued.

Variables	No. (%)	(95% CI) 5-year OS rate,%	Median OS time, months	Hazard ratio	Log-rank P-value
7th TNM stage	1,484				<0.001
IA	165 (11.1)	94.6 (90.5-98.7)	Not reached	(Reference)	
IB	74 (5.0)	89.7 (82.4-97.0)	Not reached	1.430 (0.584-3.498)	
IIA	62 (4.2)	81.9 (71.3-92.5)	Not reached	3.032 (1.362-6.751)	
IIB	226 (15.2)	69.5 (62.8-76.2)	Not reached	4.331 (2.345-8.002)	
IIIA	161 (10.8)	51.4 (42.6-60.2)	66.0 (47.2-84.8)	7.265 (3.940-13.396)	
IIIB	202 (13.6)	47.3 (39.7-54.9)	57.0 (38.3-75.2)	8.561 (4.708-15.567)	
IIIC	252 (17.0)	26.0 (19.9-32.1)	27.0 (21.1-32.9)	16.156 (9.004-28.989)	
IV	342 (23.0)	9.4 (5.9-12.9)	11.0 (9.6-12.4)	35.797 (20.060-63.879)	
8th TNM stage	1,484				<0.001
IA	165 (11.1)	94.6 (90.5-98.7)	Not reached	(Reference)	
IB	74 (5.0)	89.7 (82.4-97.0)	Not reached	1.428 (0.584-3.495)	
IIA	62 (4.2)	81.9 (71.3-92.5)	Not reached	3.037 (1.364-6.762)	
IIB	224 (15.1)	69.7 (63.0-76.4)	Not reached	4.289 (2.320-7.929)	
IIIA	334 (22.5)	49.8 (43.7-55.9)	60.0 (38.8-81.2)	7.716 (4.290-13.880)	
IIIB	171 (11.5)	32.5 (25.1-39.9)	35.0 (27.5-42.5)	13.768 (7.598-24.949)	
IIIC	112 (7.5)	18.4 (9.4-27.4)	22.0 (16.9-27.1)	19.477 (10.625-35.702)	
IV	342 (23.0)	9.4 (5.9-12.9)	11.0 (9.6-12.4)	35.994 (20.169-64.233)	

OS, overall survival; CI, confidence interval; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CA, cancer antigen.

23.8±19.3. The mean number of metastatic lymph nodes was 5.2±7.7 (median, 2; range, 0-65) in all patients and 8.0±8.3 (median, 5; range, 1-65) in patients with lymph node involvement.

Survival comparison for N category and stage migration. The main modification in the new TNM staging system was subdivision of the N3 category into N3a and N3b, and the resultant stage migration in the final TNM classification. The necessity of these modifications was unknown. In the present study, the OS curves based on the 7th TNM and 8th TNM were separately constructed and compared (Fig. 1). A log-rank test for trend revealed good discriminatory abilities in both N classifications (both P<0.001), but the 8th TNM classification exhibited a better monotonicity of gradient compared with the 7th TNM classification, as evidenced by a higher χ^2 value in the former classification (χ^2 for log-rank trend test, 311.783 vs. 297.588).

A total of 1,484 patients were included for analysis of TNM staging, and 22 patients with distant metastasis who did not undergo surgical resection were excluded due to unavailable data on T and N status. The distribution of patients according to the 7th and 8th editions of the AJCC TNM staging system is summarized in Table II. Among 1,484 patients, 1,145 (77.2%) remained in the same stage category and 339 (22.8%) migrated to a different stage, including 325 (21.9%) patients who migrated to a lower tier and 14 (0.9%) who migrated to a higher tier, compared with the 7th TNM. Given the small number of patients that migrated to a higher tier, including 2 patients in T1N3bM0 migrating from stage IIB to IIIB, 4 patients in T2N3bM0 migrating from stage IIIA to IIIB, and 8 patients in T3N3bM0 migrating from stage IIIB to IIIC, survival comparisons could not be made for these patients. Interestingly, all patients with stage migration to a lower tier were in stage III, including 177 (54.5%) patients migrating from stage IIIB to IIIA, and 148 (45.5%) patients migrating from stage IIIC to IIIB. To evaluate the suitability of these migrations, the OS of patients with stage migration was further compared to those remaining in the same stage category (Table III). For patients migrating from stage IIIB to IIIA, the survival curves had no significant difference from those that remained in stage IIIB or IIIA (P=0.342). However, patients with stage migration from IIIB to IIIA yielded a median OS time and 5-year OS rate closer to those remaining in stage IIIA (discrepancy of 8 months in median OS and 4.5% in 5-year OS rate), compared with those remaining in stage IIIB (discrepancy of 21 months in median OS and 14.1% in 5-year OS rate). Similarly, for patients who migrated from stage IIIC to IIIB, the median OS and 5-year OS rate were closer to those remaining in stage IIIB, with a discrepancy of 4 months in median OS and 2.3% in 5-year OS rate, exhibiting a significant difference from those in stage IIIC (discrepancy of 13 months in median OS and 14.3% in 5-year OS rate; overall P=0.014). The discriminatory ability

Table II. Distribution of patients according to the 7th and 8th editions of the AJCC staging system.

	AJCC 8th stage								
AJCC 7th stage	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	IV	Total
IA	165	0	0	0	0	0	0	0	165
IB	0	74	0	0	0	0	0	0	74
IIA	0	0	62	0	0	0	0	0	62
IIB	0	0	0	224	0	2[a]	0	0	226
IIIA	0	0	0	0	157	4[a]	0	0	161
IIIB	0	0	0	0	177[a]	17	8[a]	0	202
IIIC	0	0	0	0	0	148[a]	104	0	252
IV	0	0	0	0	0	0	0	342	342
Total	165	74	62	224	334	171	112	342	1,484

[a]Patients with TNM stage migration. AJCC, American Joint Committee on Cancer.

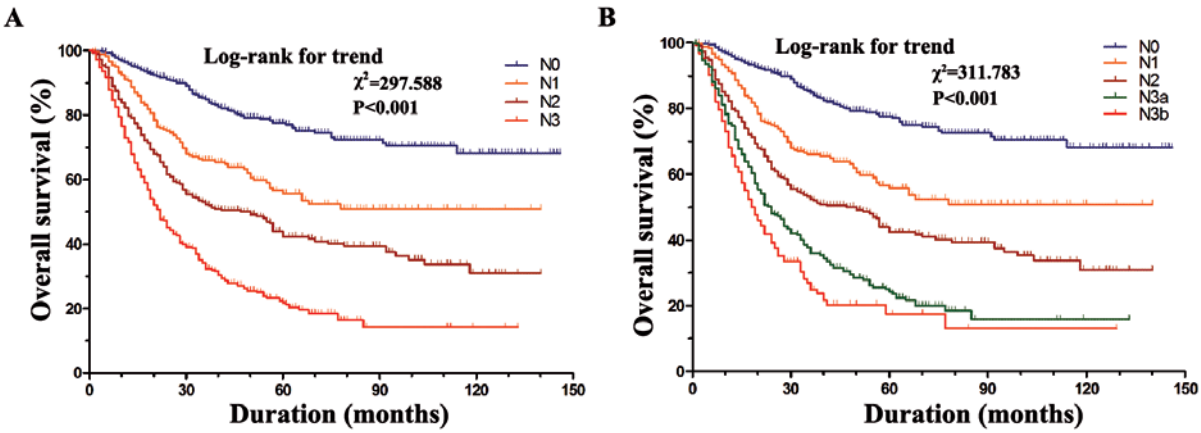

Figure 1. Kaplan-Meier survival curves for patients stratified by N category with (A) undivided N3 and (B) subdivided N3 into N3a and N3b. The log-rank test for trend showed significantly decreased survival in patients with advanced N stage by both N classifications (both P<0.001), but the 8th TNM classification exhibited a better monotonicity of gradient compared with the 7th TNM classification (χ^2 for log-rank trend test, 311.783 vs. 297.588).

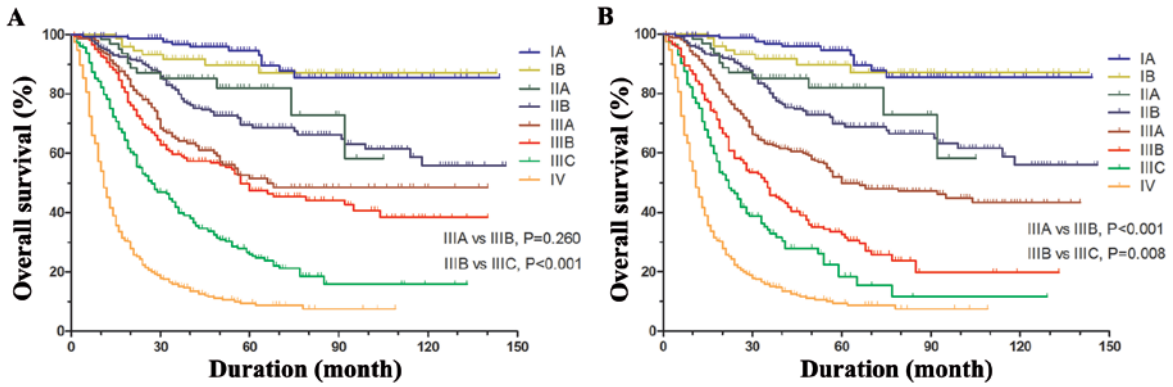

Figure 2. Kaplan-Meier survival curves for patients based on (A) the 7th AJCC staging system and (B) the 8th AJCC staging system. The 7th edition staging system exhibited insufficient prognostic discrepancy for discriminating stage IIIA from IIIB on survival curves (P=0.260), which was improved in the 8th edition (P<0.001). AJCC, American Joint Committee on Cancer.

in stage III was improved following stage migrations. The survival curves for stage IIIA and IIIB based on the 7th TNM were close (P=0.260), with improved stratification in the 8th edition (P<0.001). The survival curves of patients based on the 7th and 8th editions of the AJCC TNM staging system are shown in Fig. 2.

Table III. Survival comparison in stage III patients with stage migration.

Groups	Stage	Median OS (months)	5-year OS rate (%)	Log-rank P-value
Migration from IIIB to IIIA[a]				0.342
Remaining in IIIA	T2N3aM0/T3N2M0/T4aN1M0	68.0 (40.0-96.0)	52.3 (43.5-61.1)	
IIIB to IIIA	T4bN0M0/T4aN2M0	60.0 (34.0-86.0)	47.8 (39.8-55.8)	
Remaining in IIIB	T4bN1M0/T3N3aM0	39.0 (1.2-76.8)	33.7 (6.8-60.6)	
Migration from IIIC to IIIB[a]				0.014
Remaining in IIIB	T4bN1M0/T3N3aM0	39.0 (1.2-76.8)	33.7 (6.8-60.6)	
IIIC to IIIB	T4aN3aM0/T4bN2M0	35.0 (26.8-43.2)	31.4 (23.4-39.4)	
Remaining in IIIC	T4bN3aM0/T4bN3bM0/T4aN3bM0	22.0 (16.2-27.8)	17.1 (8.3-25.9)	

[a]Migration from stage in the 7th edition to stage in the 8th edition.

Univariate and multivariate analyses for OS in the two staging systems. Univariate analysis was performed to evaluate the risk factors of OS (Table I). Variables including age, classification of comorbidities, primary tumor size, serum CEA, serum CA 19-9, type of gastrectomy, resection extent, differentiation degree, positive resection margin, pathological T and N stage, 7th TNM stage and 8th TNM stage were identified as prognostic factors of OS. After elimination of the variables highly related to others, two Cox proportional regression models were constructed, and included age, classification of comorbidities, primary tumor size, serum CEA, serum CA 19-9, type of gastrectomy, tumor differentiation, positive resection margin and TNM stage in the two staging systems to predict the prognosis of gastric cancer patients (Table IV). In both models, an elevated level of serum CA 19-9, total gastrectomy, positive resection margin and high TNM stage were independent risk factors for predicting an unfavorable OS. A smaller value of -2log likelihood was calculated in the model for the 8th edition of the staging system (7th edition 4,738.859 vs. 8th edition 4,736.683), which indicated a better predictive capability compared with the 7th edition.

Discussion

The TNM staging system for gastric cancer has been widely used as a method for staging gastric cancer patients and is considered as the most important reference in multimodal treatment. It is also useful for determining the extent of the disease, providing guidance for treatment planning and predicting outcomes. The latest (8th) edition of the AJCC TNM staging system for gastric cancer provides additional resources that are not available in the 7th edition. The modifications introduced in the 8th edition were based on the clinicopathological and follow-up data from >25,000 gastric cancer patients in the International Gastric Cancer Association database, which includes both Asian and Western patients who underwent surgical resection with adequate lymphadenectomy and pathological assessment and were followed up for at least 5 years (6). However, the prognostic value of this new staging system remains unknown. Recently, several analyses based on a similar scale of cohort were also performed. However, their conclusion that the 8th TNM edition may not provide better accuracy in predicting the prognosis of stage III gastric cancer is opposite to the findings of the present study. This also suggested a controversy regarding the superiority of the 8th edition and a large-scale, well-designed study is required to further confirm the conclusions, until which time retrospective analyses from different centers, including the present study, may provide insights into this issue (7-9). In the present study, the suitability of these modifications in the latest 8th edition TNM staging system were evaluated.

Prior to the publication of the 8th edition, there were several issues with the 7th TNM staging system that were raised in numerous studies (10-15). Limitations to N category classification in the 7th edition were validated, and the need for relevant modifications, including the application of N3a/b to the final staging, had been put forward by several investigators (14,16-19). Through the subdivision of N3 into N3a (MLNC 7-14) and N3b (MLNC ≥15), the new staging system emphasizes the importance of the sufficient resection of lymph nodes to avoid understaging and to ensure accurate staging, which had also been previously claimed (20). Ji *et al* (21) performed a retrospective analysis for a cohort of 1,663 patients with clear eligibility criteria. The authors generally concluded that the 8th edition system is superior to the 7th edition system in terms of homogeneity, discriminatory ability and monotonicity of gradients for Chinese patients with gastric cancer, based on a sequence of reasonable analyses. However, the sample sizes for pN3a and pN3b were relatively small (30 patients in pN3a and 6 in pN3b), although significant differences in the 5-year survival rate were found between the two groups. In our current cohort, 244 patients were in the N3a and 122 in the N3b category, from which a more statistically effective comparison could be performed. Our results revealed a lower OS in patients with N3a compared with those with N3b, which was consistent with the findings from previous reports (17,19,22). In the present study, the N category with the N3 subdivision also exhibited an improved discriminatory ability on survival curves compared with that without the N3 subdivision. In the 7th edition, although N3 is subdivided into N3a and N3b, they are grouped together in the final TNM staging, which may be not conducive to properly predict stage-based prognosis. Through adopting N3a/b in the final TNM staging in the

Table IV. Multivariable analysis of factors associated with overall survival in the two staging systems.

	7th edition		8th edition	
Factors	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)		0.110		0.170
<60	(Reference)		(Reference)	
≥60	1.186 (0.962-1.461)		1.158 (0.939-1.427)	
Classification of comorbidities		0.224		0.223
0	(Reference)		(Reference)	
1	1.058 (0.812-1.377)	0.677	1.055 (0.810-1.374)	0.691
≥2	1.431 (0.951-2.152)	0.085	1.433 (0.953-2.154)	0.084
Primary tumor size (cm)		0.322		0.375
≤5	(Reference)		(Reference)	
>5	1.114 (0.900-1.380)		1.103 (0.889-1.368)	
Serum CEA		0.493		0.405
Normal	(Reference)		(Reference)	
Elevated	1.098 (0.840-1.437)		1.121 (0.857-1.465)	
Serum CA 19-9		0.009		0.012
Normal	(Reference)		(Reference)	
Elevated	1.362 (1.079-1.720)		1.350 (1.069-1.705)	
Gastrectomy type		0.015		0.035
Subtotal	(Reference)		(Reference)	
Total	1.304 (1.052-1.615)		1.158 (0.939-1.427)	
Differentiation		0.359		0.228
High/moderate	(Reference)		(Reference)	
Poor/signet-ring cell carcinoma	1.141 (0.861-1.513)		1.189 (0.897-1.575)	
Positive resection margin		0.002		0.001
No	(Reference)		(Reference)	
Yes	1.989 (1.296-3.052)		2.001 (1.305-3.069)	
TNM stage		<0.001		<0.001
IA	(Reference)		(Reference)	
IB	1.205 (0.340-4.274)	0.772	1.209 (0.341-4.286)	0.769
IIA	3.336 (1.184-9.404)	0.023	3.325 (1.180-9.374)	0.023
IIB	3.851 (1.636-9.062)	0.002	3.829 (1.625-9.021)	0.002
IIIA	5.325 (2.258-12.558)	<0.001	6.332 (2.769-14.479)	<0.001
IIIB	7.347 (3.172-17.017)	<0.001	10.452 (4.515-24.196)	<0.001
IIIC	12.264 (5.340-28.163)	<0.001	16.057 (6.754-38.176)	<0.001
IV	21.591 (9.382-49.690)	<0.001	21.801 (9.474-50.169)	<0.001
-2log likelihood	4738.859	<0.001	4736.683	<0.001

CI, confidence interval; CEA, carcinoembryonic antigen; CA, cancer antigen.

8th edition, stage migration occurred in four subcategories (T4aN3aM0, T3N3bM0, T2N3bM0 and T1N3bM0), three of which (T3N3bM0, T2N3bM0 and T1N3bM0) migrated to a higher tier, and one (T4aN3aM0) to a lower tier. However, there was only a small number of patients with stage migration to a higher tier (2 in T1N3bM0, 4 in T2N3bM0 and 8 in T3N3bM0), suggesting only a small proportion of patients would be moved to a higher tier category by the N3 subdivision in the new staging system. T4aN3aM0, a subgroup of T4, was integrated with the other three T4 subgroups with stage migration (T4bN0M0, T4aN2M0 and T4bN3aM0) for analysis. All four of these subgroups were re-classified in stage III, appearing as predominant changes resulting from modifications in the 8th TNM. The changes were divided into two aspects: Re-classification of T4bN0M0 and T4aN2M0 of stage IIIB into IIIA; and re-classification of T4aN3aM0 and T4bN2M0 of stage IIIC into IIIB. The survival comparison demonstrated that patients with T4bN0M0 and T4aN2M0 yielded a more similar median OS and 5-year OS rate to those remaining in stage IIIA (median OS, 60 vs. 68 months; 5-year OS rate, 47.8

vs. 52.3%, respectively), in comparison with patients remaining in stage IIIB (median OS, 60 vs. 39 months; 5-year OS rate, 47.8 vs. 33.7%, respectively). These findings suggest that it is reasonable to classify T4bN0M0 and T4aN2M0 into stage IIIA rather than stage IIIB. Similar results were also observed in the T4aN3aM0 and T4bN2M0 groups, which were moved from stage IIIC to stage IIIB. By subsequent analysis with survival curves and multivariable Cox proportional regression model, the 8th TNM was demonstrated to be superior to the 7th TNM in predictive capacity by distinctly discriminating survival time and rate in patients with stage IIIA from those in stage IIIB. Kim *et al* analyzed the stage distribution and migration for the AJCC 7th and 8th editions of the staging system based on a cohort of 5,507 patients from Korea (23). Although the final conclusion that the 8th edition represents a better refinement of the 7th staging system was similar to ours, their main finding of improved survival discrimination between IIIB and IIIC in the 8th staging system was different from our results, which demonstrated a good discriminatory ability among IIIA through IIIB. Another study by Fang *et al* conducted a comparative analysis of overall and disease-free survival based on the 7th and 8th editions. Although a better homogeneity of the 8th edition was indicated, which was similar to our results, by a calculated higher likelihood ratio Chi-squared statistic (728.51 for the 7th and 740.13 for the 8th edition; $P<0.001$), their study failed to perform further analysis for subgroups of stage III, in which the main stage migration occurred, and contributed to the main modification of the 8th edition (24). Therefore, the 8th edition staging system appears to be more reasonable and accurate for predicting the prognosis of patients with gastric cancer. However, there remain questions regarding the current staging system. For example, it is unclear whether molecular findings (such as HER2 immunoreactivity) should be considered in the staging of gastric cancer, or whether these findings should only be considered as an additional prognostic factor.

There were several limitations to the present study. First, this study represents a retrospective analysis of patients from a single center who received individualized adjuvant chemotherapy without a standard protocol. Second, three groups (T1N3bM0, T2N3bM0 and T3N3bM0) were not statistically analyzed due to the small sample size. These limitations may be overcome by a larger-scale study in future investigations. Third, the follow-up duration was relatively short. Thus, studies with a longer follow-up (for example, 10 years) are required to confirm and extend the findings in this study with certainty. However, despite these limitations, our findings provide an important insight into the application of the new edition of the AJCC TNM staging system for gastric cancer in China.

In conclusion, the subdivision of N3 into N3a and N3b resulted in a clearer prognostic discrepancy. A sufficient number of resected lymph nodes is important to avoid understaging according to the 8th AJCC TNM edition staging system. The 8th edition of the AJCC TNM staging system appears to be more reasonable, and it is superior to the 7th edition in predicting OS in gastric cancer patients.

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Availability of data and materials

The datasets generated and analyzed in the present study are available for the corresponding author upon reasonable request.

Authors' contributions

HW and WG made substantial contributions to data collection and were major contributors in analyzing data and writing the manuscript. TM and LZ were responsible for the maintaining the clinical database and acquisition and interpretation of data. TL, JY, YH, HC and TL made substantial contributions to data collection, data interpretation, and made critical revision of the manuscript. HL and GL made substantial contributions to the design and general supervision of the present study. All the authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University. Written informed consent was obtained from all the patients prior to entering their information into the database.

Patient consent for publication

Not applicable.

Patient competing interests

The authors declare that they have no competing interests to disclose.

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