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Validation of the 7th AJCC/UICC staging system for gastric cancer and a proposal for a new TNM system based on a prognostic score: a retrospective multicenter study

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Purpose: We validate the 7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system for gastric cancer and propose a new staging system that reflects the prognostic significances of each of T and N category.
Methods: Data from 5,957 patients who underwent curative gastrectomies from 2000 to 2007 at 4 university hospitals in Daegu Metropolitan city in Korea were analyzed for the validation of the 7th AJCC/UICC staging system for gastric cancer. The hazard ratios of the respective T and N categories were estimated and converted to weightings and summated to make prognostic score (P-score). Homogeneity and stage grouping were determined according to the P-scores.
Results: In the 7th AJCC/UICC staging system for gastric cancer, poor discrimination was noted between stages IIB and IIIA (P = 0.152). In addition, heterogeneity in stage IIB (P = 0.021) and a small gap in 5-year survival rates (1.7%) between stages IA and IB were noted. A new proposed staging system was generated on the basis of P-scores and demonstrated more discrimination between stages and more homogeneity within stages. The new staging system reflects the different prognostic impacts of N3a and N3b.
Conclusion: Several controversial issues of the 7th AJCC/UICC staging system for gastric cancer were reconfirmed in the present analysis. The TNM system based on P-score appears to be more scientifically accurate than the 7th AJCC/UICC staging system for gastric cancer.
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Key Words: TNM classification, Stomach neoplasms

INTRODUCTION

Gastric cancer is one of the leading causes of cancer-related deaths in the world [1]. Similar to other malignancies, we can predict the survival of gastric cancer patients and make plans for multidisciplinary treatments on the basis of the stage of disease; thus, the staging system is crucial in the management of patients with gastric cancer. We adopted the 7th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system starting in 2010, and it contained major changes compared with the 6th AJCC/UICC TNM staging system for gastric cancer. These changes included reclassification of T2a and T2b to T2 and T3, respectively; division of the previous N1 stage (up to 6 metastatic regional

lymph nodes) into N1 (1 or 2 metastatic regional lymph nodes) and N2 (3 to 6 metastatic regional lymph nodes); and reclassification of the previous N2 (7 to 15 metastatic regional lymph nodes) and N3 stages (more than 15 metastatic regional lymph nodes) to N3a (7 to 15 metastatic regional lymph nodes) and N3b (more than 15 metastatic regional lymph nodes) [2-4]. Although the 7th AJCC/UICC staging system for gastric cancer has been reported to be more accurate or valid by some authors [3,5-7], the system is not without controversy. One of the most common controversies is classification of the N category, such that the discriminative power of the N category in the 7th UICC/AJCC staging system has been decreased relative to that of the 6th AJCC/UICC staging system [8,9]. In addition, different prognostic significances of the subgroups of N3 (N3a and N3b) was not reflected in the final staging [10,11]. The metastatic lymph node ratio was suggested to be a complementary measure by many authors [12-15], and others noted that there was heterogeneity in the survival of subgroups in a certain stage of the 7th AJCC/UICC staging system [16]. These controversies have highlighted the need for a new staging system [17]. In this study, we validated the 7th AJCC/UICC staging system with data from a large number of patients at 4 university hospitals and propose a new staging system based on basic concepts of the TNM staging system that reflects the different prognostic significance of each T and N category using a prognostic score (P-score).

METHODS

Included patients were those who had undergone surgery for gastric cancer from January 2000 to December 2007 at 4 university hospitals in Daegu Metropolitan city in Korea. Patients who met the following criteria were excluded from the analysis: (1) nonresective surgery, (2) gastric cancer located in the cardia, (3) less than 16 total retrieved lymph nodes, (4) recurrent gastric cancer, (5) coexisting malignancy in other organs, (6) history of preoperative chemotherapy, and (7) death within 90 days of surgery that might have been caused by complications of the surgery. After excluding 274 out of 6,241 patients, data from 5,967 patients were analyzed retrospectively. The mean follow up time was 66.2 months including early deaths. Roux-en-Y esophagojejunostomy was performed after total gastrectomy except for one case of jejunal interposition. Gastroduodenostomy (Billroth I), gastrojejunostomy (Billroth II) or Roux-en-Y gastrojejunostomy was performed after distal gastrectomy. Gastrogastrostomy was performed after pylorus preserving gastrectomy. The standard extent of lymph node dissection was D2 and D1+ in patients with early gastric cancer. Follow-up data were collected on the basis of medical records and telephone interviews. Survival duration was calculated from the day of surgery to the day of the last follow-up at outpatient department or by telephone, or the day of the patient's death.

The process for generating the new staging system was as follows: (1) estimation of the hazard ratio (HR) of each T and N category; (2) transformation of HR into a weighting; (3) summation of the weightings of the T and N categories (P-score); and (4) homogeneity testing and grouping as well as testing for the appropriateness of the 5-year survival gap between adjacent stages.

Table 1. Clinicopathological characteristic of patients

Characteristic	Value
Sex	
Female	2,045 (34.3)
Male	3,922 (65.7)
Age (yr)	58.6 ± 11.5
Extent of resection	
Distal gastrectomy	4,547 (76.2)
Total gastrectomy	1,408 (23.6)
Others	12 (0.2)
Reconstruction	
Billoth I	3,071 (51.4)
Billroth II	1,476 (24.8)
Roux-en-Y	1,407 (23.6)
Others	13 (0.2)
No. of retrieved lymph nodes	39.9 ± 16.8
Depth of invasion	
Mucosa	1,723 (28.9)
Submucosa	1,298 (21.8)
Muscuaris propria	696 (11.7)
Subserosa	1,702 (18.0)
Serosal invasion	1,094 (18.3)
Invasion to adjacent organs	84 (1.4)
Lymph node metastasis	
Negative	3,623 (60.7)
Positive	2,344 (39.3)
Stage-6th TNM classification	
IA	2,692 (45.1)
IB	1,044 (17.5)
II	844 (14.1)
IIIA	577 (9.7)
IIIB	304 (5.1)
IV	506 (8.5)
Stage-7th TNM classification	
IA	2,692 (45.1)
IB	629 (10.5)
IIA	559 (9.4)
IIB	493 (8.3)
IIIA	411 (6.9)
IIIB	491 (8.2)
IIIC	604 (10.1)
IV	88 (1.5)

Values are presented as number (%) or mean ± standard deviation.

The estimated survival probability of the 7th edition of the TNM staging system and respective combinations of T and N categories were estimated using the Kaplan-Meier method and were compared by the log-rank test. The HR within the Cox's proportional hazards model was used to assess the weighting of prognostic significance of the T and N categories. At first, the variables of age and sex were included to evaluate the interaction effect with the T and N categories, but the interactions were not significant. Thus, only data from the T and N categories were included in the model, and the HR was estimated. These HRs were simplified to the nearest number ending in 0.5 to meet both convenience and accuracy. We named this number the weighting. All the weightings of the T and N categories were confirmed to be within the 95% confidential intervals of their respective HRs and summated to make P-scores. The Cox's proportional hazards model was applied using P-scores to estimate the regression coefficient. This regression coefficient was applied to assess the homogeneity and grouping of P-scores using an estimated covariance matrix and Wald test. With sufficient numbers of patients in each stage, the Z-test was used to examine the discrimination of the 5-year survival rates between adjacent stages. The log-rank score within the Cox's proportional hazards model was used to demonstrate the discriminative ability of the new staging system in comparison with the 7th AJCC/UICC TNM classification. Higher log-rank scores were regarded to have better discriminative power in terms of survival. A P-value of less than 0.05 was considered statistically significant. No adjustments were made.

RESULTS

Clinicopathological characteristics of patients

In total, 3,922 (65.7%) male patients and 2,045 (34.3%) female patients were included in this study. The mean age was 58.6 ± 11.5 years. Distal gastrectomy was performed in 4,547 patients (76.2%). Billroth I anastomosis was performed as the reconstruction method in 3,071 patients (67.5%) after distal gastrectomy. Mucosal cancer was noted in 1,723 patients (28.9%), and submucosal cancer was noted in 1,298 patients (21.8%). T4b cancer was noted in 84 patients (1.4%). The mean retrieved lymph node count was 39.9 ± 16.8. The number of patients with regional lymph node metastases was 2,344 (39.3%) (Table 1).

Validation of the 7th UICC/AJCC staging system for gastric cancer

In survival analysis, 5-year survival rates according to the T categories of the 7th AJCC/UICC staging system were 92.4% for T1a, 90.6% for T1b, 86.4% for T2, 66.2% for T3, 39.4% for T4a, and 29.7% for T4b. Although a statistically significant difference in survival was noted between T1a and T1b (P = 0.025), the difference in 5-year survival rates was 1.8%, and the difference in survival between T4a and T4b did not reach statistical significance (P = 0.052). In the N categories, the 5-year survival rates were 90.2% for N0, 77.4% for N1, 62.4% for N2, 40.0% for N3a, and 21.4% for N3b (Fig. 1). Acceptable discrimination and distribution of survival were noted with the N categories of the 7th AJCC/UICC staging system. The survival curves for both the T and N categories did not intersect. Table 2 presents the 5-year survival rates of all the combinations of the T and N categories according to the 7th AJCC/UICC TNM staging system. T and N combinations of stage IIB exhibited a statistically significant difference in survival (P = 0.021) within the stage, and the difference in 5-year survival rates between T2N2M0 and T1N3M0 was 25.3% (80.0% *vs.* 54.7%, P = 0.012). Furthermore, a significant difference in survival was noted between T3N1M0 and T1N3M0 (74.5% *vs.* 54.7%, P = 0.009). A similar tendency was identified in stage IIIA patients with marginal significance
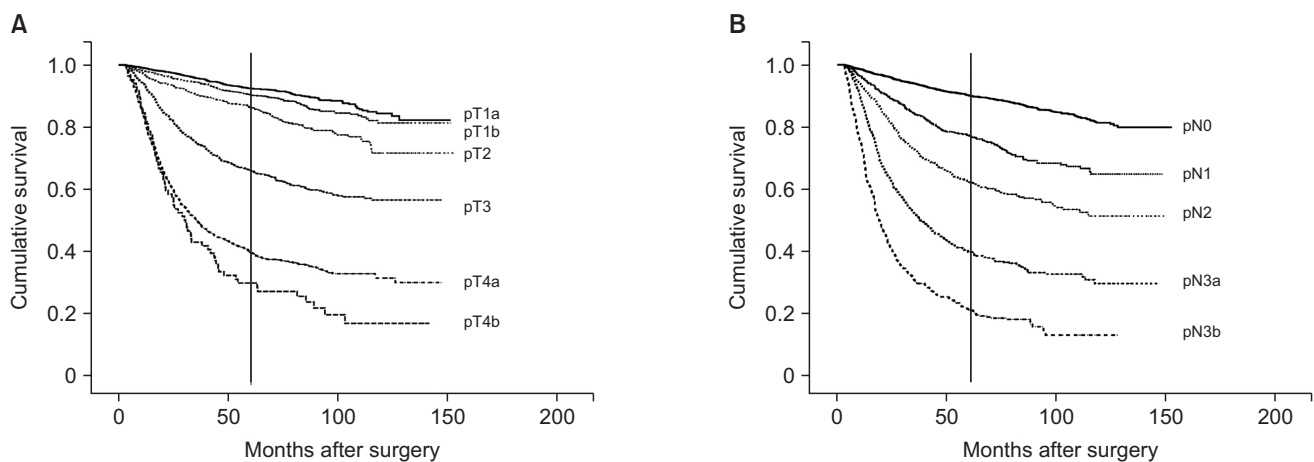

Fig. 1. Survival distributions according to T (A) and N (B) categories of the 7th American Joint Committee on Cancer/Union for International Cancer Control staging system.

Table 2. Five-year survival rates according to all combinations of T, N and M categories, including the subgroup of N3 and the results from homogeneity tests using a log-rank test within stages

Stage	No. of patients (%)	5-Year survival rate (%)	P-value
IA			
T1N0M0	2,692 (45.1)	92.7	
IB			0.225
T2N0M0	407 (6.8)	92.6	
T1N1M0	222 (3.7)	88.4	
IIA			0.980
T3N0M0	346 (5.8)	83.0	
T2N1M0	142 (2.4)	85.9	
T1N2M0	69 (1.2)	82.1	
IIB			0.021
T4aN0M0	159 (2.7)	62.3	
T3N1M0	212 (3.6)	74.5	
T2N2M0	85 (1.4)	80.0	
T1N3M0	37 (0.6)	54.7	
T1N3aM0	28 (0.5)	66.0	
T1N3bM0	9 (0.2)	22.2	
IIIA			0.067
T4aN1M0	136 (2.3)	58.9	
T3N2M0	218 (3.7)	66.0	
T2N3M0	57 (1.0)	56.5	
T2N3aM0	44 (0.7)	59.8	
T2N3bM0	13 (0.2)	46.2	
IIIB			0.129
T4bN0M0	13 (0.2)	61.5	
T4bN1M0	10 (0.2)	30.0	
T4aN2M0	196 (3.3)	48.0	
T3N3M0	272 (4.6)	41.8	
T3N3aM0	188 (3.2)	49.1	
T3N3bM0	84 (1.4)	26.0	
IIIC			0.320
T4bN2M0	12 (0.2)	41.7	
T4aN3M0	552 (9.3)	27.2	
T4aN3aM0	304 (5.1)	32.9	
T4aN3bM0	248 (4.2)	20.3	
T4bN3M0	40 (0.7)	22.5	
T4bN3aM0	26 (0.4)	19.2	
T4bN3bM0	14 (0.2)	28.6	
IV			
anyTanyNM1	90 (1.5)	17.%	

P < 0.05 indicates statistically significant survival difference within stages.

Fig. 2. Survival distributions according to the 7th American Joint Committee on Cancer/Union for International Cancer Control staging system for gastric cancer.

Table 3. Results from a Cox's proportional hazards model to estimate the hazard ratios of T and N categories and the transformation of hazard ratios into Weightings

Category	Chi-square	P-value	Hazard ratio	95% CI	Weighting
T1a	-	-	1.00	–	1.0
T1b	1.05	0.305	1.12	0.90–1.40	1.0
T2	8.29	0.004	1.43	1.12–1.82	1.5
T3	66.82	<0.001	2.42	1.97–2.99	2.5
T4a	148.35	<0.001	3.82	3.08–4.74	4.0
T4b	105.61	<0.001	5.17	3.78–7.07	5.0
N0	-	-	1.00	–	1.0
N1	24.04	<0.001	1.58	1.34–1.90	1.5
N2	60.80	<0.001	2.06	1.72–2.47	2.0
N3a	193.56	<0.001	3.41	2.87–4.05	3.5
N3b	349.40	<0.001	5.73	4.77–6.88	6.0

CI, confidence interval.

rates was noted between N3a and N3b, except in the T4bN3M0 group. Fig. 2 presents cumulative survival according to the 7th AJCC/UICC staging system. No statistically significant difference in survival was noted between stages IIB and IIIA ($P = 0.152$), and the intersection of the survival curves showed that these findings alluded to poor discriminative ability.

Proposal of a new staging system

Our proposed staging system was designed to reflect the different prognostic significance of the T and N categories while preserving basic concepts of the TNM staging system. Thus, the presence of metastatic disease (M1) was regarded as stage IV. In addition, all of the T and N categories were preserved and included in the proposed staging system, in particular, the prognostic significance of both N3a and N3b was included in the final stage. Table 3 presents HRs of the T and

($P = 0.067$), exhibiting a lack of homogeneity. Table 2 also presents the 5-year survival difference between subgroups of the N3 category. A remarkable difference in the 5-year survival

N categories and the transformation of HRs into weightings. The weightings of the T categories were 1 for T1a, 1 for T1b, 1.5 for T2, 2.5 for T3, 4 for T4a, and 5 for T4b. The weightings for the N categories were 1 for N0, 1.5 for N1, 2 for N2, 3.5 for N3a, and 6 for N3b. The gaps in the weightings between adjacent T or N categories differed according to the different HRs of the T and N categories. Grouping of T and N categories according to the P-score for the new staging system is presented in Table 4. Twenty-six combinations of T, N, and M categories were grouped to generate an 8-stage system using the Wald test.

Thus, the P-scores was 2 for stage IA, 2.5 for IIB, 3 and 3.5 for IIA, 4 and 4.5 for IIB, 5 and 5.5 for IIIA, 6 and 6.5 for IIIB, and 7 or greater for IIIC. Through new groupings, 6 of the 25 T and N combinations in the 7th AJCC/UICC staging system were moved to different stages in the new staging system. T2N2M0 of IIB moved to IIA, T3N2M0 of IIIA moved to IIB and T4aN0M0 of IIB moved to IIIA. T1N3bM0 of IIB, T2N3bM0 of IIIA, and T3N3bM0 of IIIB moved to IIIC and these shifts were caused by poor prognosis of the component N3b.

In the survival curves of the new staging system composed

Table 4. Grouping of the 26 combinations of T, N, and M categories according to P-scores

New stage	5-Year survival rate (%)	Components	P-score	No. of patients (%)	P-value	7th TNM
IA	92.7	T1N0M0	2	2,692 (45.1)	-	IA
IB	91.0	T2N0M0	2.5	407 (6.8)	0.038	IB
		T1N1M0	-	222 (3.7)		IB
IIA	83.1	T1N2M0	3	69 (1.2)	0.007	IIA
		T2N1M0	-	142 (2.4)		IIA
		T2N2M0[a]	3.5	85 (1.4)	0.547	IIB
		T3N0M0	-	346 (5.8)		IIA
IIB	69.9	T3N1M0	4	212 (3.6)	0.005	IIB
		T1N3aM0	4.5	28 (0.5)	0.392	IIB
		T3N2M0[a]	-	218 (3.7)		IIIA
IIIA	60.4	T2N3aM0	5	44 (0.7)	0.026	IIIA
		T4aN0M0[a]	-	159 (2.7)		IIB
		T4aN1M0	5.5	136 (2.3)	0.595	IIIA
IIIB	48.0	T3N3aM0	6	188 (3.2)	0.003	IIIB
		T4aN2M0	-	196 (3.3)		IIIB
		T4bN0M0	-	13 (0.2)		IIIB
		T4bN1M0	6.5	10 (0.2)	0.196	IIIB
IIIC	27.4	T1N3bM0[a]	7	9 (0.2)	0.041	IIB
		T4bN2M0	-	12 (0.2)		IIIC
		T2N3bM0[a]	7.5	13 (0.2)	0.705	IIIA
		T4aN3aM0	-	304 (5.1)		IIIC
		T3N3bM0[a]	8.5	84 (1.4)	0.268	IIIB
		T4bN3aM0	-	26 (0.4)		IIIC
		T4aN3bM0	10	248 (4.2)	0.098	IIIC
		T4bN3bM0	11	14 (0.2)	0.270	IIIC
IV	18.8	anyTanyNM1	-	90 (1.5)	-	IV

[a]Stage migration from the 7th American Joint Committee on Cancer/Union for International Cancer Control staging system to the newly proposed staging system.

Table 5. Result of the Z-test to validate the gaps in the 5-year survival rates between neighboring stages in the newly proposed staging system

| Comparison	n1	p1	n2	p2	p1-p2	SE (p1-p2)	Z-value	P-value
IB vs. IA	2,692	0.927	629	0.91	0.017	0.012464	1.363958	0.173
IIA vs. IB	629	0.91	642	0.829	0.081	0.018735	4.323367	<0.001
IIB vs. IIA	642	0.829	457	0.7	0.129	0.026083	4.945735	<0.001
IIIA vs. IIB	457	0.7	339	0.61	0.09	0.034078	2.641025	0.008
IIIB vs. IIIA	339	0.61	407	0.484	0.126	0.036268	3.474106	0.001
IIIC vs. IIIB	407	0.484	710	0.274	0.21	0.029896	7.024251	<0.001
IV vs. IIIC	710	0.274	90	0.177	0.097	0.043575	2.22607	0.026
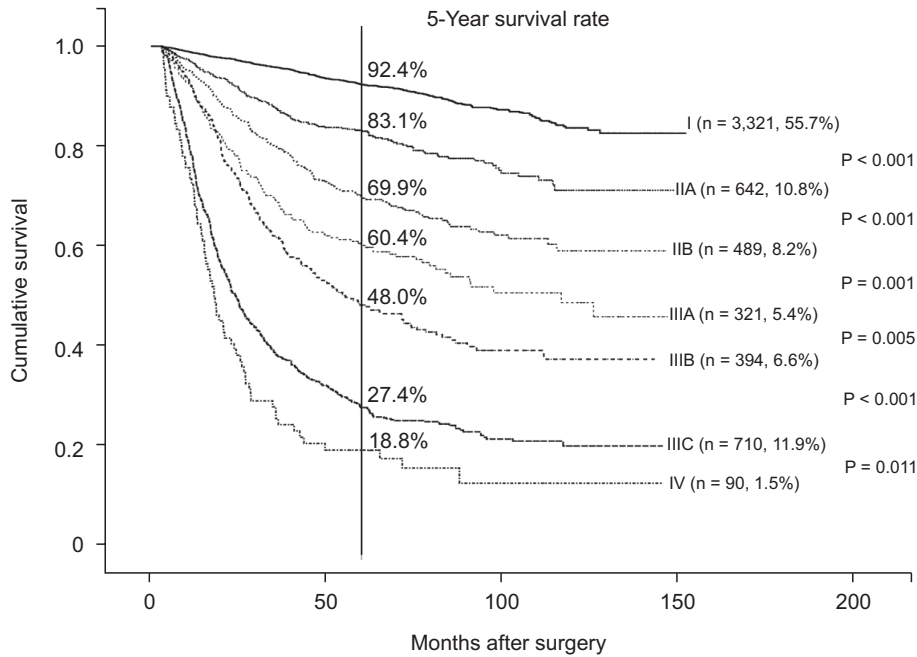
Fig. 3. Survival distributions according to the final version of the proposed staging system composed of seven stages.

of 8 stages, except for a small gap in the 5-year survival rates between stages IA and IB (92.7% and 91.0%, P = 0.041), there was good discrimination of survival between adjacent stages and an appropriate gap in the 5-year survival rates in the new staging system. Although a statistically significant difference in survival was noted by the log-rank test between stages IA and IB, the 5-year survival rate difference was only 1.7%. No statistically significant difference in the 5-year survival rate was noted between stages IA and IB (P = 0.173) by the Z-test (Table 5). Thus, stages IA and IB were unified into stage I.

Fig. 3 depicts the survival distributions of the final version of the new 7-staged staging system on the basis of P-score. This system demonstrated homogeneity with respect to survival in each stage group and distinct differences in the 5-year survival rates of these groups. The log-rank score of the proposed staging system was increased compared with the 7th AJCC/UICC staging system (2,497.1 *vs.* 2,413.6), indicating that the proposed staging system exhibited better discriminative power.

DISCUSSION

The purpose of a cancer staging system is stated in the AJCC cancer staging manual. The extent or stage of cancer at the time of diagnosis is a key factor that defines prognosis and is a critical element in determining an appropriate treatment based on the experience and outcomes of groups of prior patients at a similar stage. In addition, accurate staging is necessary to evaluate the results of treatments and clinical trials, to facilitate the exchange and comparison of information among treatment centers, and to serve as a basis for clinical and translational cancer research [2]. Until recently, many appraisals of the 7th

AJCC/UICC staging system for gastric cancer and proposals for new staging systems have been reported [18-20]. In our proposed staging system, the increments in weightings varied from 0.5 to 2.5, and this feature might disclose the different prognostic significance of each component of the T and N categories. More weighting was placed on categories with more prognostic significance, depending on their HR. Some authors have reported that the subgroups of N3 (N3a and N3b) should be included in the final stage separately because the prognosis of the patients with N3a and N3b differs significantly [10,21]. In our proposed staging system, the weightings of N3a and N3b were 3.5 and 6, respectively. This difference in the prognosis was reflected in the proposed staging system without modifications. Some authors insisted that heterogeneity existed within certain groups in the 7th AJCC/UICC staging system [16]. In the proposed staging system, the 5-year survival rate of T1N3aM0 was 66.0% and 22% for T1N3bM0. T1N3a remained in stage IIB, and T1N3bM0 moved to stage IIIC. According to prognostic significance, T2N2M0 moved from IIB to stage IIA, T3N2M0 moved from stage IIIA to stage IIB and T3N3bM0 moved from stage IIIB to stage IIIC. Some authors reported poor discrimination of survival between stage IB and IIA and between IIB and IIIA in the 7th AJCC/UICC staging system [4,8,19,20,22]. In the present study, poor discrimination of survival was noted between stage IIB and IIIA with intersection of the survival curves by the 7th AJCC/UICC staging system. However, in the staging system proposed here, the survival curves did not intersect, and a significant survival difference was observed. Dikken et al. [23] reported increased complexity without prognostic significance in the 7th AJCC/UICC staging system. Our proposed staging system is composed of seven

stages that fall in the middle of the 6th and 7th AJCC/UICC staging system with regard to complexity. Warneke et al. [19] stressed that there was no consideration for different biologic behavior between the primary tumor and lymph node metastasis. The 7th AJCC/UICC staging system reflects a mathematical model where the addition of the values of the T and N categories equals the same sum total in each subgroup. This feature is not an adequate categorization of the tumor's biologic potential or prognosis. In the proposed system, we convert the HRs of each T and N category to weightings, which reflect the prognosis by providing more weight to categories with worse biological behavior. Then, the weightings of the T and N categories are added to make P-scores. Thus, the different biological behavior between the status of the primary tumor and lymph node metastasis is simultaneously considered. Several benchmarks for comparing the performance of two staging systems have been suggested [23]. First, there should be homogeneity within stage groups. Second, there should be discrimination between stage groups; patients in different stage groups should have larger differences in survival. Third, the staging system should have good predictive accuracy. Fourth, the staging system should be as simple and intuitive as possible in clinical practice. Our proposed system, for the most part, appears to satisfy these four benchmarks. As for discrimination, in this study, the survival difference between stage IA and IB in the 7th AJCC/UICC system was small and unified to achieve relatively good discrimination of survival rates between neighboring stages. This unification of stage IA and IB was statistically verified to be rational by the result of Z-test

presented in Table 5. Conversion of the T and N categories to weightings is simple and easy to perform. The staging process is easier and more scientific compared with the 7th AJCC/UICC staging system because the stage is determined by the P-scores.

Furthermore, this study is the first to propose a staging system generated on the basis of prognostic outcome of HR of respective T and N categories to reflect different prognostic impacts of respective T and N categories overcoming the limitations of anatomical and mathematical model.

In conclusion, the newly proposed staging system preserves the basic concepts of TNM classification, reflecting different prognostic significance for the T and N categories using a P-score, dividing N3 into N3a and N3b in stage grouping, and unifying stages IA and IB into a single stage I. This system demonstrates homogeneity of each stage group with respect to survival and a distinct difference in the survival rates between stages. Therefore, the TNM system for gastric cancer based on this P-score appears to be more scientifically accurate than the 7th AJCC/UICC staging system for gastric cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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