

Prognostic implications of the eighth edition of the union for international cancer control – classification for gastric cancer patients from specialized treatment centers in Germany and Korea

A STOBE-Compliant large-scale cohort study

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Abstract

The validity of the 8th edition of the Union for International Cancer Control (UICC) staging system for gastric cancer has been evaluated only in Asian cohorts and not in European cohorts. The aim of this study was to evaluate the prognostic performance of the 8th edition of the UICC staging system in German and Korean cohorts independently and compare it with that of the 7th edition.

A total of 6121 patients (526 from Germany and 5595 from Korea) who underwent upfront surgery for gastric cancer were retrospectively reclassified according to the 8th edition. Survival according to the UICC stages was estimated by the Kaplan-Meier method and compared by log-rank tests. A Cox proportional hazards model was fitted after adjusting for clinicopathological factors, and receiver operating characteristics analysis was conducted.

The 8th edition showed significant differences in survival between each adjacent stage in the Korean cohort but not in the German cohort. Multivariate analyses revealed that the 8th edition staging was an independent prognostic factor, and its C-statistics were >0.76 in both German and Korean patients. The results were comparable to those observed with the UICC seventh edition (C-statistics was 0.768 vs 0.767 in the German cohort and 0.789 vs 0.785 in the Korean cohort for the 7th vs the 8th edition).

The 8th edition showed prognostic value in predicting the survival of gastric cancer patients in both German and Korean cohorts. However, the predictive ability of the 8th and 7th edition was similar.

Abbreviations: 10YSR = 10-year survival rate, 5YSR = 5-year survival rate, IGCA = International Gastric Cancer Association, NCC = National Cancer Center, TUM = Technical University of Munich, UICC = Union for International Cancer Control.

Keywords: cancer staging, Germany, Korea, prognosis, stomach neoplasm

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NS and WHH contributed equally as first authors.

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1. Introduction

The recently revised 8th Union for International Cancer Control (UICC) classification of patients with gastric cancer underwent only minor changes compared to the 7th edition. The primary changes were the division of the pN3-category into 2 subgroups (pN3a and pN3b) and classification of pT4-cancers according to their lymph node involvement in the new subclassification of UICC stage III.^[1,2] Additionally, GE junction cancers (Siewert type II or III) were reincorporated into the gastric cancer staging system.

These revisions were mainly based on the International Gastric Cancer Association (IGCA) staging project.^[2] This project collected data from 25,411 patients with gastric cancer, but the majority of the patients were from Asia (91.2%). Critically, the proportion of Western patients was only 8.8% (2,229/25,411). Recent reports evaluated the prognostic performance of the 8th UICC staging system in databases from China, Korea, and Taiwan.^[3–7] These studies reached similar conclusions, namely, that the prognostic performance of the 8th and 7th edition was similar. However, no study analyzed its prognostic performance in a European database.

Previously, we reported significant survival differences between Korean and German patients after balancing for possible confounders by propensity score matching. The 5-year survival rates of the Korean patients were 15% to 20% higher than those of the German patients in all the UICC stages, and this was attributed to difference in the biological behavior of cancer or ethnicity.^[8] Therefore, it is conceivable that the survival results provided by the staging project are overestimated in case of Western patients. Moreover, it is not clear whether the prognostic performance of the eighth edition was better than that of the seventh edition in a German cohort. Therefore, this study analyzed the prognostic performance of the 8th edition of the UICC staging system in German and Korean cohorts compared its performance to the 7th edition using the same methodology. Furthermore, this study aimed to clarify whether the 8th edition of the UICC staging system is applicable to Western patients for evaluating the prognosis of gastric cancer patients.

2. Materials and methods

2.1. Patients

We screened prospectively documented databases of consecutive patients who underwent upfront gastrectomy for gastric cancer in Technical University of Munich (TUM), Germany and the National Cancer Center (NCC), Korea between 1998 and 2011. Gastric cancer was histologically proven in all patients, and Siewert type II and type III cancers were included according to the newest staging recommendations. Moreover, patients who received adjuvant chemotherapy were included in this analysis. Patients with the following conditions were excluded: extension to the distal esophagus (Siewert type I), gastric stump cancer, metastatic disease, endoscopic resection for early gastric cancer, neoadjuvant/perioperative chemotherapy, residual cancer after surgery (R1/R2), hospital mortality within 30 days, and loss of follow-up within 60 months for survivors.

All surgical procedures were performed according to the Japanese gastric cancer treatment guideline, which includes D2-lymphadenectomy.^[9] All resection specimens were classified according to the TNM classification and staged according to the UICC recommendations (7th and 8th editions) by 1 or 2

specialized pathologists.^[1,10] German patients received adjuvant treatment in selected cases only after a multidisciplinary team-review. Most Korean patients received adjuvant chemotherapy based on the results of phase III trials (ACTS-GC and CLASSIC trials) for UICC stages II/III.^[11,12]

Patients were followed-up for a total of 60 months after oncologic surgery and every 6 to twelve months by the respective outpatient departments. Long-term survival (>5 years) data were collected based on additional visits by the patient or through phone contacts in TUM. In NCC, it was collected from the medical records and claims database of the Korean National Health Insurance Corporation. The last follow-up data on death were obtained in December 2016.

This study was approved by the respective local institutional review boards (No.70/18s (TUM School of Medicine), No. NCC2018-0059 (NCC, Korea)).

2.2. Evaluation of prognostic performance

The prognostic performance of the UICC stage of the eighth edition was evaluated by 2 criteria. The first criterion was whether overall survival was sequentially separated according to the respective UICC stage. For this purpose, survival curves according to each stage were depicted, and multivariate analysis was performed to identify changes in hazard ratio according to the stage. The second criterion was to check the accuracy by which each UICC stage predicted the 5- and 10-year overall survival (predictive ability) using receiver operating characteristics analysis.

2.3. Statistical analysis

Descriptive statistics on demographic and clinical tumor characteristics were calculated as the mean \pm standard deviation (continuous variables) and frequencies (categorical variables). Survival time was calculated from the day of surgery to death or the last follow up date (at least 60 months after surgery). The Kaplan-Meier method was used to estimate survival probabilities stratified by the UICC stages in both the 7th and 8th editions. The log-rank test was applied to compare the estimated survival by each UICC stage. The prognostic value of each UICC stage was assessed and modeled using the Cox proportional hazards model after adjusting for the following covariates: age, sex, tumor size, histology, Laurén classification, tumor location, and type of surgery in the Korean model and the same covariates except for histology in the German model. To illustrate the predictive ability of the eighth edition UICC stage, we estimated Harrell C-statistics and the 95% confidence interval.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). *P* values < .05 were considered statistically significant.

3. Results

3.1. Patient characteristics

3.1.1. German cohort. A total of 526 patients met the inclusion criteria, and the baseline characteristics of the patients are listed in Table 1. The proportion of male vs female patients was 64.3% vs 35.7%, and the mean age at the time of surgery was 65.3 \pm 12.1 years. The majority of the patients underwent total gastrectomies (63.7%). The tumor was most commonly located in the upper one-third of the stomach (44.1%). The Laurén

Table 1
Demographic characteristics of gastric cancer patients in Germany (TUM) and Korea (NCC).

Variables	TUM (n=526)		NCC (n=5,595)		P*	
	n	%	n	%		
Age, yr (mean±SD)	65.3±12.1		57.8±11.9		<.001	
Sex	Male	338	64.26	3711	66.33	.340
	Female	188	35.74	1884	33.67	
Operation	Subtotal	191	36.31	4092	73.14	<.001
	Total	335	63.69	1503	26.86	
Tumor size (cm) (mean±SD)	4.8±3.4		4.5±2.7		<.001	
Location	Upper	232	44.11	696	12.44	<.001
	Middle	128	24.33	1760	31.46	
	Lower	154	29.28	2570	45.93	
	Combined	12	2.28	569	10.17	
Lauren	Intestinal	268	50.95	2629	46.99	<.001
	Diffuse	138	26.24	2254	40.29	
	Mixed	64	12.17	519	9.28	
	Unknown	56	10.65	193	3.45	
pT	T1	208	39.54	3002	53.66	<.001
	T2	71	13.50	785	14.03	
	T3	136	25.86	1041	18.61	
	T4a	99	18.82	691	12.35	
	T4b	12	2.28	76	1.36	
	T4c	10	1.90	66	1.18	
pN	pN0	289	54.94	3610	64.52	<.001
	pN1	70	13.31	710	12.69	
	pN2	72	13.69	581	10.38	
	pN3a	64	12.17	477	8.53	
	pN3b	31	5.89	217	3.88	
	pN3c	10	1.90	66	1.18	
UICC, 7th Edition	IA	186	35.36	2107	37.66	<.001
	IB	55	10.46	815	14.57	
	IIA	62	11.79	976	17.44	
	IIB	55	10.46	921	16.46	
	IIIA	53	10.08	335	5.99	
	IIIB	62	11.79	288	5.15	
	IIIC	53	10.08	153	2.73	
UICC, 8th Edition	IA	186	35.36	2107	37.66	<.001
	IB	55	10.46	815	14.57	
	IIA	62	11.79	976	17.44	
	IIB	53	10.08	825	14.75	
	IIIA	77	14.64	440	7.86	
	IIIB	61	11.60	331	5.92	
	IIIC	32	6.08	101	1.81	

Chi-square test was used for comparison between NCC and TUM.

NCC=National Cancer Center, Korea, SD=standard deviation, TUM=Technical University of Munich, Germany, UICC = Union for International Cancer Control.

intestinal type was predominant (51.0%). Among the tumors located in the upper one-third of the stomach, the numbers of Siewert type II and III were 130 and 102, respectively. Median follow-up was 66 months (0–199 months) for all patients, 89 months (60–199 months) for survivors, and 28 months (0–177 months) for deceased patients.

3.1.2. Korean cohort: A total of 5595 patients met the inclusion criteria (Table 1). The proportion of male vs female patients was similar to that in the German cohort (66.3% vs 33.7%), and the mean age at the time of surgery was 57.8±11.9 years. The majority of the patients received subtotal gastrectomies (73.1%). The tumor was most commonly located in the lower one-third of the stomach (45.9%). The Laurén intestinal type was predominant (47.0%). Among the tumors located in the upper one-third of the stomach, the numbers of Siewert type II and III were 111 and 566, respectively. The median follow-up was 96.4 months

(1–120 months) for all patients, 111.4 months (60–120 months) for survivors, and 39.4 months (0–119 months) for deceased patients.

3.2. Stage migration

There was no stage migration for UICC stages IA to IIA since these did not change in the eighth edition. The UICC stages change in 71 of 526 (13.5%) German and 405 of 5595 Korean patients (7.2%) (Table 2). Major shifts were detected in the IIIB stage of the 7th edition: 38.7% (24/62) and 46.2% (133/288) changed to stage IIIA in the German and Korean cohorts, respectively, and 19.4% (12/62) and 16.7% (48/288) changed to stage IIIC in the German and Korean cohorts, respectively. Among patients with a former stage IIIC, 62.3% (33/53) and 65.4% (100/153) changed to stage IIIB in the German and Korean cohorts, respectively.

Table 2
Number of patients who were reclassified from UICC seventh to eighth edition.

		pTNM, 8th Edition							Total
		IA	IB	IIA	IIB	IIIA	IIIB	IIIC	
TUM									
UICC, 7th Edition	IA	186	0	0	0	0	0	0	186
	IB	0	55	0	0	0	0	0	55
	IIA	0	0	62	0	0	0	0	62
	IIB	0	0	0	53	0	2	0	55
	IIIA	0	0	0	0	53	0	0	53
	IIIB	0	0	0	0	24	26	12	62
	IIIC	0	0	0	0	0	33	20	53
	Total	186	55	62	53	77	61	32	526
NCC									
UICC 7th Edition	IA	2107	0	0	0	0	0	0	2107
	IB	0	815	0	0	0	0	0	815
	IIA	0	0	976	0	0	0	0	976
	IIB	0	0	0	825	0	96	0	921
	IIIA	0	0	0	0	307	28	0	335
	IIIB	0	0	0	0	133	107	48	288
	IIIC	0	0	0	0	0	100	53	153
	Total	2107	815	976	825	440	331	101	5595

NCC = National Cancer Center, Korea, TUM = Technical University of Munich, Germany, UICC = Union for International Cancer Control.

3.3. Survival analyses

Survival curves according to the respective UICC stages are shown in Figure 1. In the German cohort, there were no significant survival differences between each adjacent stage for both the 7th and 8th editions (Figure 1A/B). However, for Korean patients, all stages were significantly different except for the comparison between stage IIB and IIIA in the seventh edition ($P = .75$, Figure 1C) and stage IIIA to IIIB in the 8th edition ($P = .53$, Figure 1D).

The 5-year survival rates (5 YSR) and 10-year survival rates (10YSR) according to the respective stages are depicted in Table 3. In the German cohort, 5- and 10YSRs sequentially decreased according to the stage in both the 7th and 8th editions. Only, the 10YSRs were reversed between stages IIIA and IIIB (20.0% in IIIA and 30.4% in IIIB) in the UICC 7th edition. In the Korean cohort, the 5- and 10YSRs generally decreased according to the stages. However, comparable or reversed survival rates were observed between stage IIB and IIIA in the 7th edition (5YSR: 74.3% vs 73.7%; 10YSR: 64.0% vs 65.7% for IIB and IIIA), and between stage IIIA and IIIB (5YSR: 65.5% vs 67.4%; 10YSR: 55.9% vs 57.5% for IIIA and IIIB) in the 8th edition.

Multivariate Cox proportional hazard model analyses showed that the 7th and 8th edition stages were independent prognostic factors for overall survival in both the German and Korean cohorts, after adjusting for demographic and clinical factors (Tables 4 and 5). Moreover, the estimated hazard ratios of the UICC stage show that mortality risks were higher in the advanced stages than in the early stages.

The predictive ability of UICC eighth edition for 5- and 10 YSRs was evaluated using C-statistics and compared with that of the 7th edition (Table 6). When the UICC stage of the 8th edition was added to the multivariate survival model, the C-statistics increased from 0.686 to 0.767 for 5YSRs and from 0.683 to 0.757 for 10YSRs in the German cohort. In the Korean cohort, the C-statistics increased from 0.734 to 0.785 for 5YSRs and from 0.732 to 0.768 for 10YSRs. These increments were similar

to those induced by adding the 7th edition to Model 1 in both the German and Korean cohorts.

4. Discussion

In this study, we analyzed long-term survival according to the 8th edition of the UICC staging system and evaluated its prognostic performance in the German and Korean cohorts independently. The predictive abilities of the 8th edition of the UICC staging system were comparable to those of the 7th edition in both the German and Korean cohorts.

Western patients have different clinicopathological characteristics and their prognosis according to each stage is considerably worse than in eastern Asian patients.^[13,14] In our previous study, the survival of German and Korea patients was different, although all clinicopathological characteristics were balanced using propensity-score matching.^[8] Therefore, reevaluation of the prognostic performance of the 8th edition staging system in a European cohort was important for the evaluation of the postoperative prognosis in European patients.

This study confirmed the well-known differences in clinicopathological factors between the German and Korean cohorts. The German patients were older than the Korean patients, and the proportions of patients with upper one-third gastric cancer and total gastrectomies were higher in the German cohort than in the Korean cohort. Adjuvant chemotherapy consisting of 2 cycles of cisplatin/leucovorin/5-FU was administered only in selected cases in Germans whereas adjuvant chemotherapy was routinely administered in Korean patients with UICC II/III gastric cancer and comprised 12 months of S1 or 6 months of capecitabine/oxaliplatin. Because of the differences in clinicopathological and treatment factors, we performed separate survival analyses and calculated the predictive abilities of the eighth edition in each of the cohorts independently. The statistical matching method was not used because we aimed to evaluate whether the eighth UICC classification system was applicable to real-world Western patients.

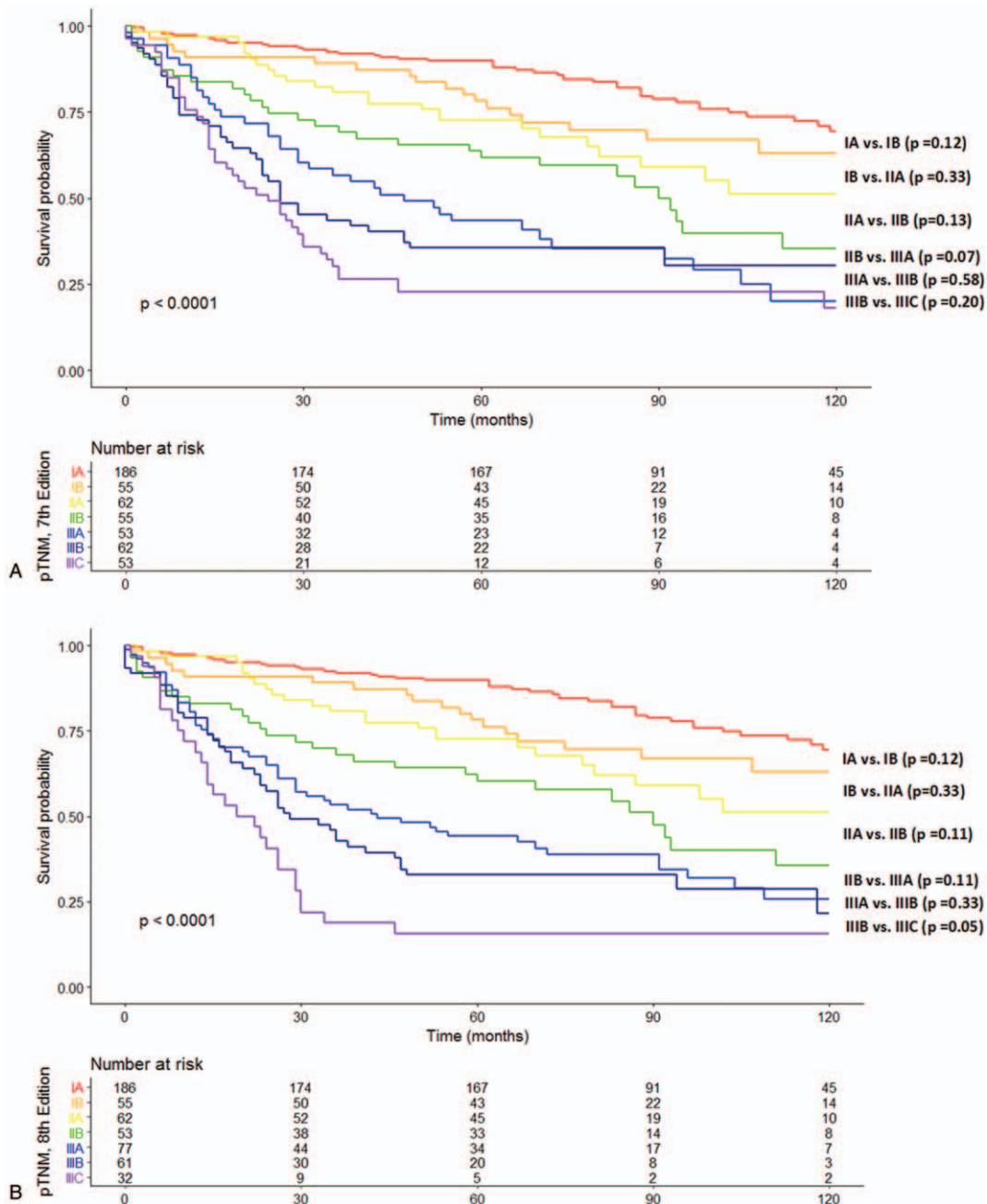


Figure 1. Survival curves according to the respective UICC stages. The Kaplan-Meier method and the log-rank test were used to compare the estimated survival according to each UICC stage. (A) Survival curves according to the seventh edition in the German cohort; (B) Survival curves according to the eighth edition in the German cohort; (C) Survival curves according to the seventh edition in the Korean cohort; (D) Survival curves according to the eighth edition in the Korean cohort. UICC = Union for International Cancer Control.

We found that the survival rates of the German patients were considerably lower in every stage than those of the Korean patients. Moreover, survival rates provided by the IGCA project (UICC 8th edition) were overestimated when applied to the German patients. The only stage that was comparable between the German and IGCA cohorts was stage IIIC. In contrast, the 5 YSRs of the Korean cohort was comparable in stages IA-IIB and higher in stages IIIA-IIIC than those of the IGCA cohort that indicated an underestimation of prognosis. This might be reflected by standardized adjuvant chemotherapy for patients

with advanced gastric cancer (stage II/III) in Korea whereas this is not the case in Germany.

In the Korean cohort, we observed significant differences in survival between most adjacent stages. Only stages IIB and IIIA in the seventh edition and stages IIIA and IIIB in the eighth edition were comparable. Additionally, multivariate analyses showed opposite results for the hazard ratios between IIB and IIIA in the seventh edition model (hazard ratio: 3.2 vs 2.8). We performed subgroup analysis focusing on stage IIB and IIIA and evaluated the proportions of each TNM classification and its survival. In

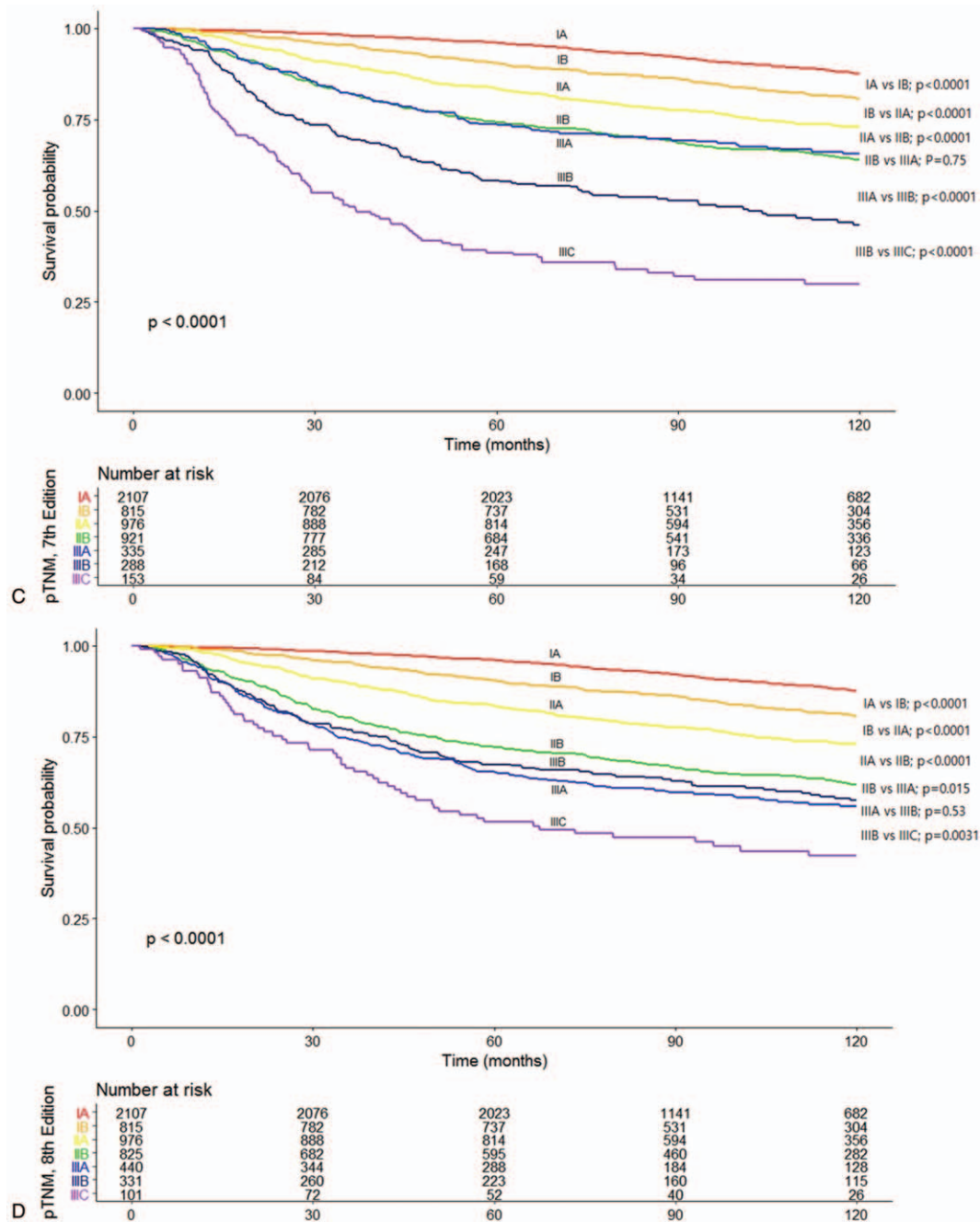


Figure 1. Continued.

stage IIB, which included T1N3, T2N2, T3N1, and T4aN0, T4aN0 had the highest proportion (approximately 40%), and the prognosis of T4aN0 was considerably poorer than those of T1N3, T2N2, and T3N1. On the other hand, the TNM classification in the stage IIIA was evenly distributed (28.3% for T2N3, 40.7% for T3N2, and 31.0% for T4aN1). Therefore, stage IIB could have a poorer prognosis than expected, which might narrow the gap between stage IIB and IIIA. The distribution of TNM classification always varied in each study cohort. Therefore, the database used to make worldwide guidelines should include different areas and ethnicities and have evenly distributed TNM classification. Moreover, it is

necessary to evaluate the prognostic performance of the new staging system in the respective cohorts and compare its performance with the former 1 because of the variation in the cohort.

Analysis of their predictive abilities using the C-index demonstrated no significant changes between the seventh and eighth editions in the German cohort, and the same pattern was observed in the Korean cohort. The reasons for this might be that only a small proportion of patients in this analysis (7% – 14%) underwent stage migration because of the proposed changes in the staging system. The C-indices themselves were comparable to previously published data from China, Japan, and Korea.

Table 3**Kaplan-Meier estimates of survival at 5-yr and 10-yr*.**

		5-yr survival rate (%)			10-yr survival rate (%)		
		TUM	NCC	P [†]	TUM	NCC	P [†]
UICC 7th	IA	89.8	96.0	<.001	69.5	87.6	<.001
	IB	78.2	90.4		63.1	80.6	
	IIA	72.6	83.4		51.1	72.9	
	IIB	61.8	74.3		35.5	64.0	
	IIIA	43.4	73.7		20.0	65.7	
	IIIB	35.5	58.3		30.4	46.1	
UICC 8th	IIIC	22.6	38.6	18.1	30.0		
	IA	89.8	96.0	<.001	69.5	87.6	<.001
	IB	78.2	90.4		63.1	80.6	
	IIA	72.6	83.4		51.1	72.9	
	IIB	60.4	72.1		35.7	61.9	
	IIIA	44.2	65.5		25.7	55.9	
IIIB	32.8	67.4	21.5		57.5		
	IIIC	15.6	51.5	15.6	42.2		

NCC=National Cancer Center, Korea, TUM=Technical University of Munich, UICC = Union for International Cancer Control.

* P values were calculated from the log-rank test.

Table 4**Univariate and multivariate Cox proportional hazards models for overall survival in in German gastric cancer patients (TUM).**

Variables	Univariate			Multivariate UICC7th			Multivariate UICC8th		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.05	1.03–1.06	<.001	1.04	1.03–1.06	<.001	1.04	1.03–1.06	<.001
Sex									
Female	1.00			1.00			1.00		
Male	1.12	0.85–1.47	.430	0.99	0.73–1.34	.962	0.98	0.72–1.32	.886
Tumor Size	1.05	1.03–1.08	<.001	0.99	0.94–1.04	.691	1.00	0.95–1.05	.873
Lauren									
Intestinal	1.00			1.00			1.00		
Diffuse	0.75	0.54–1.04	.083	1.04	0.70–1.55	.835	0.95	0.64–1.43	.812
Mixed	0.85	0.55–1.30	.454	0.86	0.55–1.36	.523	0.83	0.52–1.30	.412
Unknown	1.03	0.68–1.59	.877	0.73	0.45–1.16	.183	0.65	0.40–1.04	.069
Tumor Location									
Upper	1.00			1.00			1.00		
Middle	0.62	0.44–0.86	.004	0.70	0.48–1.03	.072	0.69	0.47–1.01	.057
Lower	0.53	0.39–0.73	<.001	0.65	0.44–0.98	.038	0.67	0.45–1.00	.050
Whole	1.14	0.50–2.60	.749	0.54	0.19–1.56	.255	0.54	0.19–1.54	.247
Operation Type									
Subtotal	1.00			1.00			1.00		
Total	1.60	1.21–2.13	.001	0.86	0.59–1.25	.420	0.82	0.56–1.20	.301
UICC 7th									
IA	1.00			1.00					
IB	1.54	0.87–2.63	.126	1.75	0.96–3.20	0.067			
IIA	2.05	1.22–3.33	.005	2.09	1.20–3.64	0.009			
IIB	3.12	1.91–4.93	<.001	3.88	2.26–6.67	<0.001			
IIIA	4.90	3.08–7.50	<.001	5.12	2.98–8.82	<0.001			
IIIB	5.61	3.57–8.50	<.001	6.23	3.69–10.53	<0.001			
IIIC	7.69	4.89–11.64	<.001	10.09	6.00–16.97	<0.001			
UICC 8th									
IA	1.00						1.00		
IB	1.54	0.87–2.68	.126				1.78	0.97–3.24	.061
IIA	2.05	1.24–3.39	.005				2.13	1.22–3.70	.008
IIB	3.19	1.98–5.15	<.001				3.86	2.23–6.67	<.001
IIIA	4.73	3.14–7.13	<.001				5.43	3.27–9.02	<.001
IIIB	6.01	3.91–9.24	<.001				6.31	3.76–10.60	<.001
IIIC	9.54	5.84–15.61	<.001				18.46	10.26–33.22	<.001

CI=confidence interval, HR=hazard ratio, UICC = Union for International Cancer Control.

Table 5
Univariate and multivariate Cox proportional hazards models for overall survival in in Korean gastric cancer patients (NCC).

	Univariate			Multivariate UICC7th			Multivariate UICC8th		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.04	1.04–1.05	<.001	1.04	1.04–1.05	<0.001	1.04	1.04–1.05	<.001
Sex									
Female	1.00			1.00			1.00		
Male	1.28	1.13–1.45	<.001	1.30	1.14–1.47	<0.001	1.29	1.13–1.46	<.001
Tumor Size (cm)	1.20	1.18–1.22	<.001	1.08	1.06–1.10	<0.001	1.09	1.07–1.11	<.001
Lauren									
Intestinal	1.00			1.00			1.00		
Diffuse	0.96	0.85–1.08	.456	1.05	0.87–1.27	0.637	1.02	0.84–1.23	.88
Mixed	0.85	0.68–1.05	.124	0.89	0.71–1.12	0.312	0.88	0.70–1.10	.255
Unknown	1.22	0.92–1.62	.176	0.81	0.59–1.13	0.21	0.78	0.56–1.08	.134
Tumor Location									
Upper	1.00			1.00			1.00		
Middle	0.81	0.68–0.95	.011	1.47	1.21–1.79	<0.001	1.45	1.19–1.75	<.001
Lower	0.91	0.78–1.07	.245	1.79	1.46–2.21	<0.001	1.77	1.44–2.81	<.001
Whole	6.39	4.83–8.46	<.001	2.68	1.96–3.68	<0.001	2.53	1.84–3.47	<.001
Unknown	2.94	1.61–5.39	.001	3.55	1.43–8.78	0.006	3.12	1.26–7.74	.014
Type of surgery									
Subtotal	1.00			1.00			1.00		
Total	1.96	1.75–2.20	<.001	1.86	1.58, 2.19	<0.001	1.88	1.60–2.22	<.001
UICC 7th									
IA	1.00			1.00					
IB	1.81	1.45–2.25	<.001	1.60	1.29–1.99	<0.001			
IIA	2.81	2.33–3.39	<.001	2.29	1.89–2.77	<0.001			
IIB	4.11	3.47–4.91	<.001	3.19	2.66–3.84	<0.001			
IIIA	4.00	3.16–5.05	<.001	2.79	2.20–3.55	<0.001			
IIIB	7.45	6.01–9.25	<.001	4.92	3.92–6.18	<0.001			
IIIC	13.26	10.45–16.84	<.001	7.85	6.06–10.18	<0.001			
UICC 8th									
IA	1.00						1.00		
IB	1.81	1.46–2.25	<.001				1.58	1.27–1.97	<.001
IIA	2.81	2.33–3.40	<.001				2.23	1.84–2.70	<.001
IIB	4.46	3.72–5.34	<.001				3.25	2.70–3.92	<.001
IIIA	5.70	4.67–6.98	<.001				3.65	2.96–4.51	<.001
IIIB	5.24	4.21–6.54	<.001				3.94	3.15–4.94	<.001
IIIC	8.52	6.34–11.45	<.001				4.75	3.49–6.47	<.001

CI = confidence interval, HR = hazard ratio, NCC = National Cancer Center, UICC = Union for International Cancer Control.

Interestingly, the predictive ability of the eighth UICC staging system in the German cohort was comparable to that of the Korean cohorts, although the IGCA reference data were mostly based on eastern Asian patients and estimation of survival rates was considerably different.

One limitation of this study is the large disparity in the number of patients included in the 2 cohorts. This is because of the lower incidence of gastric cancer and the higher proportion of patients receiving neoadjuvant chemotherapy in German than in Korea. We screened a total of 1056 German patients and

Table 6
Comparison in discriminative performance of UICC 7th and 8th edition.

	TUM		NCC		
	c-statistics	95% CI	c-statistics	95% CI	
Model 1*	60 mo	0.686	0.622–0.753	0.734	0.707–0.761
	120 mo	0.683	0.623–0.744	0.732	0.710–0.755
Model 1 + UICC 7th	60 mo	0.768	0.715–0.821	0.789	0.766–0.812
	120 mo	0.757	0.707–0.807	0.772	0.752–0.791
Model 1 + UICC 8th	60 mo	0.767	0.713–0.821	0.785	0.763–0.808
	120 mo	0.757	0.707–0.807	0.768	0.749–0.788

CI = confidence interval, NCC = National Cancer Center, UICC = Union for International Cancer Control.

*Model 1 for Korea included all variables; age, sex, histology, Lauren, tumor location, operation type, tumor size but does not included UICC stage.

*Model 1 for Munchen included all variables; age, sex, Lauren, tumor location, operation type, tumor size but does not included UICC stage.

found that approximately half of them (43.4%) received neoadjuvant chemotherapy and thus, were excluded from this study. However, a comparative analysis between the German and Korean patients was not the intention of this analysis, as it was previously demonstrated that these patient groups are not directly comparable due to ethnic/biologic and unaccounted factors.^[8] Moreover, an unintended selection bias could exist due to the retrospective character of this analysis, and the incorporation of data from specialized cancer centers in their respective countries may not reflect the common clinical reality.

In conclusion, the predictive ability of the eighth edition was similar to that of the seventh edition in both the German and Korean cohorts. Moreover, the survival rates were not significantly different between the eighth UICC stages IIIA and IIB in Korean and German patients. Survival rates from the IGCA cohort are overestimated for German patients but partially underestimated for Korean patients. The next edition should focus on the differentiation between stage IIIA and IIB and further revise the guidelines for the staging system.

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References

- [1] Brierley JD, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours*, Eighth Edition. Hoboken, NJ: Wiley-Blackwell 2017.
- [2] Sano T, Coit DG, Kim HH, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. *Gastric cancer* 2017;20:217–25.
- [3] Lu J, Zheng CH, Cao LL, 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.
- [4] Seeruttun SR, Yuan S, Qiu H, et al. A comprehensive analysis comparing the eighth AJCC gastric cancer pathological classification to the seventh, sixth, and fifth editions. *Cancer medicine* 2017;6:2804–13.
- [5] Ji X, Bu ZD, Yan Y, et al. The 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system for gastric cancer is superior to the 7th edition: results from a Chinese mono-institutional study of 1663 patients. *Gastric cancer* 2018;21:643–52.
- [6] Fang WL, Huang KH, Chen MH, et al. Comparative study of the 7th and 8th AJCC editions for gastric cancer patients after curative surgery. *PLoS one* 2017;12:e0187626.
- [7] Kim SG, Seo HS, Lee HH, et al. Comparison of the differences in survival rates between the 7th and 8th editions of the AJCC TNM staging system for gastric adenocarcinoma: a single-institution study of 5507 patients in Korea. *J gastric can* 2017;17:212–9.
- [8] Kim YW, Joo J, Yoon HM, et al. Different survival outcomes after curative R0-resection for Eastern Asian and European gastric cancer: results from a propensity score matched analysis comparing a Korean and a German specialized center. *Medicine* 2016;95:e4261.
- [9] Association JGC. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric cancer* 2011;14:113–23.
- [10] Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours*, Seventh Edition. Hoboken, NJ: Wiley-Blackwell 2011.
- [11] Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810–20.
- [12] Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012;379:315–21.
- [13] Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg* 2010;251:640–6.
- [14] Bickenbach K, Strong VE. Comparisons of gastric cancer treatments: East vs. West. *J Gastric Cancer* 2012;12:55–62.