Original Article

The Superiority of the Seventh Edition of the TNM Classification Depends on the Overall Survival of the Patient Cohort

Comparative Analysis of the Sixth and Seventh TNM Editions in Patients With Gastric Cancer From Japan and the United Kingdom

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BACKGROUND: The objective of this study was to investigate whether the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer TNM classification (TNM7) had superior discriminatory ability over the sixth edition of the TNM classification (TNM6) in patients with gastric cancer regardless of their country of origin. **METHODS:** In total, 538 patients from the Kanagawa Cancer Center Hospital (Yokohama, Japan) (KCCH) and 519 patients from the Leeds Teaching Hospitals National Health Service Trust (Leeds, United Kingdom) (LTHT) who underwent surgery for gastric cancer were selected. Overall survival was used for statistical analysis. Hazard ratios (HRs) were estimated with disease stage as a continuous variable to evaluate the discriminatory ability of the TNM stage groups. The estimates of log HRs (logHRs) for the TNM6 and the TNM7 stage groups were compared. **RESULTS:** In the KCCH cohort, 82 patients (15%) were upstaged, and 26 patients (5%) were downstaged between TNM6 and TNM7 compared with 253 patients (49%) and 53 patients (10%), respectively, in the LTHT cohort. The logHRs for a 1-stage increase within TNM6 and TNM7 were 1.06 and 1.16, respectively, in the KCCH cohort and 0.57 and 0.79, respectively, in the LTHT cohort. The differences in logHRs between TNM6 and TNM7 were significant in each cohort (KCCH: logHR, 0.11; $P = .024$; LTHT: logHR, 0.21; $P = .0002$) and between the 2 cohorts. **CONCLUSIONS:** TNM7 had superior discriminatory ability compared with TNM6 in both cohorts. The improved ability to discriminate patients with different survival probability when using TNM7 was greater in the LTHT cohort. The current findings indicated that the discriminatory ability of the TNM stage groups may depend on the baseline survival characteristics of the patient cohort. ***Cancer* 2013;119:1330-7.** © *2012 American Cancer Society.*

KEYWORDS: gastric cancer, seventh edition TNM classification, sixth edition TNM classification, discriminatory ability, United Kingdom, Japan.

INTRODUCTION

The International Union Against Cancer (UICC) tumor-lymph node-metastasis (TNM) classification is the major factor determining the treatment options offered to patients with gastric cancer. In 2010, the seventh edition of the American Joint Committee on Cancer gastric cancer TNM classification (TNM7) was published, incorporating new evidence and aiming to improve the classification's ability to accurately predict the prognosis of patients with gastric cancer.[1,2] Apart from rebranding the tumor (T) classification categories to achieve uniformity in T category names throughout the gastrointestinal tract, the gastric cancer T1 category was subdivided into T1a (mucosa) and T1b (submucosa). Upstaging occurred within the lymph node (N) category by splitting the TNM6 N1 category (1-6 positive lymph nodes) into TNM7 N1 (1-2 positive lymph nodes) and N2 (3-6 positive lymph nodes) and classifying >6 positive lymph nodes as N3 instead of N2 in TNM6. For practical purposes, the T, N, and metastasis (M) categories are condensed into TNM stage groups. With the exception of stage IA, the definition of the individual TNM stages changed substantially between TNM6 and TNM7, and the number of stage groups increased from 6 groups in TNM6 to 8 groups in TNM7. On the

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basis of the TNM classification principles, patients within the same TNM stage group should be relatively homogenous with respect to survival. Because the TNM stage groups were changed between TNM6 and TNM7 based on new evidence, the ability to discriminate between patients with different prognoses ("discriminatory ability") should be improved in TNM7. Furthermore, the TNM classification is meant to be universally applicable; thus, it is expected that the magnitude of the improvement should be the same for patients from the West and the East.

Four studies from the West[3-6] and 6 studies from the East[7-12] have compared TNM6 with TNM7 in patients with gastric cancer. Nevertheless, it remains controversial whether TNM7 is superior to TNM6, because most studies focused on the comparison of the depth of invasion (pT)[3] or lymph node status (pN) and did not compare the TNM stage groups.[8,9] Furthermore, investigators evaluated the survival curves by log-rank test alone and did not analyze their discriminatory ability.[5,7,11] Wang et al[12] calculated hazard ratios (HRs) in both the TNM6 and the TNM7 staging systems to evaluate the discriminatory ability but did not compare the HRs of the 2 staging systems statistically.

We hypothesized that: 1) TNM7 stage groups have a better discriminatory ability compared with TNM6 stage groups in statistical analysis, and 2) the superiority of TNM7 is independent of the country in which the disease occurs. Therefore, we established and compared the discriminatory ability between TNM6 and TNM7 stage groups in gastric cancer patient cohorts from 2 high-volume cancer centers in different parts of the world: the Kanagawa Cancer Center Hospital (KCCH) (Yokohama, Japan) and the Leeds Teaching Hospitals National Health Service (NHS) Trust (LTHT) (Leeds, United Kingdom).

MATERIALS AND METHODS

The Kanagawa Cancer Center Hospital Cohort

In total, 723 patients were diagnosed with gastric cancer and underwent surgery between 2000 and 2005 at the KCCH. Only patients who met the following criteria were included in the current study: 1) histologically confirmed, resectable adenocarcinoma of the stomach; 2) no evidence of distant metastases by imaging before surgery; 3) total or subtotal gastrectomy with D1 or greater lymph node dissection as primary treatment; 4) no macroscopic evidence of residual tumor at the time of surgery; and 5) clinical follow-up of patients for at least 5 years after surgery. Patients who underwent local wedge resection, who had received any form of neoadjuvant or adjuvant treatment, and those with junctional cancer were excluded from the study. Patients with evidence of distant metastases that were noted only at the time of the gastrectomy and were amenable to surgical resection and patients with microscopic residual disease at the longitudinal resection margin (pR1) were included in the study. Peritoneal cytology was performed only in a small number of highly selected patients determined by surgical findings in the KCCH cohort. Therefore, a decision was made to not consider results from peritoneal cytology when determining the disease stage for either TNM6 or TNM7. In total, 538 patients from KCCH were included in the current study. Because the current study examined overall survival (OS), patients who died of any cause at any time point after surgery were included. The median follow-up was 62 months (range, 0.01-110 months), and 377 patients (70%) survived for more than 5 years.

The Leeds Teaching Hospitals NHS Trust Cohort

To identify a similar number of patients that fulfilled inclusion and exclusion criteria similar to those stated above, an existing gastric cancer database from the LTHT was searched. Between 1988 and 2005, 556 patients were identified who underwent surgery for gastric adenocarcinoma in Leeds and fulfilled the same criteria as the KCCH cohort. Patients who underwent esophagogastrectomy for junctional cancer ($n = 37$) were excluded. In total, 519 patients from the LTHT were included in the current study. Because the current study examined OS, patients who died of any cause at any time point after surgery were included. The median follow-up was 21 months (range, 0.01-210 months), and 157 of the 519 patients (30%) survived for more than 5 years.

Data Collection

Patient characteristics and clinical, surgical, and pathological information was retrieved from hospital records at both institutions. Survival data were obtained from the outpatient clinic and Kanagawa Prefectural registry system for the KCCH cohort and from the outpatient clinic and the Northern and Yorkshire Cancer Registry for the LTHT cohort. This study was approved by the local ethics research committee in each institution.

Statistical Analysis

The chi-square test was used to compare patient characteristics. Stage migration according to TNM7 was examined in each stage using TNM6 as the reference. OS was defined as the time from surgery to death from any cause or last follow-up. The OS probability was calculated using the Kaplan-Meier method, and the 5-year OS rate was estimated. To evaluate the discriminatory ability, a Cox proportional hazards model was used and the HR was

estimated with stage group as a continuous variable. Because the number of patients in some of the stage subgroups was relatively small, only the major stage groups (eg, stages I, II, III, and IV) were used for this part of the analysis. HRs were calculated for stages II, III, and IV compared with stage I. The estimates of log HRs (logHRs) for the TNM6 and TNM7 stage groups were compared using a Z test. The standard error of the difference in logHRs was calculated using the robust variance estimator, which takes the correlation of logHRs into account.[13] P values $< .05$ were considered significant. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Ill) or SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Demographics

The clinicopathologic characteristics of the gastric cancer patient cohorts from both centers are listed in Table 1. The TNM stage group distribution of the KCCH and LTHT cohorts is illustrated in Figure 1. In both TNM staging systems, the distribution of patients in the KCCH cohort was clearly skewed toward stage I disease. The distribution of patients in the LTHT cohort in the different TNM stage groups was more even but was skewed toward stage III in TNM6.

TABLE 1. Characteristics of Patients With Gastric Cancer From Leeds (Leeds Teaching Hospitals NHS Trust) and From Yokohama (Kanagawa Cancer Center Hospital)

Characteristic	No. of Patients (%)		*P*
	LTHT, n = 519	KCCH, n = 538	
Age at time of surgery, years			< .001
≤40	5 (1)	21 (4)	
41-60	80 (15)	177 (29)	
≥61	434 (84)	340 (67)	
Median [range]	72 [29-96]	64 [25-85]	
Gender			.020
Men	331 (65)	395 (74)	
Women	188 (35)	143 (26)	
Location of tumor			< .001
Upper third	138 (27)	116 (22)	
Middle third	115 (22)	13 (2)	
Lower third	254 (49)	395 (73)	
Entire stomach	12 (2)	14 (3)	
Type of gastrectomy			< .001
Total	265 (51)	191 (38)	
Subtotal	254 (49)	347 (62)	
Lauren classification			< .001
Intestinal type	327 (63)	237 (44)	
Diffuse type	115 (22)	267 (50)	
Mixed type	77 (15)	34 (6)	
No. of examined lymph nodes			.010
<15	218 (42)	22 (4)	
≥15	301 (58)	516 (96)	
Pathological resection margin status			< .001
pR0	450 (87)	517 (99)	
pR1	69 (13)	5 (1)	
Distant metastasis: M1[a]			.090
cM0	504 (97)	512 (95)	
pM1	15 (3)	26 (5)	

Abbreviations: KCCH, Kanagawa Cancer Center Hospital (Yokohama, Japan); LTHT, Leeds Teaching Hospitals NHS Trust (Leeds, United Kingdom); pM, pathologic metastasis classification.

[a] M1 was defined according to the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer TNM classification. Note that peritoneal cytology results were not considered when determining M status (see Material and Methods).

Overall Survival and Stage Migration Analysis

The Kanagawa Cancer Center Hospital cohort

OS survival curves according to TNM6 and TNM7 stage groups are illustrated in Figure 2A and 2B, respectively. The Kaplan-Meier plot indicates that there is cross-over of survival curves of TNM6 stages IA, IB, and II; TNM7 stages IA, IB, and IIB; and TNM7 stages IIA and IIIA. The 5-year OS rates and the number of patients migrating to a different stage in TNM7 are detailed in Figure 3A. In total, 82 patients (15%) are upstaged, and 26 patients (5%) are downstaged between TNM6 and TNM7 in the KCCH cohort. It is noteworthy that the difference in the 5-year OS rate between the subgroup of patients being upstaged from TNM6 stage IB to TNM7 stage IIA and those remaining in stage IB in TNM7 is only 4%. In contrast, differences in the 5-year OS rate between patients with stage migration and those remaining in the same TNM7 stage category are much greater in TNM6 stages II, IIA, IIB, and IV (Fig. 3A).

The Leeds Teaching Hospitals NHS Trust cohort

OS curves and 5-year OS rates according to TNM6 and TNM7 stage groups are illustrated in Figure 2C and 2D, respectively. The Kaplan-Meier plot indicates that there is cross-over of survival curves of TNM6 stages IIIB and IV, TNM7 stages IB and IIA, and TNM7 stages IIIC and IV. The 5-year OS rates and the number of patients migrating to a different stage in TNM7 are detailed in Figure 3B. In total, 253 patients (49%) are upstaged, and 53 patients (10%) are downstaged between TNM6 and TNM7. Similar to the KCCH cohort, the difference in the 5-year OS rate between the subgroup of patients being upstaged from TNM6 stage IB to TNM7 stage IIA and those remaining in stage IB in the TNM7 is small at only 6%. In contrast, differences in the 5-year OS rate between patients with stage migration and those remaining in the same TNM7 stage category are much greater in TNM6 stages II, IIA, IIB, and IV (Fig. 3B).

A

		N0		N1		N2		N3	
		N0		N1		N2		N3a		N3b	
T1	T1a	160	IA IA	2	IB IB	0	IB IIA	1	II IIB	0	IV IIB
	T1b	137	IA IA	16	IB IB	8	IB IIA	3	II IIB	0	IV IIB
T2	T2	36	IB IB	15	II IIA	8	II IIB	7	IIIA IIIA	0	IV IIIA
	T3	10	IB IIA	12	II IIB	5	II IIIA	3	IIIA IIIB	1	IV IIIB
T3	T4a	18	II IIB	18	IIIA IIIA	13	IIIA IIIB	13	IIIB IIIC	18	IV IIIC
T4	T4b	1	IIIA IIIB	2	IV IIIB	1	IV IIIC	2	IV IIIC	2	IV IIIC

(No of pts; Stage TNM 6 / Stage TNM 7)

B

		N0		N1		N2		N3	
		N0		N1		N2		N3a		N3b	
T1	T1a	21	IA IA	0	IB IB	0	IB IIA	0	II IIB	0	IV IIB
	T1b	31	IA IA	6	IB IB	3	IB IIA	1	II IIB	0	IV IIB
T2	T2	25	IB IB	11	II IIA	9	II IIB	2	IIIA IIIA	1	IV IIIA
	T3	51	IB IIA	34	II IIB	39	II IIIA	25	IIIA IIIB	6	IV IIIB
T3	T4a	31	II IIB	34	IIIA IIIA	59	IIIA IIIB	68	IIIB IIIC	32	IV IIIC
T4	T4b	1	IIIA IIIB	5	IV IIIB	2	IV IIIC	5	IV IIIC	2	IV IIIC

(No of pts; Stage TNM6 / Stage TNM7)

C

KCCH	TNM6 n (%)	TNM7 n(%)
Stage I	369 (69)	351 (65)
IA	297 (55)	297 (55)
IB	72 (14)	54 (10)
Stage II	62 (12)	75 (14)
IIA	-	33 (6)
IIB	-	42 (8)
Stage III	55 (10)	86 (16)
IIIA	42 (8)	30 (6)
IIIB	13 (2)	20 (4)
IIIC	-	36 (6)
Stage IV	52 (9)	26 (5)

D

LTHT	TNM6 n(%)	TNM7 n(%)
Stage I	137 (26)	83 (16)
IA	52 (10)	52 (10)
IB	85 (16)	31 (6)
Stage II	125 (24)	140 (27)
IIA	-	65 (12)
IIB	-	75 (15)
Stage III	189 (36)	281 (54)
IIIA	121 (23)	76 (15)
IIIB	68 (13)	96 (18)
IIIC	-	109 (21)
Stage IV	68 (14)	15 (3)

Figure 1. Patient distribution is illustrated in the different stage groups according to the sixth and seventh editions of the American Joint Committee on Cancer/International Union Against Cancer TNM classification (TNM6 and TNM7, respectively) for (A) the Kanagawa Cancer Center Hospital (Yokohama, Japan) (KCCH) cohort and (B) the Leeds Teaching Hospitals NHS Trust (Leeds, United Kingdom) (LTHT) cohort. Patient distribution is illustrated considering depth of invasion (T classification) and lymph node status (N classification) only. Patients who had resectable distant metastases (M1 disease) were excluded from this analysis. The number and proportion of patients are illustrated by stage groups for (C) the KCCH cohort and (D) the LTHT cohort, including patients with M1 disease.

Comparison of Hazard Ratios in the Sixth and Seventh TNM Classifications

Because of the relatively small numbers of patients in individual stage subcategories, the HRs were calculated only for the major stage groups in each cohort. The HRs for stages II, III, and IV compared with stage I are shown in Figure 4A and 4B for the KCCH and LTHT cohorts, respectively. When stage was used as a continuous variable, the logHR for a 1-stage increase within TNM6 and TNM7 was 1.06 and 1.16, respectively, in the KCCH cohort and 0.57 and 0.79, respectively, in the LTHT cohort. The differences in logHRs between TNM6 and TNM7 were 0.11 ($P = .024$) in the KCCH cohort and 0.21 ($P = .0002$) in the LTHT cohort, indicating a statistically significant increase of the discriminatory ability of TNM7 compared with the TNM6 for both cohorts.

DISCUSSION

The objective of the TNM classification is to describe the anatomic extent of the tumor. Because of the relation between anatomic tumor extent and survival, the TNM classification allows the clinician to estimate patient survival, which is important for making treatment decisions.[14] Together with the upstaging of the N category and the rebranding of the T categories, the vast majority of TNM stage groups were newly defined with the introduction of the TNM7 for gastric cancer. Several studies have recently attempted to evaluate the gastric cancer TNM7 classification[3-12] but did not examine its discriminatory ability or assess whether the new TNM7 stage groups can identify patients with similar survival equally well in gastric cancer patient cohorts from Eastern and Western countries.

The current study is the first to demonstrate in 2 large gastric cancer patient cohorts from the West and the

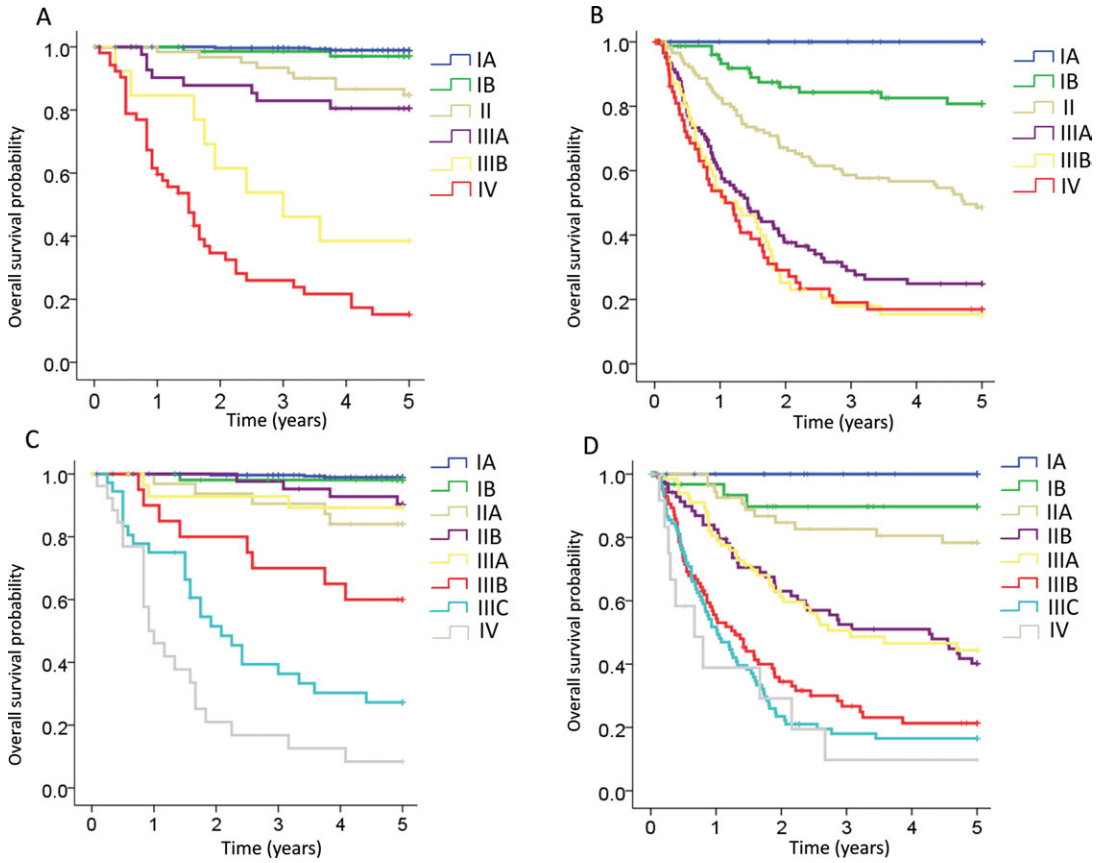

Figure 2. Kaplan-Meier overall survival curves are illustrated according to TNM stage groups. (A) Overall survival for patients in the KCCH cohort is stratified by stage groups according to the sixth edition of the American Joint Committee on Cancer/International Union Against Cancer TNM classification (TNM6). (B) Overall survival for patients in the LTHT cohort is stratified by stage groups according to TNM6. (C) Overall survival for patients in the KCCH cohort is stratified by stage groups according to the seventh edition of the TNM classification (TNM7). (D) Overall survival of patients in the LTHT cohort is stratified by stage groups according to TNM7.

East that the discriminatory ability assessed by comparing the logHR was improved significantly in TNM7 in both cohorts, confirming our first hypothesis. However, the improvement in the discriminatory ability of TNM7 was greater in the LTHT (United Kingdom) gastric cancer cohort, refuting our second hypothesis that the magnitude of improvement is independent of the country where the cancer occurred. The discriminatory ability of TNM stage groups depends on the stage-specific heterogeneity of the OS of the individual patient cohort. The heterogeneity of survival among patients with the same disease stage is one of the drivers for changing TNM stage groups, which also is reflected in the increased number of stage groups in TNM7.

In the revision of TNM6 to TNM7, the number of categories was increased from 6 to 8. Classification into TNM7 demonstrated that patients in each subcategory of TNM6 had heterogeneous survival, as illustrated in Figure 3. Whereas there is little heterogeneity in survival among patients with early stage disease (eg, TNM6 stage IA and IB) in the KCCH (Japan) cohort, prominent heterogeneity in patient survival was noted in the same disease stage in the LTHT cohort. Survival heterogeneity decreased with increasing stage in the LTHT cohort but increased with increasing stage in the KCCH cohort. Striking differences in patients' disease stage distribution and the extent of stage migration between the 2 cohorts may contribute to this effect as well as potential under staging of the N category in the LTHT cohort (see below, Limitations). However, survival heterogeneity in patients who have gastric cancer with the same TNM stage may also be related to other factors, such as age, comorbidity, histologic subtype, tumor location, and other factors and has led to the recent development of nomograms to predict prognosis more accurately for individual patients with gastric cancer.[15,16] Conversely, the number of patients in each stage was decreased by increasing the number of categories from 6 to 8, increasing the

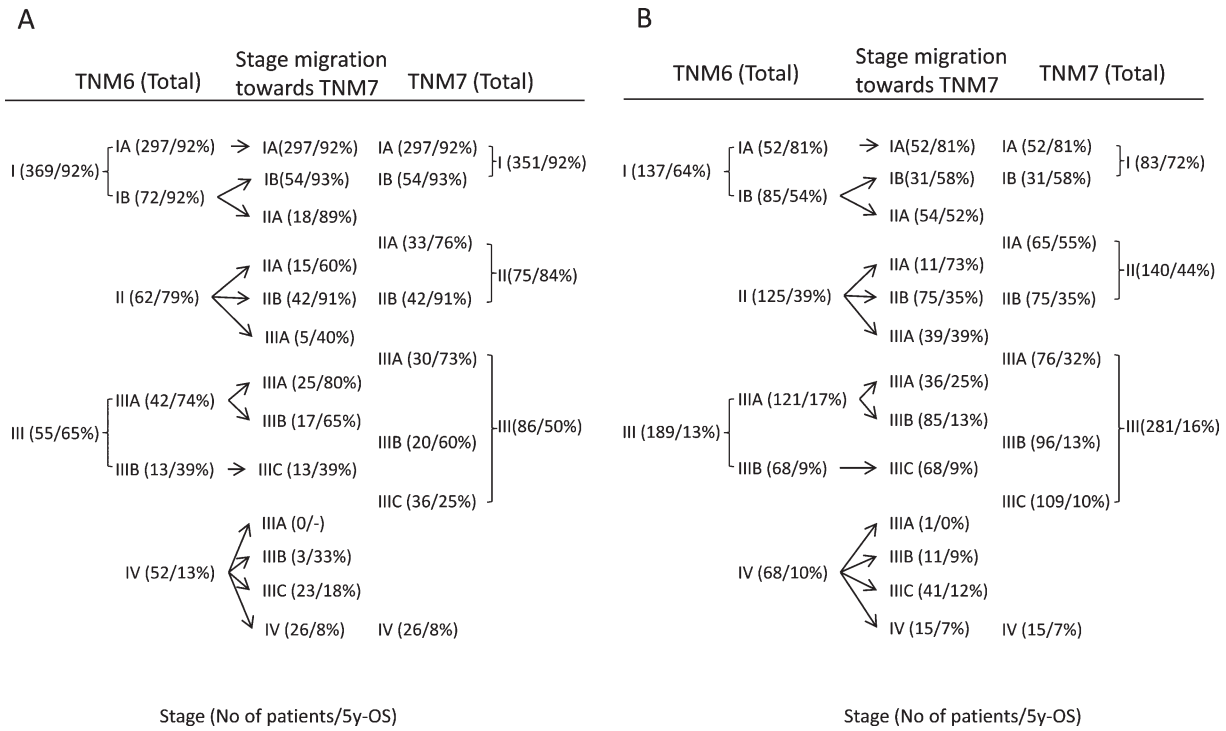

Figure 3. The 5-year overall survival (5 years-OS) rate is illustrated in (A) the KCCH cohort and (B) the LTHT cohort for all stage groups according the sixth and seventh editions of the American Joint Committee on Cancer/International Union Against Cancer TNM classification (TNM6 and TNM7, respectively). The number of patients and their 5-year overall survival rates for all TNM6 groups are subdivided by each TNM7 stage subgroup and by the number of patients who showed stage migration.

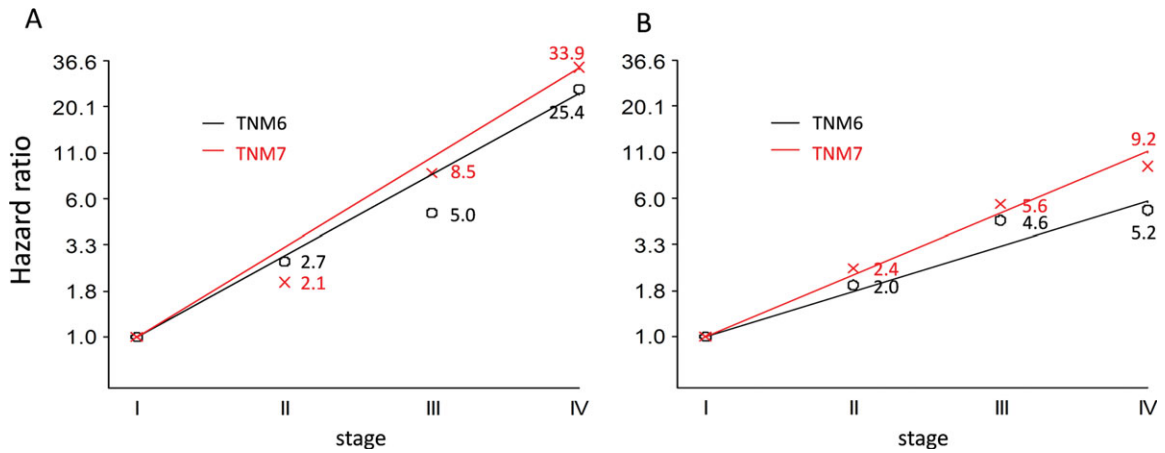

Figure 4. Hazard ratios for overall survival are illustrated as a log scale for major stage groups II, III, and IV relative to stage group I according to the American Joint Committee on Cancer/International Union Against Cancer TNM classification. The inclination of lines depicts log hazard ratios (logHRs) for (A) the KCCH cohort and (B) the LTHT cohort.

probability that survival rates would overlap because of wide 95% CIs.

In TNM7, the HR for stage I was increased in all stages in the LTHT cohort but did not increase between stages I and II in the KCCH cohort, indicating that the effect on the change in OS rates in stages I and II between TNM6 and TNM7 was different for the LTHT cohort and the KCCH cohort. It is known that patients with T1N2 and T3N0 cancers have the poorest survival of all patients classified with stage I disease according to

TNM6. These patients were upstaged to stage II in TNM7. Thus, the prognosis for patients classified with stage I disease in TNM7 should improve compared with the prognosis for patients classified with stage I disease in TNM6. The 5-year OS rate of patients with TNM7 stage I disease, was significantly better compared with the rate for patients with TNM6 stage I disease in the LTHT cohort. In contrast, the 5-year OS rate was identical for patients with TNM6 stage I disease and TNM7 stage II disease in the KCCH cohort. This highlights the probability that LTHT patients with gastric cancer with the same disease stage (eg T1N2 or T3N0) may have a very a different OS probability than KCCH patients. Conversely, in both cohorts, the group of patients with TNM7 stage II disease had a better prognosis than those with TNM6 stage II disease, which most likely is related to patients from TNM6 stage I migrating into TNM7 stage II, thus "improving" the OS rate for patients with TNM7 stage II disease. In summary, the excellent OS for all KCCH patients with TNM6 stage I disease appears to offset the effect of migrating some of these patients into TNM7 stage II as part of the TNM7 stage group revision. These results from the KCCH cohort with early stage disease confirm results from previous investigators.[4,10] With the exception of patients who have pM1 disease, all patients with TNM6 stage IV disease are downstaged to stage III in TNM7. Our study confirms in both cohorts that patients with TNM7 stage IV disease are those with the worst 5-year OS rate within the group of patients with TNM6 stage IV disease.

The current study has several limitations. First, this was a retrospective study comparing a dataset from a United Kingdom cancer center with a dataset from a cancer center in Japan. To have a similar number of patients from both centers and, hence, sufficient statistical power for analyses, the LTHT patient data had to span a period of up to 17 years. We cannot exclude the possibility that there may have been changes in clinical practice over this period, which may have had an influence on patient OS. Second, the objective of this study was to establish whether the discriminatory ability of the TNM7 classification is superior to that of the TNM6 and whether this effect is of similar magnitude in patients from the United Kingdom and patients from Japan. We noted that nearly all clinicopathologic variables, including stage-specific survival, differed between the 2 cohorts. No attempt was made to adjust for the differences or establish the causes of these differences. Because of the overall lower number of lymph nodes resected and/or retrieved by the United Kingdom surgeons and/or pathologists, we have to consider the possibility that the United Kingdom cases may be understaged, which may explain in part the relatively poor survival of patients who presumably had early disease stage. To our knowledge, there is no evidence published in the literature that there is a difference in determining the depth of tumor invasion (pT category) between East and West. Third, although we applied the same exclusion criteria to select patients for this study, no attempt was made to match patients on the basis of their demographic and clinicopathological data, assuming that disease stage is the major factor influencing patient OS.

In conclusion, stage groups according to TNM7 are superior to those according to TNM6 for discriminating patients with gastric cancer who have different outcomes in the East and the West. Our study indicates that the magnitude of this discriminatory ability depends on the stage-specific OS characteristic of the patient cohort. Our findings suggest that any change in the TNM classification in the future needs to be based on evidence from sufficiently large and sufficiently diverse gastric cancer patient cohorts to remain applicable universally irrespective of the country of origin. This most likely is achievable only by a worldwide collaboration on data collection like what was done previously for esophageal cancer.[17]

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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