PART I

Staging and prognostication

CHAPTER 2

The new American Joint Committee on Cancer/International Union Against Cancer staging system for adenocarcinoma of the stomach: increased complexity without clear improvement in predictive accuracy

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ABSTRACT

BACKGROUND

The objectives of the current study were to evaluate the changes in the 7th edition American Joint Committee on Cancer (AJCC) staging system for stomach cancer compared to the 6th edition and to compare the predictive accuracy of the two staging systems.

PATIENTS AND METHODS

In a combined database containing 2196 patients who underwent an R0 resection for gastric adenocarcinoma, differences between the two staging systems were evaluated and stage specific survival estimates were compared. Concordance probability and Brier scores were estimated for both systems to examine the predictive accuracy.

RESULTS

Nodal status cut-off values were changed, leading to a more even distribution for the redefined N1, N2, and N3 group. AJCC 6th edition stage II reflected a highly heterogeneous population, which is now adequately subdivided in the AJCC 7th edition into stages IIA, IIB, and IIIA. The predictive accuracy of N-classification improved significantly as measured by concordance. Despite increased complexity, the predictive accuracy of AJCC 7th stage grouping was significantly worse than that of the AJCC 6th edition.

CONCLUSIONS

The increased complexity of the 7th edition staging system is accompanied with improvements in the predictive value of nodal staging as compared to the 6th edition, but was no better in overall stage-specific predictive accuracy. Future refinements of the TNM-classification should consider whether increased complexity is balanced by improved prognostic accuracy.

INTRODUCTION

Cancer staging is one of the fundamental activities in oncology.[1,2] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[3] In order to maintain the staging system relevant, the International Union Against Cancer and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[4]

For gastric cancer, several changes to the 6th edition were made.[5] In the 7th edition, all gastroesophageal junction (GEJ) tumors are staged as esophageal cancers, except tumors arising in the stomach >5cm from the GEJ (Figure 1). The T classification categories have been redefined (Table 1) and the T classification of stomach cancer and esophageal cancer have been harmonized. N-categories have been modified to better represent the distribution of the number of positive lymph nodes. The M1 category has been amended to include positive peritoneal cytology. Stage IV now includes only patients with M1 disease. Finally, new stage groups have been added to the staging system (IIB and IIIC). The 7th edition staging system is more complex, with an increase in the number of permutations of TNM groupings from 56 to 80. There are now nine stage groups, compared to seven in the AJCC 6th edition (Table 2).

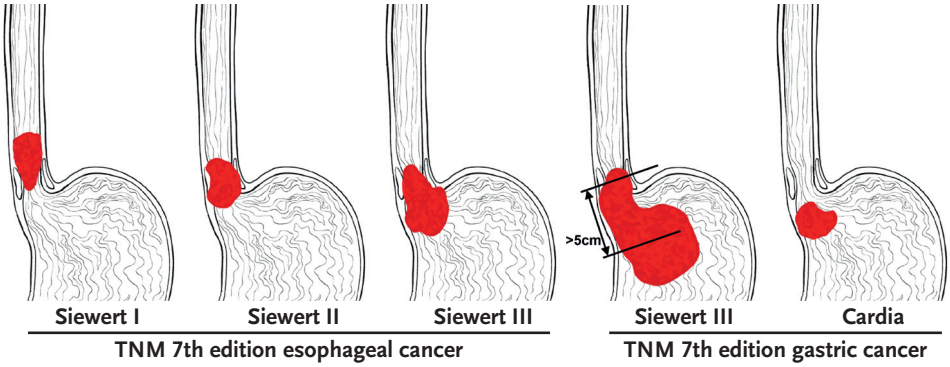
With each staging system revision, there is a tension between improving prognostic value of the staging system by adding subdivisions of existing stage groupings and introducing new predictive parameters, and the desire to keep the staging system intuitive and simple.

Table 1. Changes in the AJCC staging system for gastric cancer

T - Primary tumor (invasion depth)	AJCC 6th edition	AJCC 7th edition
no evidence of primary tumor	T0	T0
carcinoma in situ	Tis	Tis
mucosa[a]	T1	T1a
submucosa		T1b
muscularis propria	T2a	T2
subserosa	T2b	T3
serosa	T3	T4a
adjacent structures	T4	T4b
N - Regional Lymph Node Metastases		
0	N0	N0
1-2	N1	N1
3-6		N2
7-15	N2	N3a
>15	N3	N3b
M - Distant Metastases		
no distant metastases	M0	M0
distant metastases	M1	M1

[a] at least invasion of lamina propria

Figure 1. Definition of esophageal and gastric cancer according to the 7th edition AJCC staging system



The purpose of this study is to compare the 6th to the 7th edition of the AJCC staging system for gastric cancer, first by describing the differences in stage-specific survival, and secondly by examining whether the increased complexity of the 7th edition resulted in improved prognostic accuracy as compared to the 6th edition.

PATIENTS AND METHODS

The dataset used for this study is a combination of two large prospectively collected databases.

MEMORIAL SLOAN-KETTERING CANCER CENTER

Between July 1985 and December 2009, 2589 patients with an adenocarcinoma of the stomach or GEJ underwent a gastrectomy at the Memorial Sloan-Kettering Cancer Center (MSKCC) and were entered in a prospectively maintained database. Patients with tumors of the GEJ (Siewert I-III, N = 669), and patients with a noncurative (R1 or R2) resection, or M1 disease (N = 358) were excluded. As the dataset focused on curative resections, all patients with M1 disease were excluded, all of whom would have been stage IV in the 6th and 7th edition staging system. Three patients with T0N+ disease in their final pathology could not have a stage group assigned and were excluded, leaving 1559 patients for analysis. Most patients underwent a D2 lymph node dissection. Preoperative and postoperative therapy were administered according to the ongoing clinical trials and the standard of care at MSKCC during the study period. Adjuvant chemotherapy was given infrequently from 1985 to 1999. From 2000 to 2009, perioperative chemotherapy became more common for advanced stage tumors, whereas postoperative chemoradiation was also administered between 2000 and 2007. Follow-up was generally conducted according to published NCCN guidelines.[6] Survival data were updated when available until March 2010. This study was approved by the Institutional Review Board of MSKCC. This dataset was used in part to help guide changes to the AJCC 7th edition.

Table 2. Stage grouping according to the 6th and 7th edition AJCC staging system

6th edition AJCC staging system				7th edition AJCC staging system			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	**Tis**	**N0**	**M0**	**0**	**Tis**	**N0**	**M0**
IA	**T1**	**N0**	**M0**	**IA**	**T1**	**N0**	**M0**
IB	T1	N1	M0	IB	T1	N1	M0
	T2	**N0**	**M0**		**T2**	**N0**	**M0**
II	T1	N2	M0	IIA	T1	N2	M0
	T2	N1	M0		T2	N1	M0
	T3	N0	M0		T3	N0	M0
				IIB	T1	N3	M0
					T2	N2	M0
					T3	N1	M0
					T4a	N0	M0
IIIA	T2	N2	M0	IIIA	T2	N3	M0
	T3	N1	M0		T3	N2	M0
	T4	N0	M0		T4a	N1	M0
IIIB	T3	N2	M0	IIIB	T3	N3	M0
					T4a	N2	M0
					T4b	N1	M0
					T4b	N0	M0
				IIIC	T4a	N3	M0
					T4b	N3	M0
					T4b	N2	M0
IV	T4	N1-3	M0	IV	**Any T**	**Any N**	**M1**
	T1-3	N3	M0				
	Any T	**Any N**	**M1**				

T: Tumor classification, N: Nodal status, M: Metastases status, **Bold**: No changes in TNM and stage groups

DUTCH GASTRIC CANCER TRIAL

In the Dutch Gastric Cancer Trial (DGCT, 1989-1993), 1078 patients with adenocarcinoma of the stomach were randomized for D1 or D2 lymphadenectomy.[7-9] None of the patients had a tumor of the GEJ, while patients with metastatic disease (N = 367), and patients who underwent a non-curative resection (N = 74) were excluded, leaving 637 patients who underwent an R0 resection for this study. No adjuvant therapy was given to these patients in the curative setting. Follow-up was conducted every 6 months. Recurrent disease was generally confirmed with radiology, endoscopy, and/or histology. Survival data were updated when available until November 2007.

STAGING

Since the UICC and AJCC use the same staging definitions, for purposes of clarity the UICC/AJCC staging system is referred to as AJCC staging system. Tumor, nodal, and metastasis stage and stage grouping are all based on final postoperative pathology. All staging parameters (T, N, M) and stage groupings of the 6th and 7th edition staging system were calculated based on depth of invasion through the gastric wall, the number of positive lymph nodes and the presence or absence of distant metastases. No patients were excluded due to incomplete staging data.

STATISTICAL ANALYSIS

Survival probabilities were estimated with the Kaplan-Meier method, differences in survival curves were assessed using the log-rank test. The endpoint in this study was disease-specific survival (DSS). DSS was recorded from the date of surgery until the date of death of disease, whereas death from other causes and alive at last date of follow-up were recorded as censored events.

The concordance index between survival and stage for the two staging systems was calculated using a methodology previously described.[10] Concordance for a staging system can range from 0% to 100%, with 100% representing absolute concordance, 50% indicating no association (no better than flipping a coin) and 0% perfect discordance. The concordance index for a staging system was calculated by analyzing all possible pairs of two patients in the dataset. A pair of two patients is concordant if the patient with the higher stage has the shorter survival. Concordant pairs are assigned a value of 1, discordant pairs are assigned a value of 0. The concordance of the staging system is the sum of the values of all the individual pairs divided by the total number of pairs in the dataset. For pairs where the shorter survival time was censored, the stage-specific Kaplan-Meier estimate of survival was used. Pairs in which both patients were in the same stage group were assigned a value of 0.5. Therefore, the maximum concordance of the staging system could never be 100%. The maximum potential concordance in our dataset for the 6th edition was 0.818 and for the 7th edition 0.853. Confidence intervals and *P*-values for the difference in concordance indices of the two staging systems were calculated using bootstrap resampling.

To validate the results provided by concordance analysis, the Brier score was used to evaluate the expected error of the predictions in both staging systems. For every patient, the Brier score measures the difference between the survival probability predicted by the staging system, and the observed survival. Kaplan-Meier estimates were used for censored observations. The average squared deviation for all patients gives the Brier score, in which a lower score represents a better predictive accuracy.

RESULTS

PATIENTS

All 2196 patients in this analysis underwent a radical (R0) resection for an adenocarcinoma of the stomach between July 1985 and December 2009, either at MSKCC (N = 1559) or in one of the hospitals participating in the DGCT (N = 637). Patient characteristics are summarized in Table 3. Median follow-up was 98 months.

TNM STAGING

Figure 2 depicts the distribution of T-classification and N-classification of the 6th edition and 7th edition staging system for all patients (N = 2196). The redefined N1, N2, and N3 classification were more evenly distributed. Among 2196 patients, 674 (31%) were

Table 3. Patient characteristics

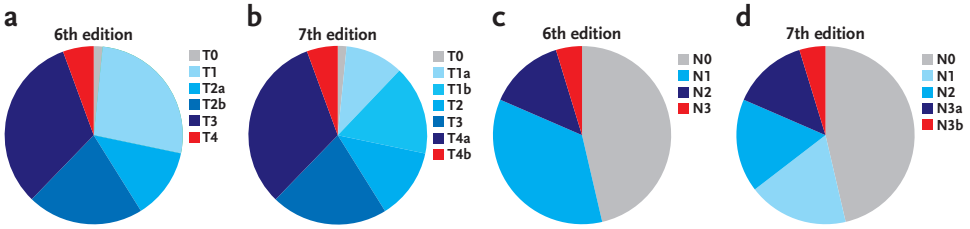
	Total (N = 2196)		MSKCC (N = 1559)		DGCT (N = 637)	
	N	%	N	%	N	%
Sex						
male	1307	*60*	943	*61*	364	*57*
female	889	*40*	616	*39*	273	*43*
Age						
median (range)	67	(22-96)	67	(22-96)	66	(31-84)
Location						
proximal	630	*29*	525	*34*	105	*17*
middle	630	*29*	430	*28*	200	*31*
distal	899	*41*	572	*37*	327	*51*
diffuse	37	*2*	32	*2*	5	*1*
Invasion depth						
no tumor	35	*2*	31	*2*	4	*13*
mucosa	231	*11*	150	*10*	81	*16*
submucosa	355	*16*	255	*16*	100	*15*
muscularis propria	282	*13*	189	*12*	93	*22*
subserosa	464	*21*	322	*21*	142	*20*
serosa	706	*32*	576	*37*	130	*14*
adjacent organs	123	*6*	36	*2*	87	*1*
Number of evaluated nodes						
median (range)	21	(0-106)	21	(0-84)	22	(1-106)
Patients with at least 15 nodes evaluated	1671	*76*	1213	*78*	458	*72*
Number of positive nodes						
median (range)	1	(0-63)	1	(0-63)	1	(0-28)
Type of surgery						
total gastrectomy	562	*26*	359	*23*	203	*32*
proximal gastrectomy	106	*5*	106	*7*	0	
distal gastrectomy	1222	*56*	788	*51*	434	*68*
esophagogastrectomy	291	*13*	291	*19*	0	
wedge/sleeve resection	14	*1*	14	*1*	0	
unknown	1	*0.1*	1	*0.1*	0	
Adjuvant therapy						
preoperative chemotherapy	245	*11*	245	*16*	0	
postoperative chemotherapy	251	*11*	251	*16*	0	
postoperative radiotherapy	80	*4*	80	*5*	0	

Table 4. Distribution of patients according to the 6th and 7th edition AJCC staging system

		AJCC 7th edition								
		0	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IIIC**	**Total**
AJCC 6th edition	**0**	**35**								35
	IA		**476**							476
	IB			**220**	210					430
	II				61	307	99			467
	IIIA						**163**	258		421
	IIIB								181	181
	IV					1	1	44	140	186
	Total	35	476	220	271	308	263	302	321	2196

Bold: patients who stay in the same stage group

Figure 2. Distribution of all patients over the T classification in the 6th edition (a) and the 7th edition (b) AJCC staging system, and N classification in the 6th edition (c) and the 7th edition (d) AJCC staging system



assigned a higher N-classification in the AJCC 7th edition. In the 7th edition staging system, the N3 category is divided into N3a (7-15 positive nodes) and N3b (16 or more positive nodes). This recognized the unique independent prognostic significance of an increasing number of positive nodes, even at the high end.

STAGE GROUPING

Differences in stage distribution between the two systems are shown in Table 4. For stage IB to IV, both T, N and M, as well as stage group definitions were altered leading to a change in stage group for 1302 of 2196 patients (59%). In total, 748 patients (34%) moved to a higher stage group, and 186 patients (9%) moved to a lower stage group. 368 patients (17%) with a stage II tumor in the 6th edition staging system were distributed between stage IIA and IIB in the 7th edition staging system. Of note, stage grouping did not make use of the N3a/N3b classification.

DISCRIMINATION BETWEEN STAGE GROUPS

Five-year survival estimates for both staging systems are shown in Figure 3 and Table 5. In the 6th edition staging system (Figure 3a), Kaplan-Meier survival estimates significantly differed for stage IA-IB, IB-II, II-IIIA and IIIA-IIIB, but not for stage 0-IA ($P = 0.64$) and IIIB-IV ($P = 0.60$). In the new staging system, stage group 0 and IA remain unchanged. Differences between the 7th edition stage groups were significant for stage IA-IB, IIA-IIB, IIB-IIIA and IIIB-IIIC but not for stage 0-IA ($P = 0.64$), IB-IIA ($P = 0.09$) and stage IIIA-IIIB ($P = 0.15$, Figure 3b). Figure 4a shows patients from the 6th edition stage II, which is subdivided into stage IIA, IIB and IIIA in the 7th edition staging system. Differences between the curves were all significant. In Figure 4b the subdivision of 6th edition stage IIIA into 7th edition stage IIIA and IIIB is shown; no significant differences between the two new stage groups were detected ($P = 0.26$). Overall, in the AJCC 6th edition, two out of six consecutive steps between stage groups were not significantly discriminant, while in the AJCC 7th edition, three out of seven consecutive steps were not significantly discriminant, indicating that the discriminant value between stage groups has decreased between the 6th and 7th edition staging system.

Figure 3. Disease-specific survival estimates according to the 6th edition (a) and 7th edition (b) AJCC staging system (N = 2196)

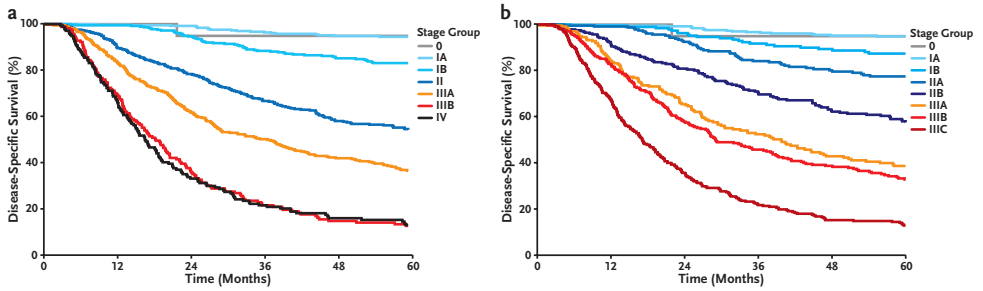
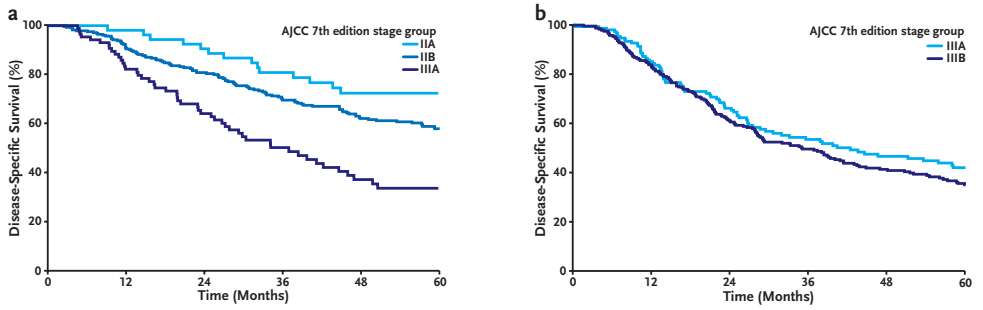


Figure 4. (a) AJCC 6th edition Stage II patients (N = 467) are distributed between stages IIA, IIB, and IIIA in the 7th edition staging system. (b) AJCC 6th edition Stage IIIA patients (N = 421) are distributed between stages IIIA and IIIB in the 7th edition staging system



PREDICTIVE ACCURACY

The concordance index of T staging did not change significantly from the 6th to the 7th edition ($P = 0.36$) (Table 6). The concordance index of N staging showed an increase from 0.659 to 0.665 ($P = 0.03$). Despite the change in definition for almost every stage group and the increased number of stage groups, the concordance estimate for the 7th edition was 0.697, which was significantly inferior to that of the 6th edition staging system (0.711, $P < 0.01$). Brier score for T, N and overall stage groupings showed no significant improvement from the 6th to the 7th edition.

DISCUSSION

The current study describes the impact of the changes made in the 7th edition of the TNM-classification for stomach cancer by comparing stage-specific survival and predictive accuracy of the 6th and 7th edition staging system in a combined dataset with over 2000 patients who underwent an R0 resection for gastric cancer.

Three earlier single institutional Asian studies have compared the 6th with the 7th TNM-classification for gastric cancer.[11-14] The first study analyzed 9998 patients treated at a Korean university hospital and found a more detailed classification of prognosis in the 7th

edition staging system, accompanied with increased homogeneity within stage groups.[11] A Chinese study found better prognostic stratification in the 7th edition staging system.[12] Another Korean study evaluated nodal classification in 295 patients, and found that in multivariable analysis, N-classification was an independent prognostic factor for survival in the 7th edition, but not in the 6th edition staging system.[14]

One strength of the current study is the use of data from multiple institutions, thereby reducing the risk of unique outcome due to single institution bias. However, both series are Western, and no Asian dataset was used. Another advantage of the current study is the high quality of the data: all patients underwent an R0 resection, and disease-specific survival was used as the outcome measure. In the three previously published studies, overall survival instead of disease-specific survival was used, and in one study 14.5% of the patients underwent an R1 resection.[12]

With the redefinition of nodal classification, the distribution of patients among the N1, N2 and N3 categories is more equal (Figure 2b), while many patients are upstaged under the new staging system. A point of discussion on nodal staging in gastric cancer is that in the Western world, lymph node yield is generally low,[15] certainly in comparison with Asian centers.[16] This leads to the potential shift of patients into a more advanced nodal classification simply by investigating more lymph nodes.[17] Several groups have suggested the use of lymph node ratio (metastatic/total lymph nodes) instead of nodal status because of its higher prognostic accuracy and the elimination of the effect of this shift.[18-20] In these studies however, cut-off values for lymph node ratio intervals are often based on the used dataset. This introduces an advantage for lymph node ratio which has a perfect fit on the used dataset, while TNM nodal classification is part of an established system. However, decreasing the threshold for N2 and N3 categories in the 7th edition staging system considerably reduces the shifting effect. A minimum number of 15 nodes, however, remains the recommended threshold for adequate nodal staging.

A limitation of the stage groupings of the 7th edition staging system is that N3a and N3b categories were combined as N3, thereby not recognizing the prognostic significance of having 7-15 positive nodes versus more than 16 positive nodes in overall stage grouping. As the introduction of N3a and N3b as separate categories in overall stage grouping will increase complexity of the staging system, while it is unknown if it will improve overall predictive accuracy, this issue needs to be further addressed in future staging systems.

There are several benchmarks for comparing the performance of two staging systems. First, there should be homogeneity within stage groups; patients within the same stage group should have small differences in survival. Secondly, there should be discrimination between stage groups; patients in different stage groups should have larger differences in survival. Third, a staging system should have good predictive accuracy; patients with a higher stage should have a worse survival. And fourth, a staging system should be as simple and intuitive as possible in clinical practice, as increased complexity impedes clinical utility.

Table 5. Five-year and median disease-specific survival (DSS) estimates for stage groupings of the 6th and 7th edition staging system (N = 2196)

	AJCC 6th edition		AJCC 7th edition	
Stage group	**5-year DSS (%)**	**median DSS (months)**	**5-year DSS (%)**	**median DSS (months)**
0	95.0	not reached	95.0	not reached
IA	94.6	not reached	94.9	not reached
IB	83.4	not reached	87.5	not reached
II	55.3	85		
IIA			77.5	278
IIB			57.6	119
IIIA	37.5	38	38.8	40
IIIB	14.0	19	32.9	29
IIIC			13.0	17
IV	14.4	17		

Table 6. Predictive accuracy of the 6th and 7th edition AJCC staging system

	AJCC edition	T-classification	N-classification	Stage group
Concordance	6th	0.666 ($P = 0.36$)	0.659 ($P = 0.03$)	0.711 ($P < 0.01$)
	7th	0.667	0.665	0.697
Brier score	6th	0.165	0.165	0.158
	7th	0.163	0.164	0.156

Concordance: higher is better, Brier score: lower is better

HOMOGENEITY WITHIN STAGE GROUPS

Establishing homogeneity within stage groups requires grouping of TNM-combinations that have similar survival estimates (Table 2). For homogeneity testing, results are highly dependent on the size of the dataset. Ahn et al. showed improved homogeneity of two homogeneous stage groups in the 7th edition compared to one homogeneous stage group in the 6th edition, using a dataset of nearly 10,000 patients.[11] In the current study, numbers are smaller and therefore significant homogeneity within stage groups is hard to detect (results not shown).

DISCRIMINATION BETWEEN STAGE GROUPS

Heterogeneity between stage groups can be assessed by comparing stage-specific survival estimates for significant differences. Whether differences between stage groups are significant is highly dependent on the size of the dataset. Small differences in survival estimates between stage groups are more likely to be statistically significant in a large dataset. In the current study, stage-specific heterogeneity has decreased in the 7th edition when compared to the 6th edition. Although AJCC 6th edition stage II contained a highly heterogeneous population (Figure 4a), and distributing these patients between stages IIA, IIB, and IIIA in the 7th edition has created three groups with a significantly different prognosis, the distribution of 6th edition stage IIIA patients into AJCC 7th edition stages IIIA and IIIB has created two stage groups with almost identical stage-specific survival (Figure 4b). Wang et al. showed decreased heterogeneity between stage groups in the 7th edition as well.[12]

PROGNOSTIC ACCURACY FOR INDIVIDUAL PATIENTS

Performance of a staging system can also be assessed on the individual patient level, by comparing survival of patients with different stages. Several ways of comparing staging systems on an individual patient level have been proposed, but there is no standard method.[21] Commonly-used methods include explained variation (or Brier score), area under the receiver operating characteristic curve, the concordance index, and a summary measure of separation (SEP). We decided to use the concordance index and Brier score to measure the prognostic accuracy of the staging systems, since they analyze different, complementary measures. Concordance index is a measure of whether ranking of patients by staging is consistent with the ranking of their outcome. Its advantages include interpretation (since it is a probability), robustness (since it is based on ranks, it is not sensitive to small changes in the data) and availability of appropriate statistical methods for estimation. It also incorporates a built-in penalty for staging systems with a higher number of categories, so that with equally performing staging systems, the system with more categories will have a lower concordance probability. It does not penalize possible shifts (miscalibrations) between predicted and observed survival. Therefore, we also used Brier score, since it looks at the actual difference (in months) between predicted and observed survival, taking possible shifts into account.

In the current dataset, concordance analysis showed no difference for T category, an improvement for N category, and a decline for stage grouping. Brier scores consistently showed no significant improvement from the 6th to the 7th edition. Therefore, it can be concluded that for individual patient outcome, no improvements were detected from the 6th to the 7th edition staging system.

Only one of the previously published studies compared the two staging systems on an individual patient level. It found increased predictive accuracy for the 7th edition staging system.[12] A disadvantage of the method employed in that study is that the metric used for comparison, the Akaike Information Criterion, measures how well the staging system fits to the used dataset, without assessing the actual prognostic accuracy.

COMPLEXITY OF THE STAGING SYSTEM

With an increasing number of stage group categories for the 7th edition of the staging system, it has become more complex. Increasing the number of categories of the staging system is not unique to gastric cancer.[4] With the increasing availability of pathologic and molecular data, there is a trend towards incorporating more and more information into newer staging systems. Although these new categories might better reflect the natural history and prognosis of these diseases, there is a limit to the improvement of prognostic accuracy achievable with a categorical anatomic-based staging system like the TNM-classification.[22,23] At the same time, the goal of creating an intuitive, easy to use staging system disappears, and in daily clinical practice, cancer staging consists of using complex tables, if it is used at all.

Meanwhile, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[24,25] and has been validated in several international patient cohorts.[26-28] The question is if the TNM-classification should aspire to the same goal of highly accurate individual patient prognostication as these nomograms. Prognostication is only one of the five goals of the TNM-classification, and all other goals are directed towards a simple intuitive international language: to aid the clinician in planning and evaluating treatment, to facilitate the exchange of information, and to contribute to research.[1]

In summary, the 7th edition of the AJCC staging system for gastric cancer has resulted in improved predictive accuracy for the N-classification but decreased heterogeneity among stage groups. The increased complexity of the 7th edition staging system is not accompanied by an improvement in prognostic accuracy of stage grouping. Staging represents a compromise in accounting for the most reproducible and prognostically relevant factors to aim at a simple, intuitive, useful, common language to describe the natural history of a tumor. It should not be confused with more complex multivariable prognostication models, which may be useful in defining groups of patients at homogenous risk of recurrence, regardless of anatomic TNM characteristics.

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