Comparison of the sixth, seventh, and eighth editions of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system for gastric cancer
A single institution experience

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Abstract

In 2018, the eighth edition of the American Joint Committee on Cancer Tumor-Node-Metastasis classification and staging system was implemented. Few reports were made comparing the performance of different editions of the American Joint Committee on Cancer (AJCC) system. Therefore, this study aimed to examine the prognostic predictability from the sixth to the eighth editions of the AJCC staging system for gastric cancer.

A total of 414 patients with gastric cancer who underwent surgery at Changhua Christian Hospital from January 2007 to December 2017 were enrolled in the study. To identify the prognostic factors for gastric cancer death, univariate and multivariate analyses were performed. The homogeneity and discrimination abilities of the sixth to eighth editions of the staging system were compared using the likelihood ratio chi-square test, linear trend chi-square test, and Akaike information criterion.

The sixth edition of the staging system had the lowest Akaike information criterion value, suggesting a better prognostic stratification than other editions. From the result of the likelihood ratio chi-square test, the T and N staging systems of the seventh and eighth editions had better homogeneity and discriminatory ability than the sixth edition. The eighth edition had better prognostic performance in patients at stage III compared with the seventh edition.

The AJCC seventh and eighth editions had improved prognostic predictability of the T and N factors compared with the sixth edition. However, the overall staging performance of the eighth edition is not superior compared to the sixth edition. Further studies with larger sample size should be conducted to compare the performance of different editions of the AJCC staging system for different ethnic populations.

Abbreviations: AIC = Akaike information criterion, AJCC = American Joint Committee on Cancer, AUC = area under the curve.

Keywords: AJCC TNM, Akaike information criterion, gastric cancer, likelihood ratio chi-square, linear trend chi-square

1. Introduction

The International Agency for Research on Cancer published the Cancer Incidence in Five Continents series (CI5-XI, mainly comprising data from 2008 to 2012) and concluded that gastric cancer incidence rates displayed marked variations in risk across the registry populations worldwide.[1] A high lifetime risk of gastric cancer with incidence of 5% or more was found in Japan, Korea, and India. An intermediate risk (around 3%) was reported in Eastern Europe, South America, and certain regions in Asia (parts of China and Golestan Province in Iran), and low risk was seen in other countries.[1] The American Joint Committee on Cancer Tumor-Node-Metastasis classification and staging

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system, which accurately describes clinical decision making and prognostic prediction, has become accepted worldwide as the most important reference for patients with gastric cancer. Accompanied by the increased knowledge of gastric cancer biological behaviors and treatment improvements, periodic reasonable revisions of the tumor-node-metastasis staging system have been made by the Union for International Cancer Control and American Joint Committee on Cancer (AJCC).[2,3] The AJCC sixth and seventh editions of the staging system were based mainly on data from the United States,[4] and the eighth edition included more than 25,000 patients with gastric adenocarcinoma from 15 countries to make the classification more applicable worldwide.[5] However, previous studies did not demonstrate continuous improvement in prognostic stratification when comparing the sixth and seventh editions[3,6,7] or the seventh and eighth editions.[3,8,9]

No previous report has been comparing the performance from the sixth to eighth editions of the AJCC staging system for gastric cancer. In this study, we aimed to evaluate the application of the eighth edition staging system based on data from a single institution for 414 Taiwanese patients with gastric cancer. Thus, we tried to find the distinctions among the sixth to eighth editions of the AJCC staging system and its prognostic implications.

2. Materials and methods

2.1. Patients

Patient data were obtained from the cancer registry database at Changhua Christian Hospital, which was at the center of Taiwan. Data collection began in January 2007 and continued until December 2012. It was critically reviewed and approved by a committee consisting of oncologists, radiotherapists, nurse specialists, surgeons, and pathologists. This study was approved by the Institutional Review Board of the Changhua Christian Hospital (IRB number: 170907). Following are exclusion criteria for patients with gastric cancer who underwent surgical intervention in the Department of Surgery at the Changhua Christian Hospital (by the International Classification of Diseases, third edition, site C161–C169). A total of 1325 patients with gastric cancer were identified. A total of 911 (68.75%) patients were excluded because of primary tumor location in the heart (80 cases); indications for endoscopic mucosal resection or endoscopic submucosal dissection (10 cases); not eligible for the International Classification of Diseases for Oncology codes for adenocarcinoma (191 cases); received pre-operative chemotherapy (12 cases); surgery not performed (433 cases); surgery performed outside a hospital facility (94 cases); in situ only (2 cases); missing or incomplete data regarding the T or N or stage (12 cases); and diagnoses of multiple cancers (77 cases).

Finally, a total of 414 patients were enrolled in the study. Baseline data included demographic characteristics (e.g., sex and age) and tumor characteristics (e.g., grade, tumor depth of invasion, regional lymph nodes, pathologic stage, and sixth to eighth edition staging). All patients were followed until February 15, 2018. Postoperative follow-up was for at least 3 to 6 months for physical and laboratory examinations and annually thereafter for 10 years after surgery or until the patient died.

2.2. Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences statistical software (version 22.0; SPSS Inc.,

Chicago, IL). P value of <.05 was regarded as statistically significant. The Kaplan–Meier method was used to analyze time-dependent survival probabilities, whereas the log rank test was used for statistical comparisons of survival curves. Overall survival was calculated from the day of diagnosis to the date of death or the last follow-up. Date of death was obtained from other causes recorded in the databases of the tumor cancer registry as censored.

Cox proportional hazards model was used to evaluate the risk of mortality associated with the prognostic value selected in the multivariate association of clinical parameters. Prognostic homogeneity was tested by the likelihood ratio chi-square test, and the linear trend chi-square analyses were used to assess the discrimination ability of different editions of the staging system in patients with gastric cancer. The higher the likelihood ratio chi-square value, the better the homogeneity of the staging scheme. A higher linear trend chi-square likelihood ratio indicated better discriminatory ability. The Akaike information criterion (AIC) was used to compare the performance of 3 editions of the staging system. A smaller AIC value indicated a more optimistic prognostic stratification. The receiver operating characteristic curve test and area under the curve (AUC) analyses were used to assess the utility of the predictive value of the different classifications in patients with gastric cancer.

3. Results

3.1. Patient characteristics

The process of data extraction from the database of cancer registry at Changhua Christian Hospital is shown in Figure 1. Characteristics of 414 patients identified as having undergone surgical resection for gastric cancer and meeting the requirements mentioned above are provided in Table 1. This study included 257 (62.08%) males and 157 (37.92%) females. Mean patient age at diagnosis was 66.27 ± 12.47 years, with a range of 24 to 96 years. According to the sixth edition of the staging system, the tumor depth of invasion was T1 in 80 (19.32%) patients, T2 in 196 (47.34%), T3 in 115 (27.78%), and T4 in 23 (5.56%) patients. According to the seventh and eighth editions of the staging system, the tumor depth of invasion was T1 in 80 (19.32%), T2 in 57 (13.77%), T3 in 139 (33.57%), and T4 in 138 (33.33%) patients. According to the sixth edition of the staging system, the number of metastatic regional lymph nodes was N0 in 138 (33.33%), N1 in 138 (33.33%), N2 in 68 (16.43%), and N3 in 70 (16.91%) patients. According to the seventh and eighth editions of the staging system, the number of metastatic regional lymph nodes was N0 in 138 (33.33%), N1 in 62 (17.98%), N2 in 76 (18.36%), and N3 in 138 (33.33%) patients.

3.2. Stage distribution and migration

Using staging from the sixth, seventh, and eighth editions of the AJCC system, patient stage migration is illustrated in Figure 2. A total 32 patients in stage IB in the sixth edition of the staging system were reclassified into stage IIA in the seventh edition; 19, 43, and 42 patients in stage II in the sixth edition of the staging system were reclassified into stages IIA, IIB, and IIIA in the seventh edition, respectively; 40 and 24 patients in stage IIIA and IIIB in the sixth edition of the staging system were reclassified into stage IIIB and IIIC in the seventh edition, respectively; 1, 3, 14,
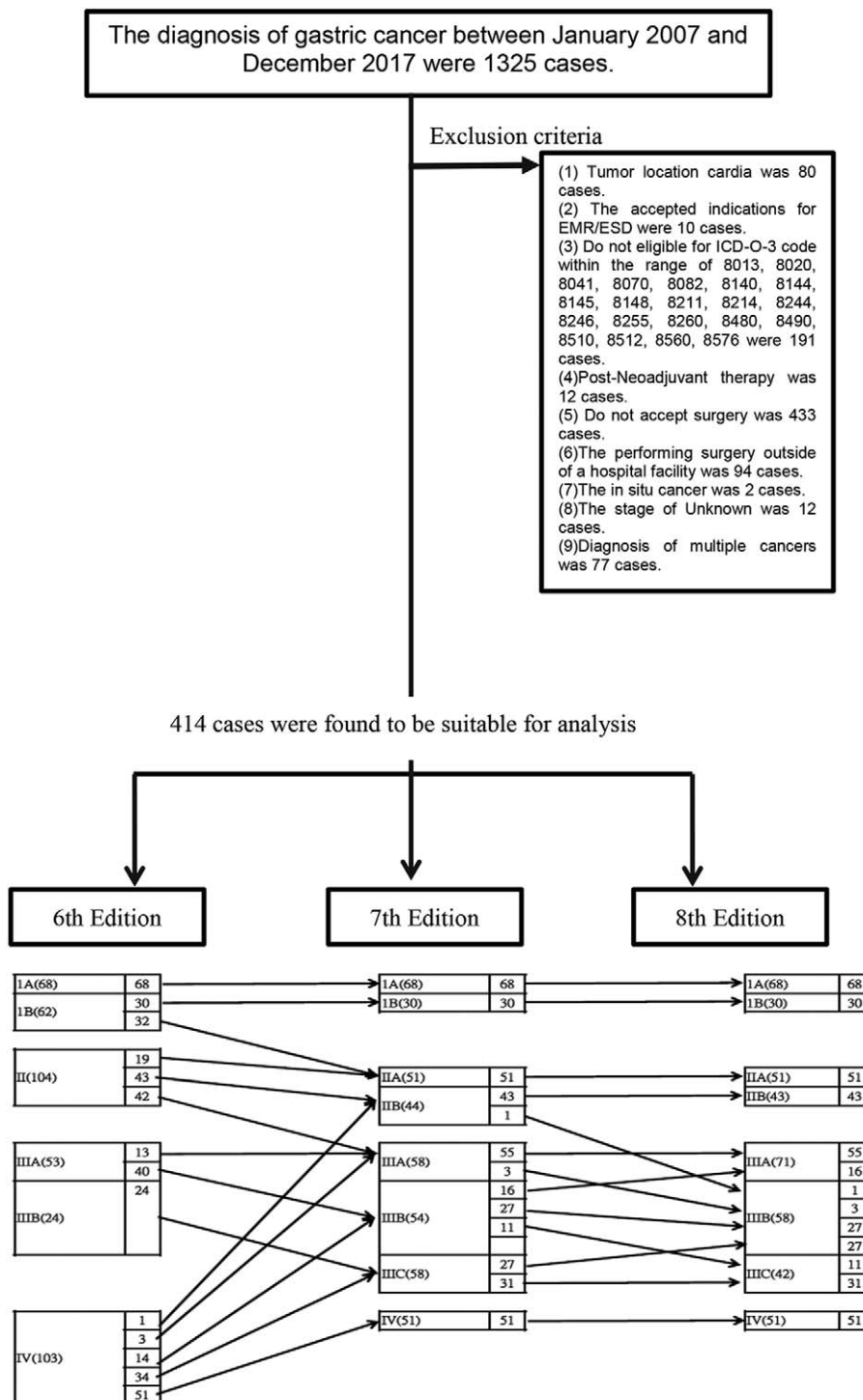
Figure 1. Patient data collection flowchart.

and 34 patients in stage IV in the sixth edition were reclassified into stages IIB, IIIA, IIIB, and IIIC in the seventh edition, respectively; 1 patient in stage IIB in the seventh edition was reclassified into stage IIIB in the eighth edition; 3 patients in stage IIIA in the seventh edition were reclassified into stage IIIB in the eighth edition; 16 patients in stage IIIB in the seventh edition were reclassified into stage IIIA in the eighth edition; 11 patients in stage IIIB in the seventh edition were reclassified into stage IIIC in the eighth edition; and 27 patients in stage IIIC in the seventh

edition were reclassified into stage IIIB in the eighth edition of the AJCC staging system.

3.3. Univariate and multivariable analyses of overall survival by different editions of the AJCC staging system

In univariate analysis, age, sex, primary site, grade, sixth edition T, sixth edition N, seventh and eighth edition T, and seventh and eighth edition N were found to be statistically associated with the

Table 1

Demographic characteristics of study population and univariate analysis of pathologic factors for 5 year survival rate.

variables	N (%)	Five year survival rate (%)	Mean survival rate (95% confidence interval)	P value
Age (range)	66.27 ± 12.47 (24–96)	47.70	5.46 (4.99–5.94)	.001
Sex				.538
Man	257 (62.08%)	46.79	5.16 (4.62–5.71)	
Female	157 (37.92%)	49.43	5.76 (4.97–6.54)	
Primary site				.001
C161: Fundus of stomach	7 (1.69%)	NA	2.40 (1.12–3.69)	
C162: Body of stomach	95 (22.95%)	51.30	6.02 (5.00–7.04)	
C163: Gastric antrum	231 (55.80%)	50.86	5.65 (5.03–6.27)	
C164: Pylorus	32 (7.73%)	46.28	4.17 (3.17–5.18)	
C165: Lesser curvature of stomach, NOS	17 (4.11%)	71.50	6.54 (4.74–8.33)	
C166: Greater curvature of stomach, NOS	2 (0.48%)	0.00	0.70 (0.00–1.72)	
C168: Overlapping lesion of stomach	30 (7.25%)	16.67	2.55 (1.33–3.76)	
Grade				.578
G1: Well/G2: Moderately	114 (27.54%)	45.59	5.04 (4.21–5.84)	
G3: Poorly/G4: Undifferentiated	300 (72.46%)	48.51	5.54 (4.98–6.09)	
AJCC 6th T (Tumor depth of invasion)				.001
1	80 (19.32%)	85.77	8.97 (8.13–9.81)	
2	196 (47.34%)	51.96	5.62 (4.99–6.25)	
3	115 (27.78%)	21.54	3.24 (2.55–3.94)	
4	23 (5.56%)	13.14	2.08 (0.91–3.25)	
AJCC 6th N (Regional lymph nodes)				.001
0	138 (33.33%)	77.16	8.20 (7.48–8.92)	
1	138 (33.33%)	47.43	5.11 (4.43–5.79)	
2	68 (16.43%)	25.23	3.30 (2.43–4.17)	
3	70 (16.91%)	11.15	2.23 (1.61–2.85)	
AJCC 7th, 8th T (Tumor depth of invasion)				.001
1	80 (19.32%)	85.77	8.97 (8.13–9.81)	
2	57 (13.77%)	64.80	6.73 (5.59–7.87)	
3	139 (33.57%)	46.66	5.04 (4.34–5.73)	
4	138 (33.33%)	20.21	3.06 (2.44–3.68)	
AJCC 7th, 8th N (Regional lymph nodes)				.001
0	138 (33.33%)	77.16	8.20 (7.48–8.92)	
1	62 (17.98%)	46.52	4.84 (3.93–5.75)	
2	76 (18.36%)	48.03	5.13 (4.25–6.00)	
3	138 (33.33%)	18.30	2.81 (2.25–3.38)	

AJCC = American Joint Committee on Cancer.

overall survival, whereas sex and grade were not significant (Table 1). In multivariate analysis for age, the sixth edition T and sixth edition N were significantly correlated with overall survival ($P < .001$). In multivariate analysis for age, the seventh and eighth edition T and seventh and eighth edition N were significantly correlated with overall survival ($P < .001$) (Table 2). Survival curves according to the sixth, seventh, and eighth editions of the AJCC system are illustrated in Figure 3. The sixth, seventh, and eighth editions of the AJCC system were further studied by receiver operating characteristic analysis to assess the predictive value of pT, pN, and stage classification on the overall survival. The seventh and eighth edition pT and pN classifications had a higher AUC than the sixth edition. The sixth and eighth edition stage classification had a higher AUC than the seventh edition (Fig. 4).

3.4. Prognostic performance of different editions of the AJCC staging system

The likelihood ratio chi-square test for T and N of the seventh and eighth editions of the staging system was 69.452 and 67.925, and T and N of the sixth edition was 67.223 and 66.795, respectively. Therefore, the T and N of the seventh and eighth

editions had better homogeneity and discriminatory ability than the sixth edition (Table 3).

The linear trend chi-square value for the sixth edition of the staging system was 94.051, seventh edition was 87.783, and eighth edition was 91.707, suggesting that the sixth edition of the staging system had better discriminatory ability than the seventh and eighth editions. The likelihood ratio chi-square value for the sixth edition of the staging system was 104.357, seventh was 102.139, and eighth edition was 107.011, suggesting that the eighth edition of the staging system had better homogeneity than the sixth and seventh editions (Table 3).

The sixth edition of the staging system had a lower AIC value, which meant a higher prognostic stratification than other editions, because the main modifications of the seventh and eighth editions were related to stage 3 gastric cancer. The T2N3bM0 tumors were up-staged from stage IIIA to IIIB, and T3N3bM0 tumors were up-staged from IIIB to IIIC. The T4bN0M0 and T4aN2M0 tumors were down-staged from IIIB to IIIA. Finally, T4aN3aM0 and T4bN2M0 tumors were down-staged from IIIC to IIIB. When comparing the performance of the seventh and eighth editions for patients at stage 3 in the current study, the AUC, linear trend chi-square value, likelihood ratio chi-square value, and AIC value were 0.58, 3.57, 3.64, and 19.30
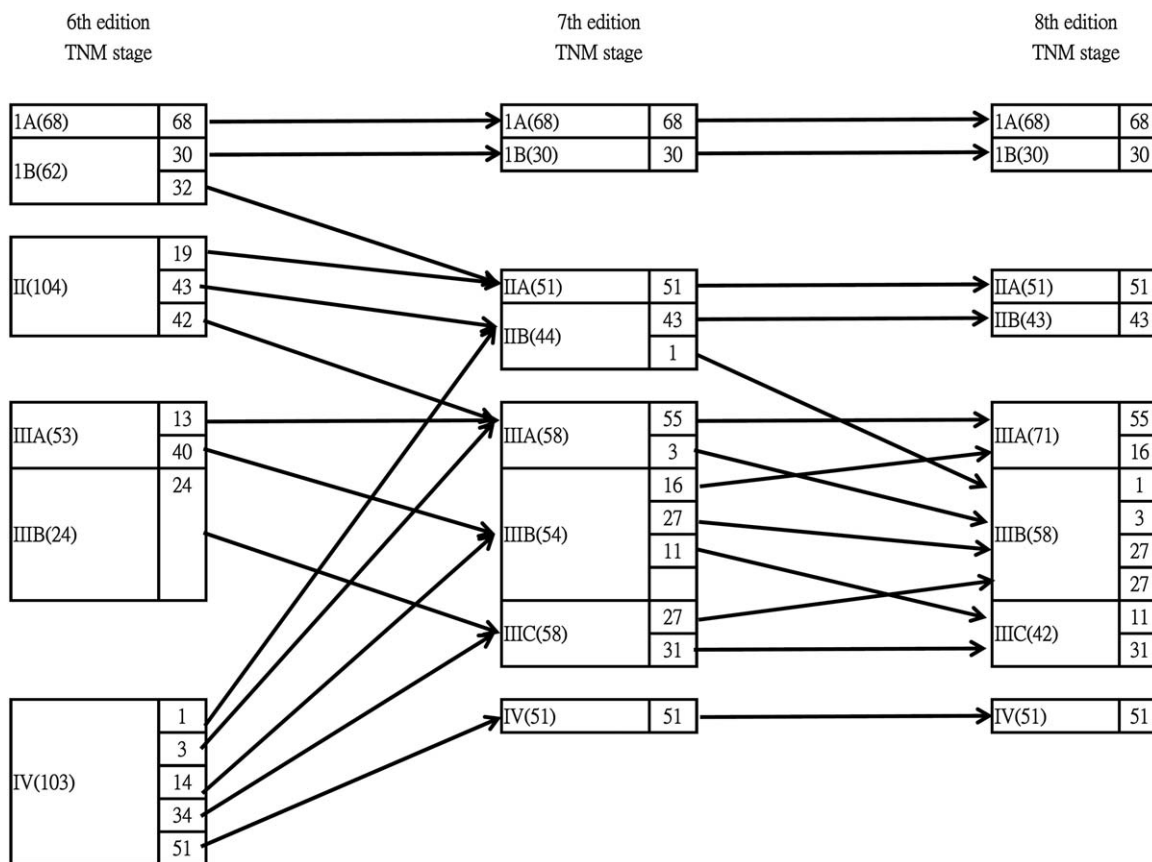
Figure 2. Patient stage classification according to the AJCC sixth, seventh, and eighth editions. AJCC = American Joint Committee on Cancer.


Table 2

**Multivariate analysis with Cox proportional hazard model for prognostic factors.**

	Univariate			Multivariate 6th edition			Multivariate 7th, 8th editions		
Variables	Hazard ratios	(95% C.I.)	P value	Hazard ratios	(95% C.I.)	P value	Hazard ratios	(95% C.I.)	P value
Age (range)	1.037	1.023–1.050	.001	1.036	1.023–1.051	0.001	1.037	1.023–1.051	.001
Sex									
Man	1								
Female	0.911	0.677–1.225	.538						
Grade									
G1: Well/G2: Moderately	1								
G3: Poorly/G4: Undifferentiated	0.915	0.669–1.252	.579						
AJCC 6th T (Tumor depth of invasion)				1.721	1.406–2.106	0.001			
1	1								
2	4.236	2.200–8.155	.001						
3	9.096	4.683–17.666	.001						
4	13.913	6.392–30.286	.001						
AJCC 6th N (Regional lymph nodes)				1.634	1.413–1.891	0.001			
0	1								
1	2.878	1.858–4.459	.001						
2	5.283	3.276–8.520	.001						
3	7.786	4.882–12.417	.001						
AJCC 7th, 8th T (Tumor depth of invasion)							1.602	1.325–1.936	.001
1	1								
2	2.955	1.383–6.317	.005						
3	4.858	2.498–9.449	.001						
4	9.783	5.075–18.860	.001						
AJCC 7th, 8th N (Regional lymph nodes)							1.478	1.278–1.710	.001
0	1								
1	2.864	1.687–4.862	.001						
2	2.875	1.781–4.639	.001						
3	6.375	4.165–9.758	.001						

AJCC = American Joint Committee on Cancer.
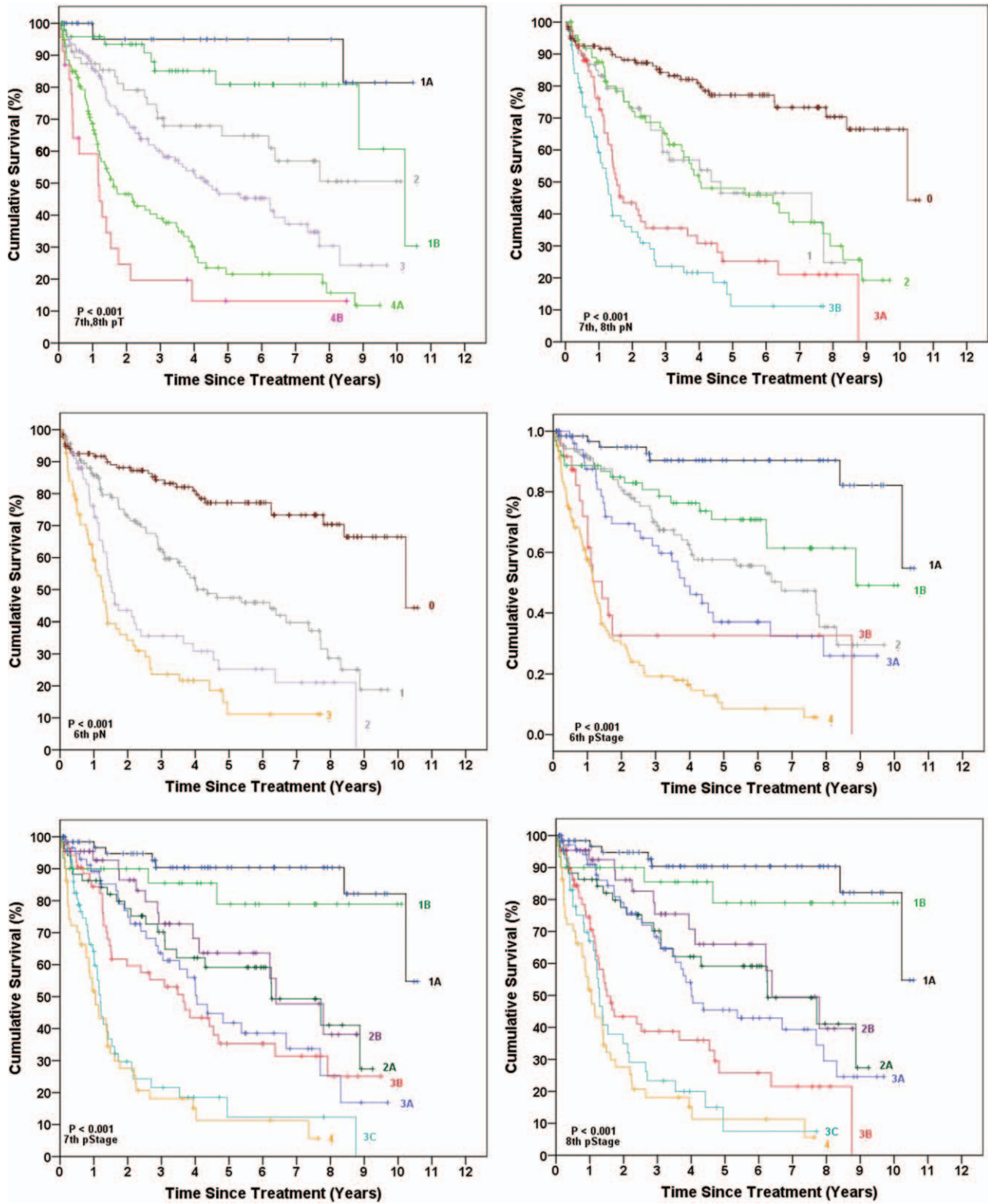
Figure 3. (A) Survival curve according to the AJCC sixth and seventh/eighth T stage. (3) Survival curve according to AJCC sixth and seventh/eighth N stage. (3) Survival curve according to AJCC sixth and seventh/eighth edition stages. AJCC = American Joint Committee on Cancer.
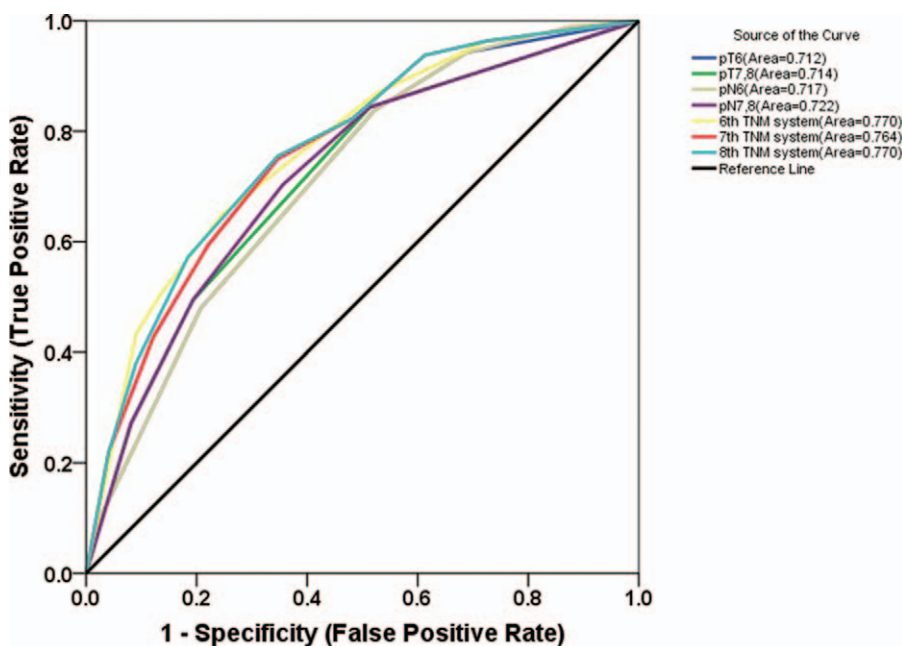
Figure 4. Predictive values of T, N, and Stage classification, AJCC TNM staging system sixth, seventh, and eighth editions. The predictive value of AJCC seventh and eighth T and N classification is better than the sixth. The predictive value of AJCC sixth and eighth stage classification is better than the seventh edition. AJCC TNM = American Joint Committee on Cancer Tumor-Node-Metastasis.

for the seventh edition and 0.61, 6.97, 7.19, and 19.11 for the eighth edition, respectively (Fig. 5). Thus, the eighth edition had better predictive performance in patients at stage 3 compared with the seventh edition.

4. Discussion

In this study, the sixth edition of the AJCC staging system was found to have a better overall prognostic stratification than the seventh and eighth editions. The sixth edition of the staging system has a higher linear trend chi-square value, indicating a better discriminatory ability. The eighth edition of the staging system has the highest likelihood ratio chi-square value, suggesting a better homogeneity of the staging scheme. In our series, the T and N classifications in the seventh and eighth editions have better homogeneity and better discriminatory ability than the sixth edition. Our study suggests the need of further modification of the 8th AJCC staging system for gastric cancer for better prognostic stratifications in the future.[10,11]

The American Joint Committee on Cancer Tumor-Node-Metastasis staging system is the global standard to guide clinical decision making and prognostic prediction that has evolved over time. The sixth edition was published in 2002, and the seventh edition in 2010. The major updates from the sixth to the seventh edition included changes in the T definition, i.e., sub-classification T1 into T1a and T1b, T4 into T4a and T4b, elimination of T2a, and T2b to T2; and changes in definitions of the N and M classifications. Stage migration occurs from the sixth to the seventh edition,[12] i.e. T4N3M0 in the sixth edition migrates from stage IV to stage IIIC in the seventh edition. The eighth edition was proposed in 2017 with a major change separating N3 into N3a and N3b in different final stage, especially stage III subgroups for prognostic improvement.[5] As gastric cancer has geographic differences in incidence and mortality,[13] application of the sixth or seventh editions data (mainly from the United States [US]) and eighth edition data (mainly from the US, Japan, and Korea) may be valid for a US population,[14] but not equally applicable to other ethnic groups such as in Egypt,[15] China,[16]

Table 3

Comparison of the performance of the 6th, 7th, and 8th editions of the AJCC TNM staging system for gastric cancer.

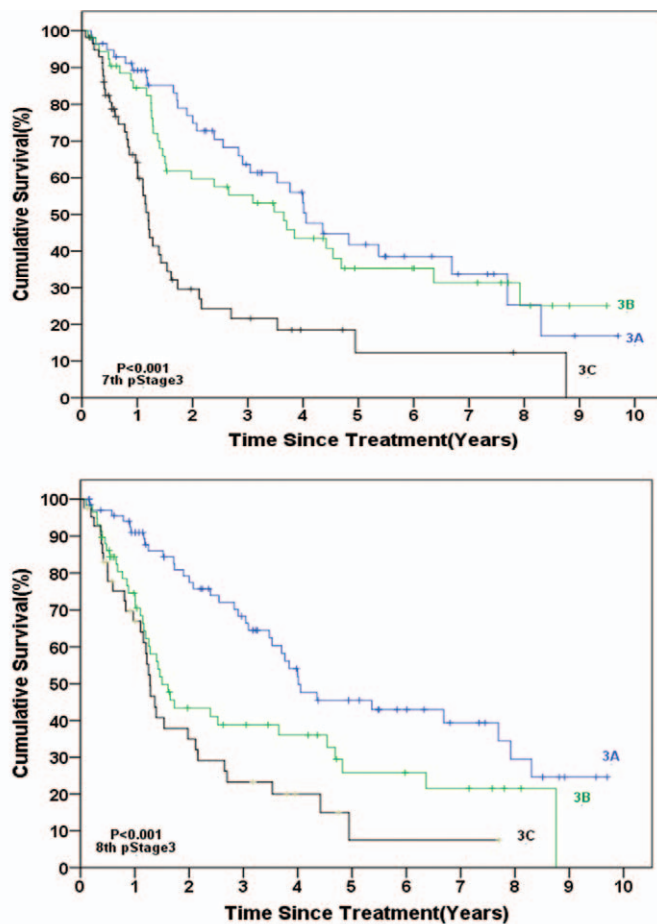| TNM staging system	Models	Linear trend chi-square	Likelihood ratio chi-square test	AIC
6th edition-T	1, 2A, 2B, 3, 4	61.453	67.223	32.257
7th, 8th edition-T	1A, 1B, 2, 3, 4A, 4B	62.800	69.452	36.555
6th edition-N	0, 1, 2, 3	*60.458*	66.795	27.429
7th, 8th edition-N	0, 1, 2, 3A, 3B	*63.010*	67.925	33.404
6th edition-stage	1A, 1B, 2, 3A, 3B,4	*94.051*	104.357	37.836
7th edition-stage	1A, 1B, 2A, 2B, 3A, 3B, 3C, 4	*87.783*	102.139	48.643
8th edition-stage	1A, 1B, 2A, 2B, 3A, 3B, 3C, 4	*91.707*	107.011	48.403

AIC = Akaike information criterion, AJCC TNM = American Joint Committee on Cancer Tumor-Node-Metastasis.

or Taiwan.[9] This study revealed the sixth edition to still have an overall better prognostic stratification than newer editions. This observation is consistent with studies including non-US, non-Japanese populations like in Italy,[6] Egypt,[15] or China.[8]

Comparing the sixth and seventh editions, the overall prognostic ability of the seventh edition is not improved in our study and in other earlier studies.[17,18] Discordant results in the overall prognostic ability are found when comparing the seventh and eighth editions. Lu et al[8] from China analyzed 1496 patients with gastric cancer at stage III and found no significant improvement in accuracy in the eighth edition. Abdel-Rahman[15] from Egypt analyzed 7934 patients who were clinically staged and 5120 patients who were pathologically staged and found that the eighth edition did not provide significant prognostic improvement. Kim et al[2] reported a single institution cohort of 5507 patients and found improved survival rate discrimination in the eighth edition as was reported in a study from the US.[14] This may reflect the geographic variation of management and/or the nature of gastric cancer. Thus, further AJCC staging system

updates may include more different ethnic populations to make it globally applicable.

The extent of lymph node metastasis proves to be the most important independent prognostic factor for patients with gastric cancer.[5] Comparing the sixth, seventh, and eighth editions strengthen the role of positive lymph nodes, by subdividing the lymph node classifications into 0, 2, 6, 15, or more. Some studies from the West[6,19] suggest that new N classifications are not superior to the sixth edition in evaluating the prognostic relevance of lymph node status. This may be related to the surgical techniques with limited lymphadenectomy (D1 lymphadenectomy) and fewer lymph nodes retrieved[6] in Western countries. The updated classification of N in the seventh and eighth editions shows better homogeneity and better discriminatory ability than the sixth edition in our series and in most series.[12,14,20] These findings reflect the trend to perform extended lymphadenectomy with more lymph nodes retrieved, improving patient outcomes[21,22] and increasing the stratification value of the new AJCC N system.

7th and 8th editions for stomach cancer stage 3

TNM Staging System	models	AUC	Linear Trend Chi-Square	Likelihood Ratio Chi-Square Test	AIC
7th edition	3A, 3B, 3C	0.58	3.57	3.64	19.30
8th edition	3A, 3B, 3C	0.61	6.97	7.19	19.11

Figure 5. Comparison of the seventh and eighth editions performance for patients with stomach cancer pathological stage 3. The eighth edition has better performance in patients at stage 3 compared with the seventh edition.

In this study, we examine the performance of the AJCC staging system for patients with gastric cancer from the sixth to the eighth edition, and we find that the newest edition may not be the best one for our patients. Since the AJCC staging system is based only on clinical parameters, including tumor size, lymph node status, and metastasis, it may not perfectly reflect complex real-world patients with gastric cancer. Deutsch et al[23] reported that surgical examination of ≥15 nodes is associated with an improved patient outcome. The addition of lymph node evaluation and lymph node ratio improved the prognostic ability of the seventh edition of the staging system, without adding significant complexity.[21,23] Choi et al[24] introduced the concept of a hybrid N staging system based on topographic and numeric status of lymph nodes. An improved N performance compared with the existing system was reported from Choi et al[24] and Galizia et al.[25] A modified T classification based on Lauren classification of gastric cancer into proximal non-diffuse, diffuse, and distal non-diffuse type was reported.[26,27] Such new strategies and the use of artificial intelligence techniques are developed to improve the prediction ability of existing staging system of existing staging systems. [28–31]

Our study has some limitations. This is an observational study, selection bias exists, and not all patients with gastric cancer are included, mainly because of the incomplete pathology records or limited follow-up information. The sample size is relatively small and generated from a single institution experience. It is a strength of our study that most of the surgeries are performed by 2 expert surgeons and managed by a multidisciplinary team in the hospital with uniform surgical techniques and postoperative care; however, additional larger-scale studies are still required before reaching stronger conclusions.

5. Conclusions

Despite the improved prognostic role of the T and N system in the seventh and eighth editions of the AJCC staging system, our study suggests the eighth edition is not superior to the sixth edition in overall prognostic stratification in our series. The eighth edition has better performance in patients at stage 3 compared with the seventh edition. Additional studies with larger sample size should be investigated to compare the performance of different editions of the AJCC staging system.

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Author contributions

Chen MW, Yen HH: Manuscript writing and drafting and final approval.
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Funding acquisition: Hsu-Heng Yen.
Investigation: Mei-Wen Chen, Hsu-Heng Yen.
Methodology: Mei-Wen Chen, Hsu-Heng Yen.
Project administration: Hsu-Heng Yen.
Resources: Hsu-Heng Yen.

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