A comprehensive analysis comparing the eighth AJCC gastric cancer pathological classification to the seventh, sixth, and fifth editions

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Abstract

To perform a comprehensive analysis comparing the prognostic and discriminative ability of the eighth AJCC gastric cancer (GC) pathological classification to that of the seventh, sixth and fifth editions, and secondly to assess their long-term significance. Patients who had undergone R0 gastrectomy were identified and restaged accordingly. To evaluate and confirm any difference in prognostic ability between the competing editions, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were computed and compared since both have different analytic strengths. The area under the curve (AUC) with 95% CI based on the time-dependent receiver-operating characteristics analyses were also calculated to assess any change in prognostic rankings from the first to tenth postoperative year. The rankings calculated by both statistical methods showed similar results, in which the seventh edition was identified as possessing the best prognostic ability. Additionally, these ranks were found to remain consistent over the ten postoperative years, but demonstrated no clinical significance as their respective 95% CIs calculated by the AIC, BIC, and AUC were found to overlap. However, the more detailed staging classifications of the eighth edition was shown to display the best prognostic demarcation for stratifying patients with higher-staged disease. This study thereby identified the eighth AJCC GC edition to possess similar long-term prognostic ability as to its previous three editions but contrastingly demonstrated the best distinctive ability for stratifying overall survival and can thus be considered as being clinically more reliable.

Introduction

Gastric cancer (GC) is the second leading cause of cancer-related death worldwide, with China having the largest pool of advanced GC cases [1], for which high-level surgical and medical prowess are required to improve survival. Patients often travel long distances to specialized cancer centers mainly for surgeries but often prefer their local hospitals for adjuvant therapies. As such, to enable a standardized treatment, staging of the disease is therefore the fundamental common language between surgical and medical oncologists.

The most recognized evidence-based GC staging system in practice is the tumor-node-metastasis (TNM) concept from the American Joint Committee on Cancer (AJCC). Since the release of its first edition in 1977 [2], it has been updated every few years based on new breakthroughs in oncology.

Starting from the fifth AJCC GC edition, the anatomic nodal classification was discontinued and reporting the number of surgically retrieved lymph nodes (LNs) became the proposed standard [3]. The sixth edition had only minor updates that did not influence the main staging
of the disease [4]. As such, in this study they were considered alike and labeled as the fifth/sixth edition. However, the seventh edition brought considerable modifications to the pathological classification of the depth of tumor invasion (pT) and completely redefined the classification of metastasized lymph nodes (pN) [5].

The eighth edition was recently released and includes the implementation of a clinical stage group, a postneoadjuvant stage group and several substantial revisions to the pathological stage group (pTNM) [6]. The major changes hallmarked in this new edition are firstly, separating the pN3ab regional lymph nodes from the seventh edition into pN3a and pN3b in its main stage groupings. Secondly, the anatomic boundary demarcating esophageal and gastric cancer for tumors arising at the esophagogastric junction (EGJ) was adjusted from 5 cm to 2 cm.

Previous publications comparing the prognostic and discriminative abilities between the seventh and the sixth gastric cancer editions lacked detailed-enough analyses, which might have contributed to the conflicting results published [7–11]. In addition, since the implemented updates mainly affect patients with higher-staged disease and Chinese patients are comparatively diagnosed at a more advanced stage, our primary aim was to use our Chinese cohort to perform a comprehensive analysis comparing the discriminative and prognostic ability of the eighth AJCC GC pathological classification to that of the seventh and fifth/sixth editions and secondly, to assess their long-term significance.

**Methods**

**Patient cohort**

From the prospectively recorded database of the Gastric Surgical Division of Sun Yat-sen University Cancer Center, Guangzhou, China, a total of 2151 GC patients who had undergone surgical resection from January 1990 to December 2013 were identified. The patients’ data were screened according to the following inclusion criteria: (1) thorough preoperative examinations including histologically confirmed adenocarcinoma of the stomach with no previous cancer history; (2) radical gastrectomy with radiological/pathological examination confirming the absence of synchronous or metachronous malignancies; (3) no neoadjuvant therapies; and (4) complete clinicopathological data to enable restaging according to the different AJCC TNM classifications.

The patients were followed every 3 months in the first 2 years after surgery, every 6 months for the next 3 years and then annually afterwards. Clinical examinations including general complete physical, hematological, and radiological tests were performed as required. The last day of follow-up was February 2017.

**Surgical treatment and pathological classification**

Patients with endoscopic or radiologic confirmation of gastric cancer involving the esophagus are often treated at the Thoracic Department of our Cancer Center. For consistency in surgical treatment, they were not included in this study. Expert gastric surgeons, each with an individual experience of at least 2000 gastrectomies, performed the surgical procedures according to the Japanese Gastric Cancer Association guidelines.

In this study, early, middle, and locally advanced disease referred to stages IA, IB to IIIA and IIIB to IIIC according to the eighth AJCC GC staging system, respectively and, combined resection referred to dissection of the spleen, pancreas and/or liver in addition to gastrectomies for achieving R0 resection.

All specimens were processed postoperatively by one of the operating surgeons before being submitted to expert pathologists whereby they were staged according to the most recent AJCC TNM classification at that time. For this study, each case was restaged according to the fifth/sixth, seventh and eighth AJCC GC pathological staging system. This retrospective study received the approval of the Institutional Review Board of the Ethical Committee of Sun Yat-sen University Cancer Center, and upon final analysis, 1797 patients were observed to match the inclusion criteria.

**Statistical analysis**

Survival time was calculated from the date of surgery till the last day of follow-up or tumor-related death. Kaplan–Meier was used to calculate survival time and for statistical comparison of prognosis. The Cox proportional hazard model with forward stepwise regression was used to compute three separate multivariate analyses, namely, Multivariate 1, 2 and 3, which consisted of the parameters found to be significant in the univariate analysis for the fifth/sixth, seventh and eighth editions, respectively.

To identify the model with the best predictive ability, their corresponding Akaike information criterion (AIC) and Bayesian information criterion (BIC) with 95% CIs from bootstrapping of the original data [12] were also computed.

Next, to assess whether their prognostic abilities would change over the years, we performed time-dependent receiver operating characteristic (ROC) analyses of the area-under-curve (AUC), based on the predictive value of multivariate analyses, with 95% CI for the first, second, third, fourth, fifth, and tenth postoperative years. Their discriminative abilities were assessed by analyzing and comparing the range and gap of their survival curves.

Statistical analyses were performed using SPSS software (version 22.0, SPSS Inc., Chicago, IL) and R statistical
Table 1. Correlation of patients demographics and clinical characteristics with survival.

| Characteristics                          | No. of cases | Cases (%) | 5-year OS (%) | HR   | 95% CI       | P-value |
|------------------------------------------|--------------|-----------|---------------|------|--------------|---------|
| Sex                                      |              |           |               |      |              |         |
| Male                                     | 1207         | 67.2      | 62.6          | Ref  |              | 0.554   |
| Female                                   | 590          | 32.8      | 60.9          | 1.049| 0.895–1.230  |         |
| Age (years)                              |              |           |               |      |              |         |
| ≤64                                      | 1318         | 73.3      | 65.1          | Ref  |              | <0.001  |
| >64                                      | 479          | 26.7      | 53.9          | 1.574| 1.346–1.841  |         |
| Tumor location                           |              |           |               |      |              | <0.001  |
| >1/3 of stomach                          | 161          | 9.0       | 39.6          | Ref  |              |         |
| Upper 1/3                                | 570          | 32.0      | 51.1          | 0.730| 0.576–0.923  |         |
| Middle 1/3                               | 155          | 8.6       | 71.8          | 0.376| 0.265–0.534  |         |
| Lower 1/3                                | 911          | 50.7      | 71.1          | 0.352| 0.277–0.447  |         |
| Tumor size (cm)                          |              |           |               |      |              | <0.001  |
| <4.5                                     | 806          | 44.9      | 74.8          | Ref  |              |         |
| 4.5 ≤ T < 8.0                            | 617          | 34.3      | 58.1          | 1.816| 1.515–2.1977 |         |
| ≥8.0                                     | 374          | 20.8      | 41.3          | 2.980| 2.468–3.598  |         |
| Bertram type                             |              |           |               |      |              | <0.001  |
| I                                        | 143          | 8.0       | 84.2          | Ref  |              |         |
| II                                       | 586          | 32.6      | 71.1          | 2.108| 1.356–3.277  |         |
| III                                      | 986          | 54.9      | 55.4          | 3.480| 2.267–5.342  |         |
| IV                                       | 82           | 4.5       | 35.5          | 6.096| 3.684–10.089 |         |
| Differentiation                          |              |           |               |      |              | 0.039   |
| High/moderate                            | 360          | 20.0      | 65.8          | Ref  |              |         |
| Poor/undifferentiated/signet cell         | 1437         | 80.0      | 61.1          | 1.227| 1.010–1.491  |         |
| Type of gastrectomy                      |              |           |               |      |              | <0.001  |
| Proximal                                 | 496          | 27.6      | 50.3          | Ref  |              |         |
| Distal                                   | 987          | 54.9      | 71.3          | 0.467| 0.395–0.552  |         |
| Total                                    | 314          | 17.5      | 50.0          | 0.971| 0.792–1.190  |         |
| Combined resection                       |              |           |               |      |              | <0.001  |
| No                                       | 1666         | 92.7      | 64.2          | Ref  |              |         |
| Yes                                      | 131          | 7.3       | 35.9          | 2.338| 1.865–2.931  |         |
| Postoperative complication               |              |           |               |      |              | 0.029   |
| No                                       | 1724         | 95.9      | 62.7          | Ref  |              |         |
| Yes                                      | 73           | 4.1       | 46.6          | 1.464| 1.037–2.067  |         |
| Retrieved lymph nodes                    |              |           |               |      |              | <0.001  |
| <16                                      | 749          | 41.7      | 55.7          | Ref  |              |         |
| ≥16                                      | 1048         | 58.3      | 66.7          | 0.649| 0.558–0.754  |         |
| Adjuvant chemotherapy                    |              |           |               |      |              | <0.001  |
| No                                       | 1321         | 73.5      | 64.3          | Ref  |              |         |
| Yes                                      | 476          | 26.5      | 55.8          | 1.335| 1.139–1.564  |         |
| Fifth/Sixth edition                      |              |           |               |      |              | <0.001  |
| pT                                       |              |           |               |      |              |         |
| T1                                       | 399          | 22.2      | 86.9          | Ref  |              | <0.001  |
| T2                                       | 383          | 21.3      | 71.0          | 2.794| 1.996–3.910  |         |
| T3                                       | 904          | 50.3      | 51.0          | 5.184| 3.850–6.981  |         |
| T4                                       | 111          | 6.2       | 35.6          | 8.494| 5.910–12.206 |         |
| Seventh/Eighth edition                   |              |           |               |      |              | <0.001  |
| pT                                       |              |           |               |      |              |         |
| T1a                                      | 271          | 15.1      | 83.9          | Ref  |              |         |
| T1b                                      | 128          | 7.1       | 93.0          | 0.460| 0.223–0.949  |         |
software (version 3.3.1, the R Foundation for Statistical Computing). A P-value less than 0.05 (2-sided) was considered to be statistically significant.

**Results**

**Patient characteristics**

Patients with stage III disease, according to the eighth edition, amounted to 51% (n = 916) of the cases. The mean age of the study population was 56.8 years (range, 16–90 years), and the 5-year overall survival rate was 65.8 ± 2.876% (rate ± SD). In this study, there was a total of 37,682 LNs examined for which an average number of 21 LNs were recorded per patient. With regard to the 131 patients who had combined resection, a small percentage of them (n = 13; 9.9%) experienced postoperative complications, among which 109 (83.2%) had tumors greater than 4.5 cm (ranging from 5 cm to 18 cm), 89.3% being locally advanced and with the majority of them (35.1%) located in the upper third of the stomach. The median follow-up time was 45 months (range, 1–259 months).

**Change in patient distribution**

No change in distribution was observed in stage IA of the three editions. Patients in stage IB (n = 203) of the
fifth/sixth edition were reclassified to stage IB (n = 107) and IIA (n = 96) in the eighth edition, those in stage II (n = 461) were reclassified to stage IIA (n = 34), IIB (n = 368) and IIIA (n = 59), and those in stage IIIA (n = 502) were reclassified to stage IIIA (n = 441) and IIB (n = 61) in the new edition. Finally, patients in stage IIIB (n = 157) of the fifth/sixth edition were reclassified to stage IIIB (n = 154) and IIIC (n = 3), and those in stage IV (n = 198) were reclassified to stage IIIB (n = 34) and IIIC (n = 164), respectively. A large proportion of the patients (n = 1346; 74.9%) were upstaged in the new GC edition, and no down-staging between these two classifications was observed.

From the seventh to the eighth edition, no change in distribution was found for 76% of the patients. A small percentage (n = 5; 1.4%) of patients from stage IIB in the seventh edition was reclassified to stage IIIB in the new edition. Those in stage IIIB (n = 332) were reclassified to stage IIIA (n = 232), IIIB (n = 75) and IIIC (n = 25), while those in stage IIIC (n = 311) were reclassified to stage IIIB (n = 169) and IIIC (n = 142), respectively. In all, 1.7% and 22.3% of patients from the seventh edition were upstaged and down-staged in the eighth edition, respectively.

Survival analysis

Of the eighteen clinicopathological factors analyzed in univariate analysis, only sex showed no correlation with survival (Table 1). A continuous decrease in 5-year overall survival (OS) rate with an increase in increment of the pTNM classification as well as a gradual increase in their HR values and larger range of 95% confidence intervals (Table 1 and Fig. 1A–C; \( P < 0.001 \)) demonstrated the progressive improvement in demarcation of prognoses between the stages from the fifth/sixth to the eighth edition.

Also, the range of 5-year survival for the eighth edition (91.2–31.3%) were found to be progressively wider from that of the fifth/sixth (91.2–33.1%) and seventh edition (91.2–32.4%), indicating that it possesses a larger area for stratification of gastric cancer patients. As illustrated in Figures 2 and 3, this improvement was especially noted between the middle and locally advanced stages of the eighth edition against the fifth/sixth and seventh edition, respectively. Additionally, the apparent differences in survival observed from stage IIB to IIIC between the seventh and eighth edition can be primarily attributable to the different survival rates expressed by patients having pN3a and pN3b nodal disease as compared to when they were merged together as pN3ab in the seventh edition (Fig. 4).

However, although the distance between the survival curves of stage IIA and IIB in the eighth and seventh
editions were relatively small, no intersection was observed, and they also expressed comparatively different 5-year OS rates, 76.5% versus 71.7% and 76.5% versus 71.5%, respectively. A highly detailed illustration of the different combinations of pT/pN (Table 2) showed great monotonicity (continuous decrease in survival with increasing stage) and distinctiveness (difference in survival between the monotonic stages) from the old to the new edition, even though there was increased complexity of staging with each updated version. Of note, this trend could not be observed for patients with pT2 disease in the seventh and eighth editions due to their relatively low number of cases.

Furthermore, three different multivariate analyses were performed for each of the different AJCC GC editions and the clinical parameters found to be independently associated with survival (favorable characteristics in parentheses; Table 3) were age (≤64; \( P < 0.001 \)), tumor location (lower third; \( P < 0.001 \)), tumor size (<4.5 cm; \( P = 0.002 \)), and total number of retrieved LN (≥16; \( P < 0.001 \)).

### Prognostic performance

Table 4 illustrates the prognostic performance of the competing AJCC staging editions based on the calculations of the two different statistical methods. The best prognostic performance is determined by the lowest AIC and BIC value. As shown, the seventh edition was identified as being superior over the fifth/sixth and the eighth edition, by that were ranked as second and third, respectively. Of note, considerable overlapping of their corresponding confidence intervals (CI) was also observed.

Furthermore, to investigate whether the above-mentioned prognostic ranking would change over time, the AUC values from time-dependent ROC analyses were performed. In here, a higher AUC values indicates the better staging system. Similarly, the seventh edition was identified as retaining its superior prognostic ability from the first to the tenth postoperative years (Table 5). In addition, as from the fifth postoperative year, the eighth
Our results demonstrated that both statistical methods showed similar ranking, for which the seventh edition was identified as having the best predictive ability in both short- and long-term despite the small numerical differences in allocating the ranks between the competing editions. In addition, the author hypothesized that since every classification constitutes of multiple subgroups, each of them might have their own predictive power. Therefore, a range of values (e.g., confidence intervals) would be more clinically reliable than an overall value (e.g., AIC, BIC) in the sense that the former would show the predictive range of each subgroup while the latter would simply depict an overall power for the whole group. Thereby, solely relying upon the raw values of AIC and BIC may not suffice for application in clinical practice [14]. Consequently, their corresponding confidence intervals were calculated and considerable overlapping was

### Table 2. The number and percentage of patients with their corresponding 5-year overall survival rates for the pT/pN combinations of the fifth/sixth, seventh and eighth AJCC TNM gastric cancer editions respectively.

| Gastric Cancer Classifications (Number/Percentage of Patients) | pN0 | OS (%) | pN1 | OS (%) | pN2 | OS (%) | pN3 | OS (%) |
|---|---|---|---|---|---|---|---|---|
| **Depth** | LNM | 0 | 1-6 | 7-15 | ≥16 |
| pT1 | Lamina propria/ Submucosa | IA (276/15.4%) | 91.2 | IB (92/5.1%) | 80.9 | II (261/4.6%) | 65.6 | IV (5/0.9%) | 60.0 |
| pT2 | Muscularis propria/Subserosa | IB (111/6.2%) | 85.0 | II (182/10.1%) | 67.8 | IIIA (65/3.6%) | 62.7 | IV (25/1.4%) | 47.4 |
| pT3 | Serosa | IIA (253/14.1%) | 72.0 | IIIA (420/23.4%) | 46.8 | IIIB (158/8.8%) | 36.8 | IV (7/0.4%) | 29.6 |
| pT4 | Adjacent structure | IIA (17/0.9%) | 67.6 | IV (29/1.6%) | 45.5 | IV (33/1.8%) | 26.5 | IV (32/1.8%) | 17.2 |

| The Sixth Edition | pN0 | OS (%) | pN1 | OS (%) | pN2 | OS (%) | pN3 | OS (%) |
|---|---|---|---|---|---|---|---|---|
| **Depth** | LNM | 0 | 1-2 | 3-6 | ≥7 |
| pT1 | Lamina propria/ Muscularis propria/Submucosa | IA (276/15.4%) | 91.2 | IB (58/3.2%) | 85.4 | IIA (34/1.9%) | 75.7 | IIIB (31/1.7%) | 64.4 |
| pT2 | Muscularis propria | IB (49/2.7%) | 87.3 | IIA (34/1.9%) | 65.9 | IIIB (19/1.1%) | 55.3 | IIIB (4/0.2%) | 50.0 |
| pT3 | Subserosa | IIA (62/3.5%) | 84.3 | IIIB (70/3.9%) | 76.1 | IIA (59/3.3%) | 60.8 | IIIB (86/4.8%) | 55.5 |
| pT4a | Serosa | IIIB (253/14.1%) | 72.0 | IIA (205/11.4%) | 53.0 | IIIB (215/12.6%) | 41.1 | IIIB (320/12.8%) | 34.5 |
| pT4b | Adjacent structure | IIB (17/0.9%) | 67.6 | IIIB (14/0.8%) | 64.5 | IIIC (15/0.8%) | 35.7 | IIIC (66/3.7%) | 18.1 |

| The Seventh Edition | pN0 | OS (%) | pN1 | OS (%) | pN2 | OS (%) | pN3 | OS (%) |
|---|---|---|---|---|---|---|---|---|
| **Depth** | LNM | 0 | 1-2 | 3-6 | ≥7 |
| pT1 | Lamina propria/ Muscularis propria/Submucosa | IA (276/15.4%) | 91.2 | IB (58/3.2%) | 85.4 | IIA (34/1.9%) | 75.7 | IIIB (261/4.6%) | 65.6 | IIIB (5/0.9%) | 60.0 |
| pT2 | Muscularis propria | IB (49/2.7%) | 87.3 | IIA (34/1.9%) | 65.9 | IIIB (19/1.1%) | 55.3 | IIIB (4/0.2%) | 50.0 |
| pT3 | Subserosa | IIA (62/3.5%) | 84.3 | IIIB (70/3.9%) | 76.1 | IIA (59/3.3%) | 60.8 | IIIB (61/3.4%) | 62.9 |
| pT4a | Serosa | IIIB (253/14.1%) | 72.0 | IIA (205/11.4%) | 53.0 | IIIB (215/12.6%) | 41.1 | IIIB (157/8.7%) | 36.4 | IIIC (5/0.9%) | 29.6 |
| pT4b | Adjacent structure | IIB (17/0.9%) | 67.6 | IIIB (14/0.8%) | 55.1 | IIIB (15/0.8%) | 35.7 | IIIC (36/3.1%) | 28.8 | IIIC (36/3.1%) | 17.2 |

Abbreviations: pN, pathological lymph node; pT/depth; pathological depth of tumor invasion; OS, 5-year overall survival rates; LNM, number of metastatic lymph nodes.

dition was found to be superior compared to the fifth/ sixth edition. However, clinically, these rankings demonstrated no significant influence due to the consistent overlapping of the 95% CI values calculated by their respective AIC, BIC, and AUC.

### Discussion

Most studies previously comparing the different GC staging editions were mainly based on simple analysis of HR values, AIC or BIC without further validating their results using other different statistical methods. In that, we felt the need for this extensive analysis by comparing their AIC and BIC values to confirm the calculated prognostic rankings since both methods have different statistical strengths [13].
## Table 3. Multivariate analyses of factors associated with 5-year overall survival for the fifth/sixth, seventh, and eighth edition.

| Characteristics | Multivariate analysis 1 | Multivariate analysis 2 | Multivariate analysis 3 |
|-----------------|-------------------------|-------------------------|-------------------------|
|                 | HR (95% CI)             | HR (95% CI)             | HR (95% CI)             |
| Age (years)     |                         |                         |                         |
| ≤64             | Ref                     | 1.447 (1.234–1.697)     | 1.421 (1.212–1.665)     |
| >64             | 1.439 (1.227–1.688)     | <0.001                  | <0.001                  |
| Tumor location  |                         |                         |                         |
| >1/3 of stomach | Ref                     | 0.930 (0.717–1.207)     | 0.988 (0.759–1.287)     |
|                 |                         | <0.001                  | <0.001                  |
| Upper 1/3       | 0.948 (0.730–1.232)     | 0.691                   | 0.948 (0.730–1.232)     |
| Middle 1/3      | 0.636 (0.440–0.919)     | 0.016                   | 0.636 (0.440–0.919)     |
| Lower 1/3       | 0.569 (0.441–0.734)     | <0.001                  | 0.569 (0.441–0.734)     |
| Tumor size (cm) |                         |                         |                         |
| <4.5            | Ref                     | 0.903 (0.782–1.045)     | 0.812 (0.693–0.950)     |
| 4.5 ≤ T < 8.0   | 1.092 (0.903–1.321)     | 0.364                   | 1.106 (0.917–1.326)     |
| ≥8.0            | 1.409 (1.143–1.738)     | 0.001                   | 1.411 (1.144–1.737)     |
| Total LN retrieved | 0.497 (0.416–0.593) | 0.001                   | 0.497 (0.416–0.593) | 0.001 |

The fifth/sixth edition (pTNM)

| IA               | Ref | <0.001 | Ref | <0.001 | Ref | <0.001 |
|------------------|-----|--------|-----|--------|-----|--------|
| IB               | 1.665 | 0.998–2.776 | 0.051 | 1.480 | 0.825–2.654 | 0.188 |
| II               | 2.750 | 1.782–4.245 | <0.001 | 2.454 | 1.441–4.718 | <0.001 |
| III              | 5.495 | 3.596–8.396 | <0.001 | 2.572 | 1.652–4.006 | <0.001 |
| IIIA             | 10.610 | 6.691–16.823 | <0.001 | 4.546 | 2.922–7.073 | <0.001 |
| IIIB             | 11.990 | 7.604–18.907 | <0.001 | 6.547 | 4.245–10.979 | <0.001 |
| IV               | 12.416 | 7.983–19.312 | <0.001 | 9.203 | 5.889–14.380 | <0.001 |
| IV               | 13.826 | 8.669–22.051 | <0.001 | 13.826 | 8.669–22.051 | <0.001 |

HR, hazard ratio; CI, confidence interval; ref, reference; T, tumor size; LN, lymph nodes; pTNM, pathological tumor-node-metastasis classification.

1 Multivariate analysis 1: Clinicopathological factors showing significance in univariate analysis and the stages of the fifth/sixth edition, excluding the seventh and eighth editions stages.

2 Multivariate analysis 2: Clinicopathological factors showing significance in univariate analysis and the stages of the seventh edition, excluding the fifth/sixth and eighth edition stages.

3 Multivariate analysis 3: Clinicopathological factors showing significance in univariate analysis and the stages of the eighth edition, excluding the seventh and fifth/sixth edition stages.
found; which implied [15] that neither clinical nor statistical significance was reached to differentiate performance superiority among them and thus, signified that they possess similar prognostic ability.

Regarding the pTNM classification, the author suggests that the pT and pN should be compared as a combination because only as such they do correlate best to their corresponding overall survival (i.e., the overall survival of patients with pT2N0 will be different from those with pT2N3b). Otherwise, they may illustrate misleading, nonuniform prognoses with increase in disease severity, for example, in Table 1 for the seventh/eighth edition, pT classification showed a noncontinuous decrease in survival. Therefore, compared to previously published studies [16–18], we opted to assess the prognostic power between the stages of the different editions rather separately analyzing pT and pN. Subsequently, our results more illustratively demonstrated an improving homogeneity and distinctiveness between the successive stage groups of the different staging editions (Table 2).

Moreover, to achieve quality cancer care, choosing the optimal treatment for patients in different disease categories might be challenging, and these concerns have been gradually addressed by the AJCC. First, they discontinued the anatomical LN staging in the fifth edition. Second, they classified patients with distant metastasis separately as stage IV in the seventh edition. Then, they separated the pN3ab subgroup to pN3a and pN3b in the latest eighth edition main stage classifications. Progressively, these changes have resulted in providing a wider range of survival from stage IA to IIIC; as illustrated in Figures 2 and 3, the survival curve of stage IIIC for the eighth edition is noticeably lower than that of stage IIIC and stage IV in the seventh and fifth/sixth edition, respectively. Therefore, the eighth edition was identified as possessing the best discriminative ability for prognostic stratification of patients with gastric cancer and this will facilitate the identification of patients with higher-stage disease for optimal therapies or enrollment in clinical trials, as the more advanced lesions have higher likelihood of nodal involvement, distant spread, recurrence and worse prognosis [19]. Therefore, this recently revised edition, the eighth AJCC GC staging system, is a fundamental update and can be considered clinically more reliable than its previous versions.

This study is the most comprehensive one to evaluate the differences between the AJCC gastric cancer staging editions of the past two decades. However, it was limited by the fact that patients with gastric adenocarcinoma invading the EGJ could not be included for homogeneity of surgical treatment, as most of such cases were not operated by the same group of surgeons. Additionally, despite having a significant cohort of patients with R0 resections, due to greater subdivisions of classification in the eighth edition, the number of cases with pT2 disease was limited, however, since the new staging system mainly concerned patients with higher staged disease, this limitation strength was not significant to affect the statistical results of this study.

In conclusion, our comprehensive statistical assessment demonstrated that the eighth AJCC GC edition possess similar prognostic ability as the seventh, sixth, and fifth
editions, which remained consistent in the long term. In addition, this new edition was also shown to provide the best discriminative ability and can thus serve as the new benchmark to stratify gastric cancer patients with higher stage disease.

**Conflict of Interest**

All authors have signed the Form for Disclosure of Potential Conflicts of Interest, and no conflicts of interest were reported.

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