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Which staging system better predicts 10-year survival for gastric cancer? A study using an international multicenter database

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ABSTRACT

Purpose: Our aim was to evaluate the prognostic performance of the 8th edition AJCC staging system for gastric cancer survival after 10 years or more.

Patients and methods: An international multicenter database was constructed (total n = 4537) by combining gastric cancer cases from the SEER database (n = 3066) and the database (n = 1471) of the Department of Gastric Surgery, Fujian Medical University Union Hospital. The relative discriminatory abilities were assessed using the likelihood ratio chi-square test, Akaike's Information Criterion (AIC) and Harrell's concordance index (c-statistic).

Results: The 10-year overall survival rate for all the patients was 32.2%. A 2-step multivariate analysis showed that the 8th edition staging system was an independent factor for long-term overall survival. It also had higher likelihood ratio chi-square score, c-statistic and smaller AIC values compared with the 7th edition. However, stages IB and IIA of the TNM staging system showed a similar prognosis (both $P > 0.05$). Based on the survival data, we revised the 8th edition by merging stages IB and IIA into 1 category in the training set. The modified staging system demonstrated superior prognostic stratification with a higher c-statistic, likelihood ratio chi-square score and smaller AIC values compared to the 8th edition. Similar results were observed in the external validation set.

Conclusion: The 8th edition AJCC TNM classification predicts the 10-year survival of gastric cancer patients more accurately than the 7th edition. However, by merging stages IB and IIA into 1 category, we propose a revised TNM stage system that provides an optimal prognosis.

Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide [1,2]. The American Joint Committee on Cancer (AJCC) tumor-lymph node-metastasis (TNM) classification is currently the most important prognostic indicator for gastric cancer, which is the primary instrument for tailoring oncological treatment for patients with stomach neoplasms. The 7th edition of the AJCC classification system showed better prognostic stratification than the sixth edition by several reports [3–5]. Due to differences in ethnicity, pathophysiology, therapeutic method and prognosis between Eastern and Western countries [3], some studies

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showed different findings when evaluating the 7th edition of the AJCC classification [5,6], which influences the general applicability of the staging system. In 2016, the 8th edition of the AJCC TNM staging classification system for stomach carcinoma was published [7], which was reviewed and refined based on worldwide data to appropriately compare treatment results in different regions. A key change adopted in the 8th edition was dividing pN3 into pN3a and pN3b in the final pathologic stage, which makes the new edition more detailed but also more complex than the older edition. However, all of these TNM systems are based on 5-year gastric cancer survival and have not been used to assess longer survival times, such as 10-year survival. For the first time, this study utilizes an international dataset of 4537 gastric cancer patients with more than 10 years of follow-up data to analyze the prognostic value of the 8th edition of the AJCC TNM classification system and investigate potential areas of improvement for improved long-term overall survival.

Patients and methods

Patients

To develop an international dataset with both Western and East Asian gastric cancer patients, data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database and combined with data from the Department of Gastric Surgery at the Fujian Medical University Union Hospital (FMUUH) in Fuzhou, China. The following factors were obtained from the data: age, sex, ethnicity, histology, surgery performed, T-classification, N-classification, M-classification, stage, total number of lymph nodes examined, and total number of positive lymph nodes, vital status, and survival. Patients in the SEER database with gastric cancer (ICD-O-3 code within the range of 8000–8152, 8154–8231, 8243–8245, 8250–8576, 8940–8950, and 8980–8990) who received gastrectomy between 1988 and 2003 were eligible for this study. The FMUUH gastric cancer databases of primary GC patients treated with radical-intent surgery were prospectively collected from 1997 to 2005. The inclusion criteria were defined as follows: the presence of primary gastric cancer; no distant metastasis; more than 15 examined lymph nodes; at least 18 years of age. All the patients with incomplete or unknown information or with stage IV disease were eliminated from the dataset. Patients who died within 1 month after operation were also excluded. The final SEER databases and FMUUH cohort used in this study included 3066 and 1471 patients, respectively. The survival duration was measured from the time of surgery to either the last date that survival information was collected or the confirmed date of death. All the patients were observed until death or the final follow-up date (SEER: December of 2013; FMUUH: December of 2016). The median follow-up for the two data sets was 183.0 months (SEER) and 204 months (FMUUH), respectively. All the staging data within the database were updated and coded to conform to the 7th and 8th editions of the AJCC TNM staging system [7,8]. In FMUUH, the adjuvant chemotherapy using 5-fluorouracil (5-FU)-based regimens was recommended to the majority of patients with advanced gastric cancer.

Statistical methods

Statistical analyses were performed using SPSS statistical software (version 18.0, SPSS Inc, Chicago, IL) and STATA version 12.0 (StataCorp, College Station, TX). The Kaplan-Meier method was used to estimate time-dependent survival probabilities. Evaluation of the monotonicity, distinctiveness, and homogeneity of the respective survival curves were conducted to judge staging adequacy. The log-rank test was used for statistical comparisons of the survival curves. A 2-step multivariate analysis was performed to investigate the validity of the revised TNM system [9]. In the 1st step of the multivariate analysis, all the significant factors in the univariate analysis were included as well as the 7th edition TNM system; the 8th edition system was excluded. In the 2nd step of the multivariate analysis, the 8th edition was also included. Then, the data were randomly divided into two subsets using SPSS version 18.0 (SPSS, Chicago, IL, USA) to create a 75/25 split, with one subset used for modified staging system development and the other used for validation testing [10]. The relative discriminatory abilities of the different TNM staging systems were assessed using the likelihood ratio chi-square test, the linear trend chi-square test, the Akaike Information Criteria (AIC) and the Harrell's concordance index (c-statistic). A higher likelihood ratio chi-square score means better homogeneity; a higher linear trend chi-square score shows better discriminatory ability and monotonicity; and smaller AIC values represent better optimistic prognostic stratification [11]. A high c-statistic indicates a better discriminatory ability [12,13]. Significant differences were assumed at P values less than 0.05 in a two-tailed test.

Results

Study population

The patient and tumor characteristics of the international multicenter dataset, which was developed by combining the SEER ($n = 3066$) and FMUUH ($n = 1471$) databases, are presented in Table 1. The proportion of female patients and median age were significantly higher in the SEER databases (both $P < 0.05$). And the SEER databases had significant racial diversity. Total gastrectomy was performed more frequently in the FMUUH databases (57.6% vs 18.1%, $P < 0.05$). The means number of positive lymph nodes was higher despite a similar lymph node retrieval in the FMUUH databases. In terms of tumors, more patients in the FMUUH databases had well-differentiated tumors, but the T stage, N stage and pTNM stage were significantly higher than those in the SEER databases (all $P < 0.05$).

Long-term overall survival analysis

The univariate analyses indicated that age, ethnicity, histological type, type of gastrectomy, the 7th edition TNM system and the 8th edition system were associated with long-term overall survival. In the 1st step of the multivariate analysis, age, ethnicity, histological type, type of gastrectomy, and the 7th edition TNM system were confirmed to be independent prognostic factors (all $P < 0.05$). When the 8th edition TNM system was included in the 2nd step of the multivariate analysis, only the 8th TNM system remained significant, and the 7th edition was no longer significant (Table 2).

Comparison of the prognostic value between the 7th and 8th TNM systems

The median follow-up period was 196.0 (range, 1–311) months for the combined dataset. The ten-year survival probability of the entire cohort was 32.2%, whereas the ten-year survival probabilities for AJCC stages IA, IB, IIA, IIB, IIIA, IIIB and IIIC for the 7th vs the 8th edition were 69.1% vs 69.1%, 53.0% vs 53.0%, 55.3% vs 55.3%, 41.6% vs 42.3%, 31.6% vs 32.6%, 23.6% vs 20.0% and 14.5% vs 12.1%, respectively. According to the two systems, there were similar survival curves for stage IB and IIA (Table 3), whereas the Kaplan–Meier plot showed good discriminatory ability between the other substages (Fig. 1A).

Table 4 compares the long-term prognosis among patients with different stages of the 7th edition TNM system stratified by the 8th edition TNM system, and among those patients in different stages

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