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Consensus Statement

Development of a risk-scoring system to evaluate the serosal invasion for macroscopic serosal invasion positive gastric cancer patients

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ABSTRACT

Background: The status of serosal invasion is often discordance between pathological and intraoperative evaluation. Our study sought to develop a risk-scoring system (RSS) to predict the probability of pT4a for macroscopic serosal invasion (MSI) positive patients and reevaluate the serosal invasion status.

Patients and Methods: A total of 1301 pT3/pT4a gastric cancer patients with curative surgery were reviewed. We constructed the RSS to predict the probability of pT4a and assigned MSI-positive patients into different risk groups based on the risk scores. The prognostic significance of these risk groups was also evaluated.

Results: Univariate and multivariate analyses identified that tumor location, Lauren type, Borrmann type, tumor size, lymphovascular invasion and pN stage were risk factors related to pT4a. Survival analyses showed that pT3 MSI-positive patients in high-risk group had similar survival with pT4a patients. We incorporated these two groups into one stage and proposed a novel revised-T stage. Two-step multivariate analyses indicated that the revised-T stage showed better prediction ability for prognosis and peritoneal recurrence assessment than original pT stage and MSI status.

Conclusions: In our present study, we developed a RSS to predict the probability of pT4a for MSI-positive patients. Based on our RSS, we proposed a treatment algorithm to reevaluate the tumor invasion for MSI-positive patients in clinical practice. Future studies should include other preoperative predictors to improve the clinical utility of our model.

Introduction

Recently, American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) tumor-node-metastasis (TNM) classification, which based on the depth of tumor invasion, number of regional metastasis lymph nodes and distant metastasis, is the most widely used staging of gastric cancer (GC) [1]. However, the pathological T stage is often inconsistent with the T stage evaluated by surgeons during operations, especially the status of serosal invasion [2–4]. And about half of the patients were macroscopic serosal invasion (MSI) positive and finally identified as the serosal-limited tumor invasion pathologically [4–6]. Several studies also demonstrated that MSI-positive patients had worse prognosis as well as higher incidence of peritoneal recurrence [3,5–8].

Peritoneal recurrence is the most common pattern of recurrence and almost half of advanced GC patients died of peritoneal recurrence even after curative resection [9–11]. Previous studies indicated that intraperitoneal free cancer cells are significantly associated with peritoneal recurrence [12–15]. When tumor invades into the serosal layer, cancer cells may exfoliate from the lesion where the normal serosal are disrupted by tumor invasion [8,16]. Thus, the status of serosal invasion is extremely critical for detection of intraperitoneal free cancer cells and prediction of peritoneal recurrence.

Although hyperthermic intraperitoneal chemotherapy (HIPC) may improve the overall survival (OS) and decrease the peritoneal

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recurrence among patients with pathological serosal invasion [17], the efficacy of this treatment for MSI-positive patients remains controversial [18,19]. Considering the morbidity and mortality rate of this treatment, the accurate assessment of tumor invasion is prerequisite for these patients [20].

Based on above considerations, we sought to reevaluate the tumor invasion status for these patients by developing a risk-scoring system (RSS).

Patients and Methods

Study population

A total of 2062 GC patients who underwent gastric resection and combined D2/D3 lymphadenectomy and achieved R0 resection at the Department of Surgical Oncology, the First Affiliated Hospital of China Medical University from January 1987 to December 2006 were collected. Of these patients, 1366 patients were confirmed as pT3/pT4a pathologically according to the seventh edition of the UICC/AJCC TNM staging system [1]. We mainly included these patients for analyses because the majority of MSI-positive patients were finally identified as pT3/pT4a histologically [2,4,6,21].

Among 1366 patients, 28 patients died in the postoperative period (<3 months). All patients received follow-up after being discharged from hospital, every quarter of the first 3-year, 6 months during the fourth and fifth year, and once a year thereafter. Follow-up evaluations included patient history, physical examination, carcinoembryonic antigen (CEA), carbohydrate antigen19-9 (CA19-9) and CA72-4. The gastroscopy and computed tomography (CT) scan were performed once a year. At the time of the last follow-up (March 31, 2011), the median and mean follow-up time was 32.0 and 61.8 months, respectively (range 3–313 months). 24 patients were lost and these patients were excluded from our study (follow-up rate: 98.2%).

Of the remaining 1314 patients, 13 patients with incomplete information were also excluded. Finally, 1301 patients were selected for further analysis. A total of 753 patients received post-operative intravenous adjuvant chemotherapy and/or intraperitoneal chemotherapy. No one received neoadjuvant chemotherapy and/or radiotherapy. At the time of the last follow-up, 622 patients died of cancer-related diseases and 362 patients died of other diseases or causes unknown. Peritoneal recurrence was diagnosed mainly by CT scan and sometimes identified by cytology of ascites or intraoperative biopsy if operations were performed. Of the 622 patients, 293 were identified with peritoneal recurrence. This study was approved by the Institutional Ethics Committee of China Medical University.

Development and evaluation of risk-scoring system

Logistic regression analysis was used to identify the risk factors of tumor invasion diagnosed as pT4a. The score of each risk factor was estimated based on the results of multivariate analysis. The β-coefficients of multivariate analysis were rounded up to the nearest half integer and then multiplied by 2 to avoid decimals [22]. We calculated the total points of each patient and divided the patients into quartiles approximately. Then three risk groups (low-, medium-, and high-risk group) were established with the middle two quarters combined.

The total risk score of each patient was used as a risk factor for the model evaluation. The performance of the developed RSS was evaluated with respect to discrimination and calibration. Discrimination was measured by the concordance statistic (c-statistic), which is equivalent to the area under the receiver operating characteristic (ROC) curve [23]. The calibration of the model was evaluated by plotting the calibration curve and testing the statistical significance of Hosmer-Lemeshow goodness-of-fit test ($P > 0.05$ indicating good fit). Both of the c-statistic and the calibration curve were internally validated by bootstrap method to reduce the over fit bias (200 repetitions).

Decision curve analysis (DCA) was constructed to evaluate the clinical usefulness of RSS [24]. This analysis estimates the clinical net benefit of our model by summing the benefits (true-positive) and subtracting the harms (false-positive).

Survival analysis and peritoneal recurrence assessment

To elucidate the prognosis influence of our RSS, we compared the OS between these risk groups in each pN stage and pT stage. Meanwhile, we compared the OS of pT3 MSI-positive patients in different risk groups with pT4a MSI-positive patients. Based on these results, patients who had similar survival were incorporated into one T stage and a novel revised-T stage was formed. Additionally, two-step multivariate analysis was also used to compare the novel revised-T stage with original UICC/AJCC pT stage in the prediction of peritoneal recurrence and the prognosis assessment. Patients died of other diseases or with causes unknown ($n = 362$) were excluded when we evaluated the peritoneal recurrence.

Statistical analysis

Continuous variates were described as mean ± standard deviation (SD) and categorical variates were described as count and percentages. Comparisons between groups were performed by using Pearson χ^2 test for categorical variates and two-tailed Student's *t*-test for continuous variates. Univariate analyses were performed to indentify the significant risk factors related with pT4a and peritoneal recurrence. Multivariate analyses were used to identify the independent risk factors. The OS rates were estimated by Kaplan-Meier curves and the comparisons were identified by the log-rank test. Multivariate Cox proportional hazards regression model was used to identify the independent prognosis predictors. Only those variates with P values < 0.05 in univariate analyses were selected into the multivariate analyses.

The analyses were performed using the R software version 3.2.0 (http://www.r-project.org/) and SPSS version 21.0 (SPSS, Chicago, IL). A two-tailed *P* value < 0.05 was considered as statistically significant in all analyses.

Results

Study population and model development

Clinicopathological characteristics of MSI-positive and -negative patients were presented in Supplementary Table S1. The comparison between these two groups identified the significant differences in tumor size, tumor location, Borrmann type, pN stage, pT stage, the number of positive lymph nodes and the ratio of positive.

The results of univariate analysis identified that tumor size, tumor location, Borrmann type, Lauren type, lymphovascular invasion and pN stage were significant risk factors related to pT4a. Further multivariate analysis confirmed that tumor size, tumor location, Borrmann type, Lauren type, lymphovascular invasion and pN stage were significantly related to pT4a (Supplementary Table S2).

Based on the results of multivariate analysis, we constructed a user-friendly RSS (Table 1). The score was assigned to each risk factor using the β-coefficients, as described in method. The median risk score was 5 (range 0–11). Patients were divided into 3 risk groups: low-risk (0–3 scores, 20.3%), medium-risk (4–6 scores,

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