



Preoperative lymph node size is helpful to predict the prognosis of patients with stage III gastric cancer after radical resection

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ABSTRACT

Objective: To investigate the association between preoperative lymph node size (Ns) and prognosis of radical gastrectomy for gastric cancer.

Methods: The clinical and pathological data of 970 patients undergoing radical gastrectomy for gastric cancer were retrospectively analyzed. The correlation between Ns and the identified variables for the prediction of overall survival (OS) and disease-free survival (DFS) was examined.

Results: Three hundred and thirty-one (34.1%) of 970 patients developed recurrence, which was most commonly in local lymph nodes. The average Ns was 1.52 cm in patients with recurrence, which was significantly higher than the 1.14 cm observed in patients without recurrence ($p < 0.001$). Patients were categorized into three groups as follows (Ns category): Ns0: ≤ 1.10 cm, Ns1: 1.10–1.70 cm, and Ns2: > 1.70 cm, determined using the X-tile program. In univariate and multivariate analyses, Ns category, age, tumor size, lymphadenectomy, adjuvant chemotherapy and TNM stage were independent prognostic factors for DFS. Stratified analysis only in stage III was there a significant difference in the Ns category based on TNM stage. Furthermore, in the stage III subgroup, univariate and multivariate analyses revealed that Ns category, lymphadenectomy, and TNM stage was independent prognostic factors for DFS. A nomogram were developed to predict the 3-year DFS rate.

Conclusions: Preoperative Ns is an independent prognostic factor for DFS of patients after radical surgery for gastric cancer. The proposed nomogram combined with Ns could be a simple and effective approach to predict the 3-year DFS of stage III patients.

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1. Introduction

Gastric cancer is the fourth most common malignancy and the second most common cause of cancer-related death worldwide [1–3]. Lymph node (LN) metastasis is the most common pattern of metastatic spread in gastric cancer. Therefore, gastric cancer patients, especially in the advanced stages, present with enlarged LNs. Complete dissection of perigastric LNs, including enlarged LNs, is necessary to achieve an ideal curative effect in gastric cancer. Nevertheless, 20–50% of gastric cancer cases still recur [4–8]. Furthermore, local LN recurrence is the most common recurrence pattern [9–11], and it seriously affects the postoperative quality of

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life of patients with gastric cancer. Therefore, it has become important to effectively predict recurrence and disease-free survival (DFS) of patients. Accordingly, postoperative lymph node size (Ns) is related to the recurrence of cancer at local LNs as reported in several retrospective studies [12,13]. However, the actual clinical value of the postoperative Ns is not high compared with that of preoperative Ns. Therefore, we studied the relationship between preoperative Ns, recurrence and DFS, because there are few studies on this topic. The aim of this study was to investigate the association between the preoperative Ns and prognosis of patients, especially in terms of recurrence and DFS, by analyzing the clinicopathologic data of patients with gastric cancer who underwent radical gastrectomy.

2. Materials and methods

2.1. Patients

The clinical data of 1081 patients with gastric cancer, who underwent radical gastrectomy by the same group of surgeons at Fujian Medical University Union Hospital in China between December 2009 and May 2012 were retrospectively analyzed. Patients with T4b who underwent combined organ resection ($n = 58$), had remnant gastric cancer ($n = 14$), underwent splenectomy due to enlarged LNs at the splenic hilus ($n = 1$), received neoadjuvant chemotherapy ($n = 37$) or died within 1 month ($n = 2$) were excluded. Ultimately, 970 patients were included in the study. Multidetector-row computed tomography (MDCT) were examined within 1 week before surgery. The original MDCT images were reviewed by two experienced radiologists. The Ns is the maximum diameter of the largest LN, that the mean of two assessments was calculated. And two experienced radiologists measured Ns with a high degree of consistency (Supplementary Fig. 1). This study was approved by the ethics committee of Fujian Medical University Union Hospital (Approval number: 2016KY041). Staging was determined according to the 7th edition Union for International Cancer Control (UICC) TNM classification system. Adjuvant chemotherapy with 5-Fluorouracil was recommended for patients with pTNM stage II or higher.

The inclusion criteria included the following: (1) preoperative, histologically confirmed gastric cancer by endoscopic biopsy pathology; (2) no distant metastasis of the liver, lung, abdominal cavity and more based on the above examination; (3) no evidence of obviously enlarged abdominal para-aortic LNs or invasion of pancreas, spleen, liver, colon and other peripheral tissue; and (4) pathologically negative resection margins (R0 resection). The exclusion criteria included the following: (1) peritoneal dissemination or distant metastases confirmed during the operation; (2) incomplete pathological data; and (3) combined splenectomy due to enlarged splenic hilar LNs.

Recurrence was defined as the presence of a biopsy-proven tumor showing adenocarcinoma cells or the presence of imaging that was highly suspicious of tumor recurrence. Recurrence was categorized as locoregional, peritoneal, or hematogenous. Locoregional recurrence was defined as any cancer at the regional LNs, anastomotic or resection margin, or operation bed. Peritoneal recurrence was documented by cross-sectional imaging of MDCT or by positive cytology in ascetic fluid. Hematogenous metastasis was defined as any metastasis lesion detected in the liver, lung, bone, brain, adrenal gland and other organs.

2.2. Follow-up

After surgery, all patients were regularly followed up. Postoperative follow-ups were performed every 3 months for 2 years

and then every 6 months from years 2–5. Most routine patient follow-up appointments included a physical examination, laboratory tests (including assessment of CA19-9, CA72-4, and CEA levels), chest radiography, abdominopelvic ultrasonography or CT as well as an annual endoscopic examination. OS was calculated from the day of surgery until death or the final follow-up date, whichever occurred first. DFS was calculated from the day of surgery until recurrence, or tumor-related death, or the final follow-up date. The final follow-up dates were in June 2016.

2.3. Statistical analysis

X-tile (Version 3.6.1, Yale University) was used to calculate the optimal cutoff points for Ns using the minimum p value from log-rank χ^2 statistics according to the DFS [14,15]. The statistical analyses were performed using SPSS v.18.0 for Windows (SPSS Inc., Chicago, IL). All continuous variables were presented as the mean \pm standard deviation. Chi-square or Fisher's exact tests were used for categorical variables. Cumulative survival rates were compared using the Kaplan–Meier method and log-rank test. Independent variables predicting survival were evaluated by using the Cox proportional hazards model, sharing all variables with P values < 0.05 in the univariate analysis. A nomogram was built based on the Cox proportional hazards regression model for predicting 3-year DFS which can be easily generalized to predict that of other time point using R software version 3.31 (<http://www.r-project.org/>). With this nomogram, the category of each prognostic factor is assigned a score using the topmost 'Points' scale, and then a sum is counted across all patient characteristics so as to obtain the 'Total points' that are eventually converted into the desired statistics. Discrimination was quantified using Harrell's concordance index (C-index). P values < 0.05 were considered statistically significant.

3. Results

3.1. Patient survival

Of all enrolled patients, 900 (92.8%) completed a postoperative follow-up, and the median follow-up period was 51.0 months (range 3.0–76.0 months). Age, BMI, ALB, ASA, operation method, tumor location, tumor diameter, the type of lymphadenectomy, gastrectomy, reconstruction, surgery time, pT stage, pN stage, pTNM stage and adjuvant chemotherapy were all prognostic factors in univariate analysis. The overall 1-year and 3-year survival rates were 87.7% and 70.7%, respectively (Table 1). The survival curve showed a significant difference in the OS between patients at different TNM stages, except for IIA, IIB, and IIIA patients. On the other hand, the median follow-up period for DFS was 50.0 months. The 1-year and 3-year DFS rates were 82.9% and 67.5%, respectively. Based on the DFS survival curve, except for in IIA, IIB, IIIA and IIIB patients, there was a significant difference in the DFS between patients with tumors at different TNM stage (Supplementary Fig. 2).

Three hundred and thirty-one patients (34.1%) developed tumor recurrence. The most common recurrence pattern was locoregional (44.10%). In particular, LN recurrence was the most common type of local recurrence. Two hundred and sixty-nine patients (81.27%) experienced recurrence in a single mode, whereas 62 patients (18.73%) experienced multiple modes (Supplementary Fig. 3A). The recurrence rate increased with the increasing TNM stage (Supplementary Fig. 3B). The average Ns was 1.52 cm in patients with recurrence, which was significantly higher than the 1.14 cm in patients without recurrence ($p < 0.001$).

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