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Does a minimum number of 16 retrieved nodes affect survival in curatively resected gastric cancer?

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Abstract

Background: According to the TNM classification, the analysis of 16 or more lymph nodes is required for the appropriate staging of gastric cancer. The aim of this study was to evaluate whether this number of resected lymph nodes also affects survival.

Methods: This was a multicenter retrospective study based on an analysis of 992 patients with gastric adenocarcinoma who underwent curative resection between January 1980 and December 2009. Patients were classified according to the number of resected lymph nodes (<16 and ≥16 lymph nodes), the anatomical extent of lymph node dissection (D2 vs. D1), and the staging criteria of the seventh edition of the UICC/AJCC TNM staging system. Survival estimates were determined by univariate and multivariate analyses.

Results: Based on the univariate and multivariate analyses, the resection of 16 or more lymph nodes was associated with significantly better survival [$p = 0.002$; hazard ratio (HR) (95% confidence interval [CI]): 0.519 (0.345–0.780)]. Patients with a lymph node count <16 had a significantly worse survival rate than patients with a lymph node count ≥16 in the pN0 ($p = 0.001$), pN1 ($p = 0.007$) and pN2 ($p = 0.001$) stages. In the majority of cases, ≥16 lymph nodes were retrieved when D2 dissection was performed.

Conclusions: In gastric cancer the retrieval of less than 16 lymph nodes may cause inaccurate staging and/or inadequate treatment, thus affecting survival rates. These patients should be considered a high-risk group for stage migration and worse survival compared with those who have a retrieval of more than 16 lymph nodes.

Keywords: Gastric cancer; Lymph node; Staging; Prognosis

Introduction

Lymph node metastasis is the most important predictor of survival in patients with gastric cancer.[1,2] The classification of lymph node metastasis that is most appropriate for predicting the prognosis of patients with gastric cancer who have undergone curative surgery remains controversial. To date, three main classifications of lymph node metastasis have been applied to predict the prognosis of gastric cancer patients worldwide, namely, classifications that are based on the number of positive nodes, the location of positive nodes, and the ratio between the metastatic and examined nodes. By 2010, the two main lymph node classifications, namely, the 7th edition of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM staging system[3] and the 14th Japanese gastric cancer classification,[4] were consistent

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regarding the concept that the absolute number of positive lymph nodes represents the gold standard in the reporting of pathological staging in gastric cancer. Both classifications established the positive node cut-off values for the N categories as follows: N1 = 1–2 nodes; N2 = 3–6 nodes; N3a = 7–15 nodes; and N3b = 16 or more nodes. As a consequence, both classifications recommend the examination of 16 or more regional lymph nodes to determine the correct N status even though this recommendation is not intended to be a stringent requirement.

Three main factors significantly influence the reporting of pathological lymph node status, including the surgical extent of lymph node dissection, accuracy in the pathological examination, and individual differences in the total number of lymph nodes[5–8]; under-staging is most likely to occur when too few lymph nodes are examined.[9]

Together with debates on the staging of cancer, large population studies have demonstrated a strong association between the number of lymph nodes analyzed and improved survival,[10,11] which indicates that an adequate number of lymph nodes retrieved through an extended lymph node dissection may have a significant impact on the prognosis of patients with gastric cancer who receive potentially curative treatment.

The extent of lymph node dissection continues to represent an important issue with regard to surgical research in gastric cancer; in addition, whether a higher lymph node count should be considered a requirement for proper staging or as an indicator of adequate surgical treatment is still a matter of controversy.

The aim of this study was to investigate the impact of the lymph node count, with a focus on a cut-off of 16 lymph nodes, on staging and survival in patients with gastric cancer who received curative resection.

Materials and methods

This multicenter retrospective study was based on an analysis of 1465 patients with gastric adenocarcinoma who underwent surgery with curative intent between January 1980 and December 2009 at 3 surgical units in Italy (1st General Surgery Unit and Digestive Surgery of Catholic University of Rome; Department of Surgery University of Turin, San Giovanni Battista Hospital, Turin). Only patients who underwent curative resection (R0) were included in this study. According to the 7th edition of UICC/AJCC TNM, esophago-gastric junction cancers were excluded from the study. When available, patients with positive peritoneal cytology were excluded from the study as considered R1 resection. The patients with locally advanced gastric cancer (T3/4 N+) who underwent preoperative chemotherapy as a neoadjuvant treatment were excluded from the study.

Clinical- and cancer-specific data were collected prospectively and entered into a database. The primary clinico-pathological data, such as age, gender, extent of gastrectomy, extent of lymphadenectomy, tumor diameter, tumor site, Lauren's histotype, tumor stage, grading, total lymph node count (TLC, i.e., total number of harvested lymph nodes), number of metastatic lymph nodes (MtLNs), number of negative lymph nodes (NeLNs), and survival data, were analyzed. The tumor stage was coded according to the TNM system, as described in the UICC/AJCC 7th edition.

For the purpose of the study, the patients were divided into two groups according to the UICC/AJCC recommendation as follows: patients with <16 harvested lymph nodes (TLC− group) and patients with ≥ 16 harvested lymph nodes (TLC+ group).

The extent of stomach resection was related to the primary tumor site; specifically, total gastrectomy was performed in all proximal tumor locations, and subtotal gastrectomy was performed in distal tumor locations, provided that a 5- to 6-cm safety margin was present. The extent of the lymph node dissection was based on the individual surgeon's judgment and attitude and was defined according to the 14th Japanese Gastric Cancer Association (JGCA) rules. The intent of resection was described as curative when all macroscopic and microscopic disease seemed to have been removed and was considered palliative when there was intraoperative macroscopic evidence of residual or metastatic disease. Immediately after the operation, the specimens were carefully prepared, and the lymph node stations were dissected by a member of the surgical team according to the JGCA rules to achieve an accurate pathological staging.

A close postoperative follow-up was planned for all patients and included clinical history, physical examination, complete blood count and blood serum analysis (every 3 months for the first 2 years and every 6 months thereafter), endoscopy (every 6 months in the first year and once a year thereafter), abdominal ultrasound (every 3 months in the first year and every 6 months thereafter), and chest and abdominopelvic computed tomography (CT) scans (every year). Postoperative adjuvant chemotherapy was administered according to the local hospital's protocol.

Continuous variables were analyzed using the Man–Whitney test and t-test (when appropriate), and Spearman's rho was used to estimate the bivariate correlations. The chi-square and Fisher's exact test were used for the analysis of other parameters. P values of <0.05 were considered statistically significant.

Overall survival was calculated according to the Kaplan–Meier method from the date of operation, while the log-rank test was used to assess any significant differences between the groups.

Multivariate analysis of prognostic factors related to overall survival was performed using Cox's proportional hazards model with the forward likelihood method; variables that were statistically significant at the $p < 0.1$ level