

Is Metastatic Lymph Node Ratio Superior to the Number of Metastatic Lymph Nodes to Assess Outcome and Survival of Gastric Cancer?

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Key Words

Gastric cancer · Lymph node metastasis ·
Metastatic lymph node ratio · Prognosis · Staging

Summary

Background: The aim of this study was to determine the prognostic value of metastatic lymph node ratio (n ratio). **Patients and Methods:** We retrospectively analyzed 202 patients who had undergone curative gastrectomy. The prognostic factors including UICC/AJCC TNM classification and n ratio were evaluated by univariate and multivariate analysis. **Results:** The n ratio was significantly higher in patients with gastric tumors with undifferentiated histology, greater size, lymphatic vessel, blood vessel and perineural invasion (PNI), and advanced stage. Multivariate analysis indicated that n ratio and pN classification were independent prognostic factors, as were age, tumor size, Borrmann classification, PNI, and tumor differentiation. The receiver operating characteristics (ROC) analysis showed that the sensitivity and the specificity of the presence of lymph node metastasis with 16 lymph nodes resected – which was required to assess the presence of lymph node involvement – were 67.1 and 66.6%, respectively. Three-year overall survival (OS) rates and the median OS time were lower in patients with <16 lymph nodes resected compared to the patients who had >16 lymph nodes resected ($p = 0.04$). **Conclusions:** Our results showed that n ratio and pN classification were independent prognostic indicators for OS of patients with radically resected gastric cancer, but the superiority of n ratio to pN stage could not be proved.

Schlüsselwörter

Magenkarzinom · Lymphknotenbefall ·
Lymphknotenbefallsrate · Prognose · Staging

Zusammenfassung

Hintergrund: Ziel dieser Studie war es, den prognostischen Wert der Lymphknotenbefallsrate zu bestimmen. **Patienten und Methoden:** Insgesamt wurden 202 Patienten, bei denen eine kurative Gastrektomie durchgeführt worden war, retrospektiv analysiert. Die Prognosefaktoren, einschließlich der UICC/AJCC-TNM-Klassifikation und der Lymphknotenbefallsrate, wurden mittels uni- und multivariater Analyse beurteilt. **Ergebnisse:** Die Lymphknotenbefallsrate war signifikant höher bei Patienten mit Magentumoren charakterisiert durch eine undifferenzierte Histologie, einen größeren Umfang, Invasion der Lymph- und Blutgefäße, perineurale Invasion (PNI) sowie ein fortgeschrittenes Stadium. Die multivariate Analyse zeigte, dass die Lymphknotenbefallsrate und die pN-Klassifikation unabhängige Prognosefaktoren sind, ebenso wie Alter, Tumorgöße, Borrmann-Klassifikation, PNI und Tumordifferenzierung. Die ROC (receiver operating characteristics)-Analyse ergab eine Sensitivität und Spezifität bezüglich des Vorhandenseins von Lymphknotenmetastasen bei 16 entfernten Lymphknoten (erforderliche Anzahl zur Beurteilung des Lymphknotenbefalls) von 67,1 bzw. 66,6%. Die 3-Jahres-Gesamtüberlebensraten sowie die mittlere Überlebensdauer waren niedriger, wenn <16 statt >16 Lymphknoten entfernt worden waren ($p = 0,04$). **Schlussfolgerungen:** Unsere Ergebnisse zeigen, dass die Lymphknotenbefallsrate und die pN-Klassifikation unabhängige Prognosefaktoren für das Gesamtüberleben von Patienten mit radikal reseziertem Magenkarzinom sind. Eine Überlegenheit der Lymphknotenbefallsrate gegenüber dem pN-Stadium konnte jedoch nicht nachgewiesen werden.

Introduction

Gastric cancer is still one of the most frequent tumors and the leading cause of cancer death in the world. Although the incidence rate has declined, its prognosis has not improved much, and the cumulative 5-years survival rates of all patients with gastric cancer have changed only slightly over the past 4 decades but remain under 20% [1, 2]. Surgery represents the cornerstone of any curative procedure. A correct definition of poor prognostic factors may help to guide more aggressive adjuvant treatments protocols postoperatively [3, 4].

It is well documented that lymph node metastasis is one of the most important prognostic factors in gastric cancer, but the classification of lymph node status (N categories) is controversial [5–9]. In Japan, the extend of lymph node metastasis is classified by anatomical pathway of metastatic lymph nodes according to the Japanese Classification of Gastric Carcinoma (JCGC) which was proposed by the Japanese Research Society of Gastric Cancer (JRS GC) [10]. In 1997 and 2002, the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), in the 5th edition of the tumor, node, metastasis (TNM) system, redefined N categories based on the number of metastatic lymph nodes [11, 12]. The prognostic value of the pN (pathologic lymph node) classification has been evaluated, and it has been accepted as a simple and reproducible method for accurate staging [12, 13]. The pN classification needs the examination of at least 15 lymph nodes, and extended lymphadenectomy may cause a ‘stage migration’ due to the increase in the number of metastatic lymph nodes [14–17].

Recently, a new prognostic indicator of the ratio of metastatic lymph nodes to the total number of lymph nodes (n ratio) was proposed for gastric cancer with curative resection [5–8, 14, 15, 17–20]. The superiority of the n ratio classification to location-based or number-based N classifications has been reported by some investigators, and they also showed that it is an independent prognostic indicator for gastric cancer [15, 18–26]. In the present study, we evaluated the prognostic importance of n ratio and compared this ratio with UICC/AJCC TNM classifications in patients with radically resected gastric cancer. Furthermore, the association of the other clinicopathological factors with overall survival (OS) was studied.

Patients and Methods

This study consisted of 202 gastric carcinoma patients who had undergone curative gastrectomy at the Dr. Lutfi Kirdar Kartal Education and Research Hospital between May 2001 and December 2008. The clinicopathological findings were determined according to the JCGC. All patients underwent either distal partial gastrectomy, proximal partial gastrectomy, or total gastrectomy with regional lymph node dissection to D1, D2, or D3. Lymph node involvement was classified according to the 1997 UICC/AJCC TNM classification (N0, no metastasis; N1, 1–6

metastatic lymph nodes; N2, 7–15 metastatic lymph nodes; N3, > 15 metastatic lymph nodes). Clinical information about age, gender, resection type, tumor location, histopathology, tumor stage, tumor size, histological grade, lymph node involvement, the depth of tumor invasion, lymphatic vessel invasion (LVI), blood vessel invasion (BVI) and perineural invasion (PNI), resection margins, Borrmann classification, histological type, adjuvant chemotherapy and radiation therapy type, responses to treatment, and survival were obtained from patient charts. The eligibility criteria included histologically confirmed R0 gastric resection which was defined as no macroscopic or microscopic residual tumor and a postoperative survival time of > 3 months. Patients with distant metastasis at diagnosis were excluded from the study. The n ratio was determined by the best cutoff approach in terms of the log-rank test. N ratio 0, 0%; N ratio 1, 1–9%; N ratio 2, 10–25%; and N ratio 3, >25%.

The UICC advised that when less than 15 nodes are examined, pN classification can not be applied accurately [14, 15, 17]. Therefore, a receiver operating characteristics (ROC) analysis was performed. It was shown that the sensitivity and the specificity of the presence of lymph node metastasis with 16 lymph nodes resected during surgery, which were required to assess the presence of lymph node involvement accurately, were 67.1% (95% confidence interval (CI), 59.2–74.3%) and 66.6% (95% CI, 49.8–80.9%), respectively (area under the curve (AUC) = 0.707; $p = 0.0001$).

Statistical Analysis

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software. The significance of the differences among the means were determined by the Mann-Whitney U-test and Kruskal-Wallis test. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test. Disease-free survival (DFS) was defined as the time from curative surgery to disease progression or recurrence or to the date of death or last known contact. In addition, OS was described as the time from diagnosis to the date of the patient’s death or last known contact. The ROC curve was calculated to indicate the variability of sensitivity and specificity for cutoff points of different numbers of dissected lymph nodes, which was considered as disease stage [27]. Univariate and multivariate analysis of prognostic factors related to survival were performed with the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. The 95% CI was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were considered to be statistically significant.

Results

A total of 202 patients with radically resected gastric cancer were retrospectively analyzed. Of those, 66 were women and 136 were men. The median age was 60 ranging from 29 to 87 years. Ninety-eight patients were younger than 60 years (48.5%). The median number of dissected and metastatic lymph nodes were 20 (range, 3–67) and 3 (range, 0–62), respectively. Based on the number of lymph node metastasis, 39 (19.3%) patients were classified as pN0, 74 (36.6%) as pN1, 54 (26.7%) as pN2, and 35 (17.3%) as pN3. The majority of patients were T3 (108 patients, 53.5%). The correlation between the n ratio and the clinicopathological findings are shown in table 1. The n ratio was significantly greater in cases with undifferentiated tumor, a large tumor, tumors with LVI,

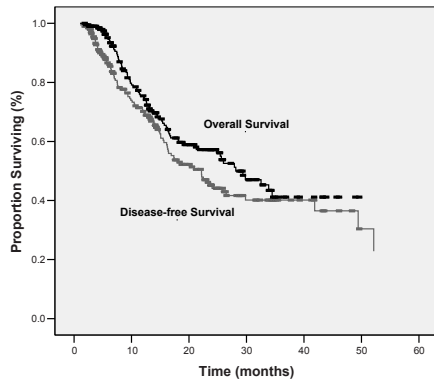


Fig. 1. Disease-free survival and overall survival in all gastric carcinoma patients who had undergone curative gastrectomy.

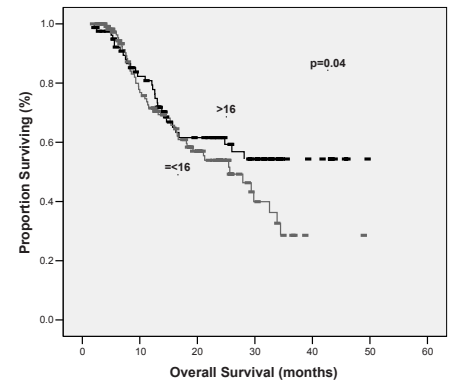


Fig. 2. Overall survival curves according to the number of resected lymph nodes (<16 vs. >16).

BVI and PNI, and advanced stage. In addition, the n ratio was significantly correlated with the pT and pN classification.

At the median follow-up of 19.5 months (range, 3.5–97), 3-year DFS and OS were 40.1 and 41.1%, respectively. The median DFS time was 22.1 months (standard error (SE), 2.6; 95% CI, 16.9–27.3), and the median OS time was 28.1 months (SE, 3.2; 95% CI, 21.7–34.5) (fig. 1). The subgroup analysis indicated that one of the 38 stage II patients was pT1N1, 24 (63.1%) patients were pT2N1, and 13 (34.2%) patients were pT3N0. In stage IIIA, 12 (25%) cases with pT2N2, 35 (72.9%) cases with pT3N1, and 1 (2.1%) patient with pT4N0 were detected. There was no significant difference for OS and DFS found according to subgroup analysis in the stage II and IIIA groups ($p > 0.05$).

Using n ratio classification, 39 (19.3%) patients were classified as n ratio 0, 19 (9.4%) patients as n ratio 1, 39 (19.3%) patients as n ratio 2, and 105 (52%) patients as n ratio 3. The median OS time was 64.9 in n ratio 0, 32.5 in n ratio 2, and 16.8 in n ratio 3 ($p = 0.001$). The median OS interval was not reached in the n ratio 1 group.

In the majority of patients (59.9%), >16 lymph nodes had been dissected during surgery. Three-year DFS and OS were 50.3 and 54.3%, respectively. However, in patients with <16 lymph nodes examined, DFS and OS were 25.5 and 28.6%. The median OS interval was 64.9 and 25.6 months according to the number of resected lymph nodes in both groups. The OS rate and median OS interval of patients with <16 lymph nodes resected were significantly worse than those of patients with >16 lymph nodes resected ($p = 0.04$; table 2, fig. 2).

The univariate analysis showed that tumor size, depth of invasion, LVI, BVI, PNI, pN classification, n ratio, and the number of dissected lymph nodes (<16 vs. >16) were important prognostic factors. The results of the univariate analysis are listed in table 2. The n ratio is closely associated with OS of patients with radically resected gastric cancer in univariate analysis. Therefore, we carried out a multivariate analysis with the Cox proportional hazards model in order to further evaluate the prognostic significance of the n ratio. Multivariate analysis indicated that n ratio and pN classification were independent prognostic factors ($X^2: 10.6, p =$

0.001, hazard ratio (HR), 1.45; 95% CI, 1.16–1.88; $X^2, 15.8; p < 0.0001$; HR, 11.6; 95% CI, 3.47–38.9), as were age (<60 vs. >60 years), tumor size, Borrmann classification, PNI, and tumor differentiation. Table 3 shows the results of the multivariate analysis.

Discussion

In the present study, we found that the n ratio and pN classification are independent prognostic indicators in patients with radically resected gastric cancer. Two main staging systems for gastric cancer include the UICC and JCGC. The most important difference between these staging systems is the method of evaluating the status of lymph node metastasis, which influences survival in resectable gastric cancer. Accurate and uniform disease staging is essential to predict prognosis and to determine treatment modality in gastric cancer. In the JCGC system, the regional lymph nodes are classified into 3 groups (N1–N3) based on the location of positive lymph nodes in relation to the primary tumor, whereas the UICC system is based on the number of metastatic lymph nodes alone [10, 11]. Although it remains unreliable as to which is the most important, the location or the number of metastatic lymph nodes, some studies showed that the number of metastatic lymph nodes, but not their level, is an independent prognostic indicator [28, 29].

Previous reports have emphasized the superiority of the UICC/AJCC TNM staging system, because of its simplicity, reliability, and stratification [8, 30]. On the other hand, in this staging system, the number of resected lymph nodes is very important because stage migration occurs in 5–15% of cases [14]. To resolve these limitations, recently n ratio as a new prognostic factor has been proposed by several authors [14, 15, 18, 26]. It has proved to be a good alternative to prevent the stage migration phenomenon, and it is also usable in patients with < 15 lymph nodes dissected, or D1 lymphadenectomy, or noncurative resection [14–21]. In our study, the n ratios' mean was significantly greater in tumors with undifferentiated histology, greater size, LVI, BVI, PNI, and advanced

stage. Furthermore, the n ratio was significantly correlated with depth of invasion and pN classification. Our results were compatible with the literature [26].

Univariate analysis indicated that tumor size, LVI, BVI, PNI, pT, pN classification, and n ratio were statistically significant prognostic factors. However, both n ratio and pN classification were the most significant prognostic factors in the multivariate analysis, but a higher HR was obtained when pN classification was compared with n ratio (11.6 vs. 1.45). Although several authors have shown the superiority of n ratio compared with pN classification in the literature [25, 26], we did not find that n ratio was superior to pN classification. This difference to previous literature may be related to small sample size in our study.

In a study including 164 Turkish patients with D2 lymph node dissection [25], the authors found that sex, age, tumor location, tumor size, Borrmann classification, Lauren classification, lymphovascular invasion, pT, pN classification, and n ratio were statistically significant prognostic factors in a univariate analysis. In addition, in the multivariate analysis, Borrmann classification, pN classification, and n ratio were found as the most significant prognostic factors in their study, whereas the significance of age and pT classification was lost in step 5 of the analysis. We found that pT, pN classification, and n ratio were significant prognostic indicators as compatible with their results, whereas age and sex were not detected as prognostic factors by univariate analysis. On the other hand, age together with pN classification, n ratio, tumor size, Borrmann classification, PNI, and tumor differentiation were independent prognostic factors. This mild difference may be associated with our heterogeneous population including patients with D1, D2, and D3 lymph node dissection.

Bando et al. [15] reported that there was a statistically significant difference between the survivals of patients within n ratio groups. Kodera et al. [18] analyzed 656 gastric cancer patients who had had a D2 lymphadenectomy, and they reported that there were significant differences among n ratio groups. In the study carried out by Inoue et al. [17], n ratio was selected as the most significant prognostic factor in 474 patients who underwent an R0 resection and D2 lymph node dissection.

We found significant differences in OS rate and median OS time for n ratio groups of 0, 1–9%, 10–25%, and >25%, and in the multivariate analysis n ratio and pN classification were de-

tected to be an independent prognostic factor. Saito et al. [26] studied 777 gastric cancer patients who had undergone curative gastrectomy. They reported that n ratio but not pN classification was an independent prognostic factor. The authors concluded that the n ratio was useful for evaluating the status of lymph node metastasis in gastric cancer [26]. Celen et al. [25] showed that both pN classification and n ratio were the most significant prognostic factors, and a higher HR was obtained for n ratio than for pN classification [25]. Our findings are compatible with their results.

We included patients with a D1 lymphadenectomy. Because the number of lymph node metastases is sometimes affected by the number of lymph nodes dissected, in cases with D1 lymphadenectomy stage migration might occur. The ROC analysis calculated that the dissection of 16 lymph nodes during surgery was required to assess the presence of lymph node involvement. The OS rate and median OS interval of patients with < 16 lymph nodes resected were significantly worse than those of patients with > 16 lymph nodes resected during surgery (54.3%, 64.9 months vs. 28.6%, 25.9 months, respectively, $p = 0.04$). However, this significance was not detected in the multivariate analysis.

In conclusion, our study indicated that n ratio and pN classification were independent prognostic indicators for OS for patients with radically resected gastric cancer. However, the superiority of n ratio over pN classification could not be proved. This may be related to the insufficient sample size of our study. The n ratio is a useful and reliable technique for evaluating lymph node metastasis.

Supplemental Table Files

Table 1. Correlation between n ratio and clinicopathological characteristics

Table 2. Overall survival (OS) in univariate analysis according to clinicopathological factors

Table 3. Multivariate analysis of various clinicopathological factors in patients with radically resected gastric cancer

To access the tables please refer to www.karger.com/DOI=000277927.

Conflict of Interest

The authors declare no conflict of interest.

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