

# Prognostic Significance of N1 and N2 Metastatic Lymph Node Ratio After Distal Gastric Cancer Surgery

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## Research

**Keywords:** Gastric Cancer, Radical Gastrectomy, Metastasis Lymph Node Ratio of N1, Metastasis Lymph Node Ratio of N2, Prognosis

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# Abstract

**OBJECTIVE:** To investigate prognostic significance of n1 and n2 station metastatic lymph node ratio(rN) after distal gastric cancer surgery.

**METHODS:** A total of 408 patients who underwent radical distal gastrectomy (D2) under general anesthesia in 2012-2014. The critical value of rN1 and rN2 were calculated respectively. Prognostic factors were identified by univariate and multivariate analyses.

**RESULTS:** An rN1 of 0.140 and rN2 of 0.100 was found to be the best cut-off value to determine the prognosis of patients with distal gastric cancer ( $p < 0.001$ ). Univariate and multivariate analysis show that gender, age, nerves invaded, carcinoma nodules, LNS, LNS1, LNS2 were non-prognostic factors. tumor size, depth of invasion, blood vessels invaded, degree of differentiation, rN, PLNS1, rN1, PLNS2, rN2, pTNM were prognostic factors. Among prognostic factors, the partial regression coefficients were, from high to low, pTNM, rN2, rN2, rN.

**CONCLUSION:** RN1 and RN2 is a better prognostic tool for gastric cancer patients after curative distal gastrectomy. which is a beneficial and reliable technique for evaluating lymph node metastasis.

## Introduction

Gastric cancer is a common malignant tumor in the world, as is digestive. According to epidemiological survey of the national cancer registration, gastric cancer ranks the second in incidence and fatality in China, with nearly 500,000 patients dying every year[1], resulting a heavy medical treatment and public health burden and restricting health needs of people. In recent years, with the continuous updating guidelines at home and abroad and the deepening of evidence-based medicine research, the standardized operation and comprehensive treatment of gastric cancer surgery have been widely promoted in clinical in China. [2]. With a progress of endoscopic diagnosis and treatment, the proportion of early gastric cancer haven increased, but advanced still accounts more than 80%.[3], So surgery will still play an important role in the treatment of gastric cancer for a long time. However, postoperative still have a high rate of local recurrence and distant metastasis.[4]. Currently, no one effective treatment for recurrence. So accurate judgment of postoperative will evaluate the state of the disease. The precise stage involves a series of troubles, such as prognosis, follow-up treatment, treatment plan and the time of treatment. In clinical, the 8th TNM staging system (UICC/AJCC) have been accepted widely. The TNM divided patients into different stages according to the depth of tumor invasion (stage T), the number metastasis lymph node (stage N) and distant metastasis (stage M)[5-6]. The pN of TNM(UICC/AJCC) has the phenomenon of "staging migration"[7-8]. In view of staging migration of pN, some researchers proposed that metastasis lymph node ratio, that is, the ratio of metastatic positive lymph nodes to dissected lymph nodes, as a new index of gastric cancer for prognostic [9,10]. Metastasis lymph node ratio is an important prognostic index for patients of gastric cancer, and precise staging is crucial for follow-up treatment of postoperative. Although there are some studies on metastasis lymph node ratio about the prognosis of

gastric cancer, Although there are some studies on metastasis lymph node ratio about the prognosis of gastric cancer, but which all were on rN, and prognostic significance of n1 and n2 metastatic lymph node ratio after distal gastric cancer surgery has not been reported.

## Patients And Methods

From January 2010 to January 2014, a total of 618 patients were diagnosed as gastric cancer by pathological after endoscopic biopsy in our hospital. 449 patients chose to surgical treatment. However, only 408 patients met the following conditions: The tumor only in the lower third of stomach; confirmed by pathology to be gastric cancer; no distant metastasis in preoperative and intraoperative examination; radical gastrectomy with D2 or D2+ lymph node dissection, and the number of dissected lymph nodes was more than 15; R0 resection confirmed by pathology of postoperative; postoperative lymph nodes were sorted according by 15th edition of Japanese Gastric Cancer Management Protocol<sup>[12]</sup> (all sorted by physicians with senior research expertise in the specialized field of gastric cancer. Collect pathological data, including: gender, age, tumor size, depth of invasion, blood vessels invaded, nerves invaded, carcinoma nodules, degree of differentiation, LNS, rN, LNS1, PLNS1, rN1, LNS2, PLNS2, rN2, and pTNM. Survival time, whether Survival with tumor. The basic criterion includes the absence of macroscopic or microscopic residual tumors. The survival time was the time when diagnosis was made to the last contact, or to the date of death, or to the date when the survival information was collected. All surviving patients were followed up for more than 5 years. All behaviors were carried out with the consent of family members and approved by local ethics committee.

**STATISTICAL ANALYSIS:** All data were analyzed by SPSS 24.0 (IBM Corp., Armonk, NY, USA) software. The best cut-off value of rN1 and rN2 were obtained by survival analysis, kaplan-meier, log-rank. Univariate and multivariate analyses were performed with the Cox proportional hazards model to evaluate the importance of clinicopathologicals as prognostic factors.  $P < 0.05$  were considered statistically significant.

## Results

### *Clinicopathological parameters (Table 1).*

The clinicopathological parameters of patients are summarized in Table 1. A total of 408 cases were included in the analysis, there were 272 males (66.7%) and 136 females (33.3%) at the age of 35-83 years ( $58.30 \pm 10.63$  years). The tumor diameter was  $4.55 \pm 1.87$  cm. Based on the 8th TNM (UICC/AJCC), 48 were at stage pT1 (11.8%), 48 at stage pT2 (11.8%), and 280 at pT3 (68.6%), 32 at pT4 (7.8%), respectively. As for degree of differentiation, 136 were differentiated (33.3%) and 272 were undifferentiated (66.7%). There were 244 (40.2%) vascular invasions and 164 (59.8%) non-invasions. There were 244 (40.2%) nerve invasion and 164 (59.8%) nerve non-invasion. Cancer nodules were 36 (8.8%) and absent 372 (91.2%). LNS ranged from 12 to 73 ( $31.88 \pm 10.80$ ). PLNS ranged from 0 to 32 ( $7.55 \pm 8.10$ ). rN was 0-0.911 ( $0.230 \pm 0.231$ ). rN1 was 0-0.840 ( $0.245 \pm 0.237$ ). rNS1 was 0-1.000 ( $0.178 \pm 0.266$ ).

### ***The influence of rN1 and rN2 on the prognosis for patients (figure1.2):***

The best cut-off values of rN1 and rN2 ,were calculated by survival analysis and kaplan-meier and log-rank,were 0.140 and 0.100, respectively. There was significant difference in 5-year survival ratio between rN1 >0.140 and rN1 <0.140 ( $p<0.05$ ). As rN1 gradually increased, the 5-year survival ratio gradually declined.When rN1 exceeded 0.140, 5-year survival ratio significantly decreased, which was statistical significance. The same as above,it was significant difference for rN2 >0.100 and rN2 <0.100 ( $p<0.05$ ). As rN2 gradually increased, 5-year survival ratio gradually decreased. When rN2 exceeded 0.100, 5-year survival ratio significantly decreased, which was statistically significant.

***Univariate and multivariate analysis (Table 2, Table 3) :*** Univariate and multivariate analysis of prognostic factors were analyzed by Cox proportional hazards model,gender (B= -0.170 P=0.551>0.05), age (B= 0.015 P=0.255>0.05), nerves invaded (B=0.507 P=0.063>0.05),LNS(B=0.017 P=0.175>0.05),LNS1 (B=0.021 P=0.139>0.05), LNS2(B=0.007 P=0.858>0.05) were non-prognostic factors,tumor size(B=0.501 P=0.001<0.05), depth of invasion(B=0.989 P=0.001<0.05),blood vessels invaded (B=0.619 P=0.023<0.05),carcinoma nodules(B= 0.825 P=0.042<0.05),degree of differentiation(B=0.484 P=0.038<0.05),rN(B=2.424 P=0.001<0.05),PLNS1(B=0.098P=0.001<0.05),rN1(B=3.244 p=0.001<0.05),PLNS2(B=0.126 p=0.001<0.05), rN2(B=3.664 p=0.001<0.05), pTNM (B=3.861 p=0.001<0.05) were prognostic factors. Among factors, the prognostic factors were pTNM > rN2 > rN1 >rN, it is suggested that rN1 and rN2 are effective and reliable prognostic index.

## **Discussion**

Gastric cancer is one of the most common malignant tumors in the world, causing thousands of deaths each year and remains a global health burden. [13]. With the introduction of new treatment concepts for gastric cancer, surgical treatment just a part of treatment process, and postoperative treatment plays an increasingly important role. The postoperative treatment mainly depends on pathological and the precise staging of postoperative. According to historical literature, the TNM stage of 8th edition is determined by the number of metastatic lymph nodes. It is an international consensus that 15 or more metastatic lymph nodes must be removed during radical gastrectomy [14]. However, the difficulties and technical gaps in lymph node selection from postoperative specimens,even tiny lymph nodes, and the gap of technical in dissect lymph node by surgeons will lead to staging migration, affect the stage, which will affect the prognosis of patients due to the wrong postoperative treatment schedule. According to historical literature,metastatic lymph nodes ratio can reduce staging migration[15-16]. At present, there have been some studies on the effect of metastasis lymph node ratio on prognosis of gastric cancer, and the role of metastasis lymph node ratio has been confirmed. Our findings suggest that: gender, age, nerves invaded,LNS,LNS1, LNS2 were non-prognostic factors,tumor size, depth of invasion,blood vessels invaded,carcinoma nodules,degree of differentiation,rN,PLNS1,rN1,PLNS2, rN2, pTNM were prognostic factors. This is consistent with the studies of S. R. Lee. Et al. [17] and J R Siewert.et al. [18]. Generally speaking, nerves invaded indicates a poor prognosis. However, the analysis in this study concluded that nerves invaded was not statistically significant, the probable cause is the statistical error. multivariate

analysis of prognostic factors were analyzed by Cox proportional hazards model, the prognostic factors were pTNM > rN2 > rN1 > rN, it is suggested that rN1 and rN2 are effective and reliable prognostic index. Secondly, survival analysis of rN1 and rN2 suggests: when the value of rN1 exceeded 0.140 or rN2 exceeded 0.100 and increased gradually, the 5-year survival ratio decreased significantly, showing statistical significance, which was a point of this retrospective study. Since there has been no relevant literature report, it is difficult to make a comparative judgment. The clinical significance of this research needs to be confirmed by more prospective study results.

## Conclusions

In conclusion, when the TNM is delayed, the value of rN2 more than 0.01, and the value of rN1 more than 0.140, biggest tumor, undifferentiation, nerve invasion, Cancer nodules, the prognosis is poor, and a postoperative comprehensive treatment can be conducted to achieve a better prognosis.

## Abbreviations

**LNS:** The number of lymph nodes dissected

**LNS1:** The number of N1 lymph nodes dissected

**LNS2:** The number of N2 lymph nodes dissected

**PLNS:** The number of positive lymph nodes dissection

**PLNS1:** The number of N1 positive lymph nodes dissection

**PLNS2:** The number of N2 positive lymph nodes dissection

**rN:** Metastasis lymph node ratio

**rN1** Metastasis N1 lymph node ratio

**rN2** Metastasis N2 lymph node ratio

## Declarations

### ***AVAILABILITY OF DATA AND MATERIALS:***

All data generated or analyzed during this study are included in the articles.

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**Contributions:** Data collection and analysis were performed by Wan Bai, Yin-Chun Wang. The other authors contributed to the literature study analysis for discussion and participated in surgical procedures. All authors read and approved the final manuscript in its present form.

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**ETHICS DECLARATIONS:**

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Yes.

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## Figures

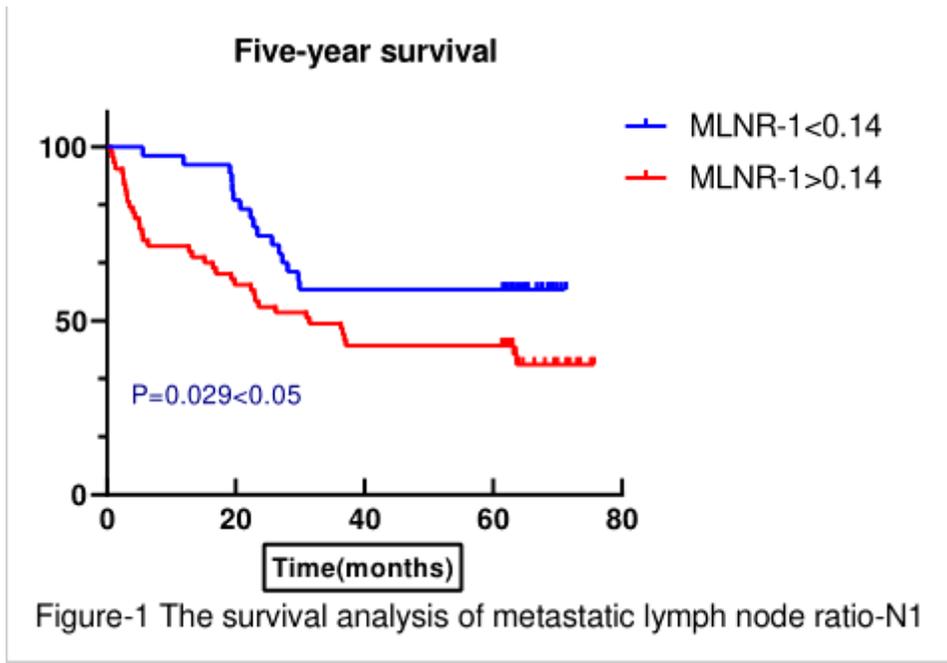


Figure 1

Figure 1

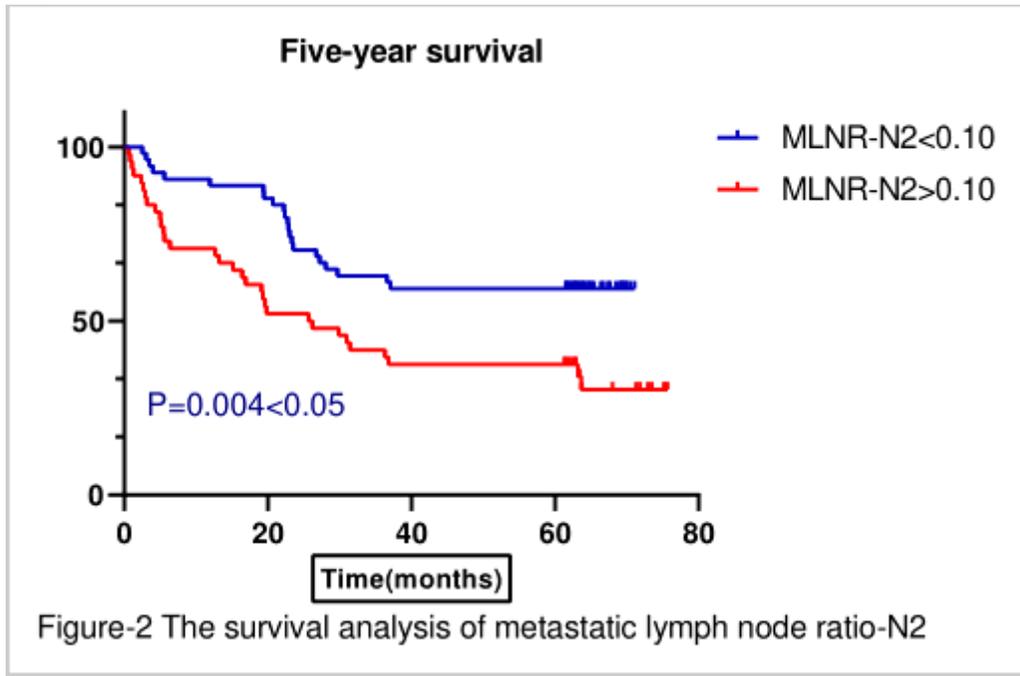


Figure 2

Figure 2

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