

Prognostic impact of metastatic lymph node ratio on gastric cancer after curative distal gastrectomy

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Abstract

AIM: To investigate the prognostic impact of metastatic lymph node ratio (rN) on gastric cancer after curative distal gastrectomy.

METHODS: A total of 634 gastric cancer patients who underwent curative resection (R0) of lymph nodes at distal gastrectomy in 1995-2004. Correlations between positive nodes and retrieved nodes, between rN and retrieved nodes, and between rN and negative lymph node (LN) count were analyzed respectively. Prognostic factors were identified by univariate and multivariate analyses. Staging accuracy of the pN category (5th UICC/TNM system) and the rN category was compared according to the survival rates of patients. A linear regression model was used to identify the relation between rN and 5-year survival rate of the patients.

RESULTS: The number of dissected LNs was related with metastatic LNs but not related with rN. Cox regression analysis showed that depth of invasion, pN and rN category were the independent predictors of survival ($P < 0.05$). There was a significant difference in survival

between LN stages classified by the rN category or by the pN category ($P < 0.05$). However, no significant difference was found in survival rate between LN stages classified by the pN category or by the rN category ($P > 0.05$). Linear regression model showed a significant linear correlation between rN and the 5-year survival rate of gastric cancer patients ($\beta = 0.862$, $P < 0.001$). Pearson's correlation test revealed that negative LN count was negatively correlated with rN ($P < 0.001$).

CONCLUSION: rN category is a better prognostic tool than the 5th UICC pN category for gastric cancer patients after curative distal gastrectomy. Increased negative LN count can reduce rN and improve the survival rate of gastric cancer patients.

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Key words: Stomach neoplasm; Gastrectomy; Lymphadenectomy; Metastatic lymph node ratio; Prognosis

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INTRODUCTION

Gastric cancer, a common malignancy worldwide, is the

second most common cause of cancer-related death^[1]. Despite recent advances in multimodality treatment and targeted therapy, complete resection remains the only curative treatment modality. Lymph node metastasis is one of the most important prognostic factors for gastric cancer^[2-4], and accurate categorization of lymph node metastasis or optimization of pN category is critical for decision making of its subsequent therapies after surgery. Compared with total gastrectomy, distal gastrectomy is one of the most important operative procedures for gastric cancer, which can decrease postoperative morbidity and mortality and improve the postoperative life quality and nutrition condition of gastric cancer patients^[5-8]. Although there are some studies on the prognostic significance of rN in gastric cancer^[9-11], few relevant researches are available on gastric cancer after curative distal gastrectomy. Therefore, the aim of this retrospective study was to evaluate the prognostic value of metastatic lymph node ratio (rN) for gastric cancer after curative distal gastrectomy.

MATERIALS AND METHODS

Between January 1995 and November 2004, 1289 patients diagnosed as primary gastric cancer were treated with curative resection at Department of Oncology, Fujian Medical University Union Hospital (Fuzhou, China). Of the 1289 patients, 709 underwent distal gastrectomy, 75 were excluded from the study for T4 lesions in order to avoid data heterogeneity due to more extensive resections and higher positive margins. Finally, 634 patients were enrolled in this study. Curative surgery was defined as complete tumor removal with no macroscopic residual tumor, no invasion of carcinoma cells in the margin, and no evidence of distant metastasis. Clinical and histopathologic data about each patient were classified according to the Japanese Classification of Gastric Carcinoma (JCGC)^[12]. Lymph nodes were meticulously dissected from the *en bloc* specimens, and the dissected lymph nodes were classified by surgeons who reviewed the excised specimens after surgery based on the JCGC. Based on the 5th edition of UICC/TNM system^[13], pN category was defined as pN0 with no metastatic lymph nodes, pN1 with 1-6 metastatic lymph nodes, pN2 with 7-15 metastatic lymph nodes, and pN3 with > 15 metastatic lymph nodes, respectively. rN intervals were determined using the best cut-off approach and the survival rate of patients (log-rank statistic) was considered a dependent variable. The best-fit cut-off values of rN intervals were rN0: 0%, rN1: 1%-20%, rN2: 21%-50%, and rN3: > 50%, respectively. The patients were followed up by trained investigators through e-mail, telephone, visiting patients or recording the consultations of patients at the outpatient clinic. 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. The median follow-up time of

Table 1 Clinical parameters of patients included in this study
n (%)

Characteristics	Patients (<i>n</i> = 634)
Gender	
Male	467 (73.6)
Female	167 (26.4)
Age (yr)	56.1 ± 12.1
Tumor size (cm)	4.3 ± 1.7
Tumor location	
Lower	521 (80.8)
Middle	71 (11.2)
Lower and middle	42 (8.0)
Digestive tract construction	
Billroth I	469 (74.0)
Billroth II	148 (22.3)
Roux-en-Y	17 (3.7)
Pathology	
Differentiated	140 (22.1)
Undifferentiated	494 (77.9)
Depth of invasion	
pT1	118 (18.6)
pT2	174 (27.4)
pT3	342 (54.0)
pN category	
pN0	195 (30.8)
pN1	232 (36.6)
pN2	156 (24.6)
pN3	51 (8.0)
rN category	
rN0	195 (30.8)
rN1	172 (27.1)
rN2	156 (24.6)
rN3	111 (17.5)
Number of resected LNs	23.1 ± 8.6

the entire cohort was 62.0 mo (range 1-172 mo). A total of 591 patients were followed up, accounting for 93.2%.

Statistical analysis

Pearson's correlation coefficient (*r*) was used to study the relations between positive nodes and retrieved nodes, between rN and retrieved nodes, and between rN and negative LN count. Survival rate was calculated with the Kaplan-Meier method. Cox proportional hazard model was used in multivariate analysis, with a backward elimination model for all covariates. A linear regression model was established to correlate rN with survival based on Kaplan-Meier 5-year survival estimates at each rN interval, using 5% of rN interval as an independent variable. *P* < 0.05 was considered statistically significant. All statistical analyses were performed using the statistical package for social science (SPSS) version 13.0 for Windows.

RESULTS

Clinicopathological parameters of patients

The clinicopathological parameters of patients are summarized in Table 1. There were 467 males and 167 females at the age of 22-87 years (56.1 ± 12.1 years). The tumor diameter was 4.3 ± 1.7 cm. Gastric cancer was found at the lower third (L), lower and middle third (LM),

and middle third (M) of stomach in 521, 41, and 71 patients, respectively. Based on the Japanese Classification of Gastric Carcinoma^[12], 118 were at stage pT1, 174 at stage pT2, and 342 at pT3, respectively. As far as the histological grades were concerned, 140 were differentiated and 494 were undifferentiated. Lymph node metastasis was observed in 439 patients (69.2%). Based on the 5th UICC/TNM pN category^[13], 195 patients (30.8%) were classified as pN0, 232 (36.6%) as pN1, 156 (24.6%) as pN2 and 51 (8.0%) as pN3, respectively. Using the rN category, 195 patients (30.8%) were classified as rN0, 172 (27.1%) as rN1, 156 (24.6%) as rN2, and 111 (17.5%) as rN3, respectively. The median of total LN number was 23 (range 5-61, mean 23.1 ± 8.6) in each patient.

Correlation between LN metastasis and retrieved nodes

Pearson's correlation test showed that the number of metastatic lymph nodes was significantly related with that of retrieved nodes ($r = 0.252$, $P < 0.001$, Figure 1A), but the rN was not related with the number of retrieved nodes ($r = -0.075$, $P > 0.05$, Figure 1B).

Univariate and multivariate survival analysis

The 5-year survival rate of the entire cohort was 57.6%. The clinicopathological variables tested in univariate analysis are shown in Table 2. The factors influencing the 5-year survival rate were tumor diameter ($P = 0.036$), pathology types ($P = 0.003$), depth of invasion ($P < 0.001$), pN category ($P < 0.001$) and rN category ($P < 0.001$). The covariates of gender ($P = 0.991$), age ($P = 0.423$), tumor location ($P = 0.058$) and digestive tract construction ($P = 0.064$) had no significant influence on the survival rate. Multiple survival rates were calculated with the Cox's proportional hazard regression model. In order to confirm the influence of rN, the prognostic factors including tumor diameter, pathology types, depth of invasion and pN category except for rN category in univariate analysis were analyzed by stepwise regression. As a result, two independent prognostic parameters, namely depth of invasion ($P < 0.001$) and pN category ($P < 0.001$), were obtained. When rN category was included in the Cox's regression, the two independent prognostic parameters were also obtained. The risk ratios and their 95% confident interval are listed in Table 3.

Comparison of survival rates between subsets of patients in either LN classification

The subgroups of patients, defined by the pN category, were discriminated with rN category. A significant difference was observed in survival rates between LN stages classified by the rN category or by the pN category ($P < 0.05$, Table 4), whereas no significant difference was found in survival rates between LN stages classified by the pN category or by the rN category (Table 5).

Projected rN impact on overall survival rate

The linear regression model demonstrated that the regression equation of assumed linearity was $y = -0.814x + 74.4$ ($\beta = 0.862$, $P < 0.001$). The regression line of this

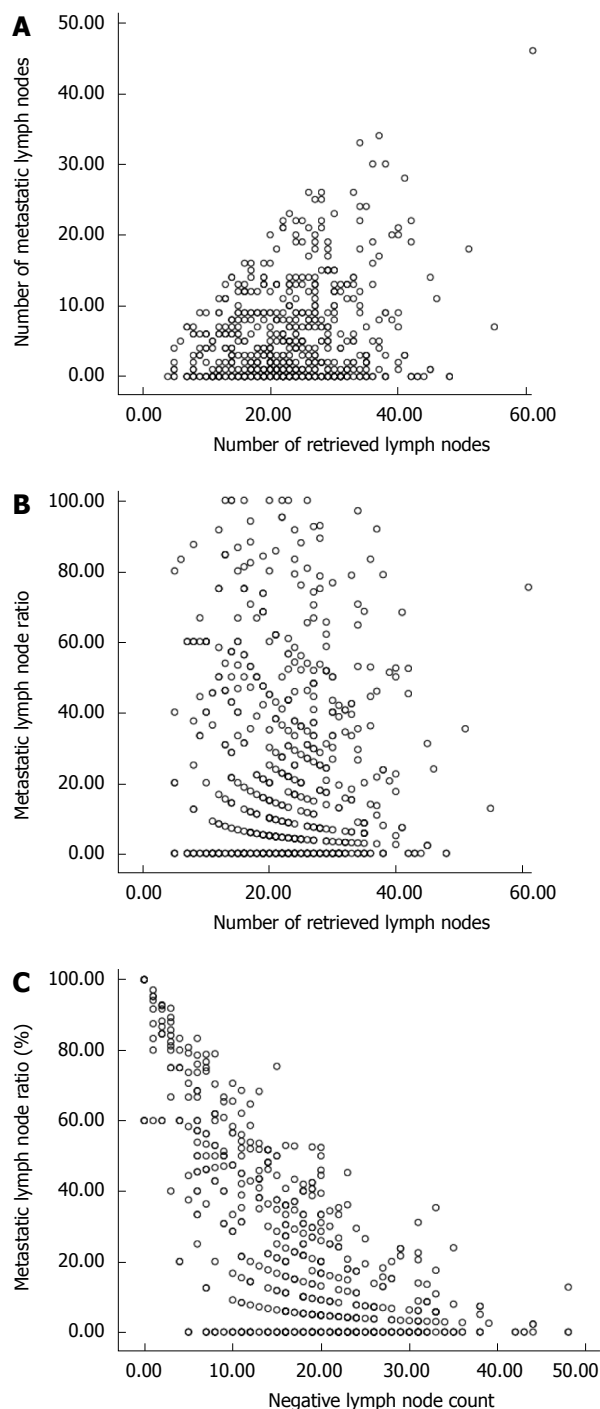


Figure 1 Pearson's correlation tests. A: A significant correlation between the number of lymph node metastases and retrieved lymph nodes; B: No significant correlation between the metastatic lymph node ratio and the number of retrieved lymph nodes; C: A significant correlation between rN and the negative lymph node count.

calculated rN effect on the 5-year survival rate is shown in Figure 2. The hypothetical baseline 5-year survival rate (based on the y-intercept, i.e. 0% rN) was 74.4%. When rN was increased 10%, the calculated 5-year survival rate was decreased by 8.14%.

Correlation analysis between rN and negative LN count

Pearson's correlation test showed that the negative LN

Table 2 Univariate analysis of variables for gastric cancer patients after curative distal gastrectomy

Parameters	n	5-yr survival (%)	χ^2	P
Gender			< 0.001	0.991
Male	467	58.1		
Female	167	56.3		
Age (yr)			0.641	0.423
< 60	370	58.9		
≥ 60	264	56.0		
Tumor size (cm)			4.409	0.036
≤ 4	343	61.0		
> 4	291	53.6		
Tumor location			5.693	0.058
Lower	521	57.7		
Middle	71	63.7		
Lower and Middle	42	45.4		
Digestive tract construction			5.508	0.064
Billroth I	469	60.7		
Billroth II	148	48.5		
Roux-en-Y	17	51.0		
Pathology			9.135	0.003
Differentiated	140	68.1		
Undifferentiated	494	54.6		
Depth of invasion			70.466	0.000
pT1	118	90.6		
pT2	174	64.4		
pT3	342	42.9		
pN category			142.279	0.000
pN0	195	83.3		
pN1	232	59.3		
pN2	156	33.9		
pN3	51	20.0		
rN category			217.494	0.000
rN0	195	83.3		
rN1	172	68.6		
rN2	156	40.7		
rN3	111	17.2		

Table 3 Multiple stepwise regression analysis with the Cox proportional hazards model

Parameters	β	SE	Wald	P	RR	95% CI
rN excluded						
Tumor size	-0.025	0.117	0.045	0.832	0.976	0.776-1.227
Pathology	0.000	0.161	0.000	0.999	1.000	0.730-1.370
Depth of invasion			27.144	0.000		
pT2 vs pT1	0.956	0.259	13.59	0.000	2.601	1.565-4.325
pT3 vs pT1	1.253	0.247	25.668	0.000	3.500	2.156-5.683
pN category			20.572	0.000		
pN1 vs pN0	0.556	0.188	8.754	0.003	1.734	1.206-2.519
pN2 vs pN0	0.829	0.203	16.673	0.000	2.291	1.539-3.410
pN3 vs pN0	1.02	0.248	16.916	0.000	2.772	1.705-4.507
rN included						
Tumor size	-0.033	0.117	0.078	0.779	0.968	0.769-1.218
Pathology	0.011	0.161	0.005	0.945	1.011	0.738-1.385
Depth of invasion			24.388	0.000		
pT2 vs pT1	0.908	0.263	11.974	0.001	2.48	1.483-4.149
pT3 vs pT1	1.206	0.252	22.827	0.000	3.34	2.036-5.477
rN category			17.927	0.000		
rN1 vs rN0	0.502	0.199	6.349	0.012	1.651	1.118-2.440
rN2 vs rN0	0.842	0.205	16.928	0.000	2.322	1.554-3.468
rN3 vs rN0	0.867	0.234	13.758	0.000	2.380	1.505-3.763

β : Coefficient of regression.

Table 4 Comparison of survival rates for patients classified by rN category or by pN category

N stage	n	rN1		rN2		rN3		P
		n	OS (%)	n	OS (%)	n	OS (%)	
pN1	232	169	68.6	54	36.3	9	22.2	0.000
pN2	156	3	66.7	95	40.8	58	20.4	0.007
pN3	51	NA	NA	7	57.4	44	11.6	0.012

OS: Overall 5-year survival rate; NA: Not applicable.

Table 5 Comparison of survival rates for patients classified by pN category or by rN category

N stage	n	pN1		pN2		pN3		P
		n	OS (%)	n	OS (%)	n	OS (%)	
rN1	147	169	68.6	3	66.7	NA	NA	0.638
rN2	156	54	36.3	95	40.8	7	57.4	0.188
rN3	51	9	22.2	58	20.4	44	11.6	0.257

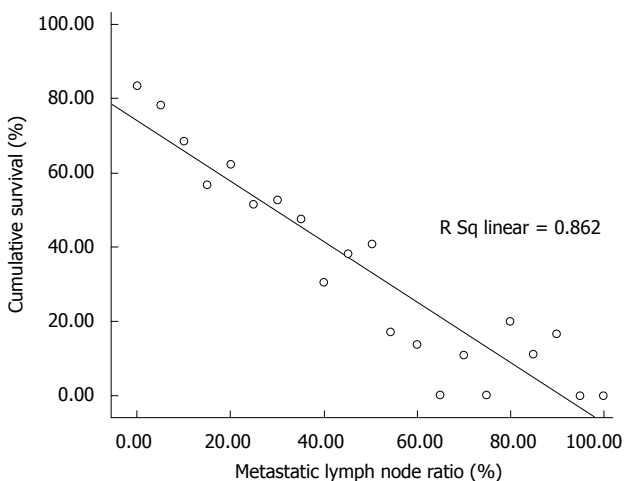


Figure 2 Regression line of rN impact on the 5-year survival rate.

count was negatively correlated with rN ($r = 0.684$, $P < 0.001$, Figure 1C).

DISCUSSION

Accurate staging of gastric cancer is of great importance

in clinical practice, especially when adjuvant treatment is considered. Metastasis to lymph nodes is considered the main prognostic factor for gastric cancer patients who undergo radical resection. In 1997, the International Union against Cancer (UICC) proposed that the category of lymph node involvement should be classified according to the number of metastatic lymph nodes. It has been reported that the category based on the number of metastatic lymph nodes is more sensitive than that based on the location of metastatic lymph nodes in prognostic eval-

uation of gastric cancer^[14-16]. However, the UICC/TNM classification (5th edition) only recommended that 15 or more lymph nodes should be examined for the accurate staging of gastric cancer. From the statistical viewpoint, the number of metastatic lymph nodes increases in proportion to the number of dissected nodes, suggesting that pN category can be influenced by the extent of lymphadenectomy. In addition, the pN category may be changed by adding or reducing one positive lymph node, suggesting that gastric cancer classified as N1 after limited lymph node dissection may be classified as N2 or N3 after extensive lymphadenectomy. This phenomenon is the so-called stage migration^[17,18]. Sun *et al.*^[19] reviewed 2159 gastric cancer patients who underwent gastrectomy with a curative intent, and found that there is a closed linear correlation between the number of retrieved LNs and the number of metastatic nodes, while there is no correlation between rN and the number of retrieved nodes, which is consistent with the results of our present study, suggesting that patients with identical rN, even with a different number of detected metastatic nodes, will have a similar outcome, and that rN category is superior to the 5th UICC/TNM classification in terms of minimizing stage migration.

Fukuda *et al.*^[20] compared the pN category of the UICC/TNM in 1997 with a classification based on the metastatic lymph node ratio in patients who underwent R0 resection using the regression analysis, and identified that the metastatic lymph node ratio is the most important prognostic factor for gastric cancer. The results of univariable and multivariable analyses of potential prognostic factors in this study showed that the rN category was one of the independent prognostic parameters. Kunisaki *et al.*^[21] analyzed 1472 early gastric cancer patients undergone curative gastrectomy, and found that rN can identify subsets of patients with a significantly different survival rate within UICC/TNM pN1, pN2 and pN3 categories, suggesting that the outcome of patients with the same number of metastatic nodes, or with a larger number of retrieved LNs, is unfavorable. In the present study, however, a significant difference was observed in survival rates between lymph-node stages classified by the rN category or by the UICC pN category, but no significant difference was found in survival rates between lymph-node stages classified by the UICC pN category or by the rN category, indicating that the UICC/TNM classification can demonstrate stage migration and heterogeneous stratification for disease-specific survival. However, the metastatic lymph node ratio showed less stage migration and homogenous stratification in this study. The N category is currently defined by the number of positive nodes, but routine H&E staining may not exactly reflect the prognosis of lymph node metastasis due to lymph node micro-metastasis^[22-25]. Therefore, the rN category may give more accurate prognostic information on nodal involvement than the current pN category of TNM, thus having a great impact on the selection of patients who may benefit from the adjuvant treatment.

A study from Italy^[11] showed that the number of metastatic lymph nodes is significantly related with rN, and that the more the number of metastatic lymph nodes is, the

higher the rN will be, indicating that gastric cancer patients with a higher rN have a greater risk of death after surgery and a shorter survival time. In this study, when the rN was increased 10%, the calculated 5-year survival rate was decreased by 8.14%, whereas when the rN was decreased 10%, the calculated 5-year survival rate was increased by 8.14%, suggesting that the long-term survival can be improved by reducing rN. Moreover, Person's correlation test showed that rN was negatively correlated with the negative LN count ($P < 0.001$), indicating that removal of more negative lymph nodes can reduce rN.

In conclusion, increased negative LN count can reduce rN, thus improving the long-term survival of patients with gastric cancer after curative distal gastrectomy.

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COMMENTS

Background

Distal gastrectomy is one of the most important operative procedures for gastric cancer. Although the staging system of gastric cancer has been refined step by step, staging techniques never stop updating. So far, few studies are available on the relative contribution of metastatic lymph node (LN) ratio to the prognostic evaluation of gastric cancer after curative distal gastrectomy.

Research frontiers

Some researches have shown that metastatic lymph node ratio (rN) is an excellent predictor for the survival rate of patients with colon cancer, pancreatic cancer, breast cancer and other carcinomas. Some related studies on gastric cancer have also found the potential effect of rN on prognostic evaluation, but no consensus on stratification cutoffs, especially lack of data on gastric cancer after curative distal gastrectomy.

Innovations and breakthroughs

The authors investigated the validity of metastatic LN ratio as a prognostic factor by retrospectively reviewing 634 gastric cancer patients who underwent curative resection (R0) with distal gastrectomy in 1995-2004. The relation between rN and survival was discovered.

Applications

Metastatic LN ratio can provide accurate information on LN metastasis and lymphadenectomy for gastric cancer after curative distal gastrectomy. Moreover, the rN category is an important prognostic factor and increment of negative LN count can reduce rN, thus improving the survival rate of gastric cancer patients.

Peer review

This is an interesting study about the prognostic value of metastatic lymph node ratio (MLR) for 634 gastric cancer patients who underwent curative subtotal gastrectomies at a single institute. The study was well designed.

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