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ABOUT COVER

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Retrospective Study

Predictive value of positive lymph node ratio in patients with locally advanced gastric remnant cancer

Meng Zhuo, Lei Tian, Ting Han, Teng-Fei Liu, Xiao-Lin Lin, Xiu-Ying Xiao

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Abstract

BACKGROUND

Traditional lymph node stage (N stage) has limitations in advanced gastric remnant cancer (GRC) patients; therefore, establishing a new predictive stage is necessary.

AIM

To explore the predictive value of positive lymph node ratio (LNR) according to clinicopathological characteristics and prognosis of locally advanced GRC.

METHODS

Seventy-four patients who underwent radical gastrectomy and lymphadenectomy for locally advanced GRC were retrospectively reviewed. The relationship between LNR and clinicopathological characteristics was analyzed. The survival analysis was performed using Kaplan-Meier survival curves and Cox regression model.

RESULTS

Number of metastatic LNs, tumor diameter, depth of tumor invasion, Borrmann type, serum tumor biomarkers, and tumor-node-metastasis (TNM) stage were correlated with LNR stage and N stage. Univariate analysis revealed that the factors affecting survival included tumor diameter, anemia, serum tumor biomarkers, vascular or neural invasion, combined resection, LNR stage, N stage, and TNM stage (all $P < 0.05$). The median survival time for those with LNR0, LNR1, LNR2 and LNR3 stage were 61, 31, 23 and 17 mo, respectively, and the differences were significant ($P = 0.000$). Anemia, tumor biomarkers and LNR stage were independent prognostic factors for survival in multivariable analysis (all $P < 0.05$).

CONCLUSION

The new LNR stage is uniquely based on number of metastatic LNs, with significant prognostic value for locally advanced GRC, and could better differentiate overall survival, compared with N stage.

Key Words: Gastric remnant cancer; Positive lymph node ratio; Clinicopathological characteristics; Prognosis

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Core Tip: Lymph node (LN) counts of gastric remnant cancer (GRC) patients are often insufficient, and the prognostic ability of traditional LN stage (N stage) is therefore limited. This study investigated the predictive value of LN ratio (LNR) according to clinicopathological characteristics and prognosis of patients with locally advanced GRC. Compared with N stage, the new LNR stage had significant prognostic value for patients with locally advanced GRC, and it could better differentiate overall survival in patients, compared with N stage.

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INTRODUCTION

Gastric remnant cancer (GRC) is currently defined as carcinoma in the remnant stomach following partial gastrectomy, regardless of the disease being benign or malignant[1]. According to the Chinese surgeons' consensus opinion for the definition of gastric stump cancer (2018 edition), GRC is defined as carcinoma arising in the remnant stomach ≥ 5 years after gastrectomy for benign disease, or ≥ 10 years after gastrectomy for gastric cancer. GRC has been reported to represents 1%-3% of all gastric cancers[2-4]. According to the American Joint Committee on Cancer (AJCC) traditional lymph node (LN) stage (N stage) of gastric cancer has been well explored[5-7]. However, the evaluation of N stage in GRC remains uncertain, which is mainly because the number of LNs required to ensure accuracy needs to be at least 15[7, 8]. Indeed, surgery for GRC usually fails to retrieve the 15 LNs necessary for the initial operation[5,9].

Since traditional N stage has its limitation in GRC patients, establishing a new predictive stage is necessary. Positive LN ratio (LNR) is defined as the ratio of the number of metastatic LNs to the total number of LNs retrieved. In patients with gastric cancer, LNR might be more appropriate than N stage in predicting clinicopathological characteristics and prognosis[10-12]. However, the value of LNR stage in patients with GRC remains unclear. The purpose of this study was to evaluate the impact of LNR on clinicopathological characteristics and prognosis in patients with GRC.

MATERIALS AND METHODS

Patients

Patients with insufficient clinical data or no retrieved LNs were excluded from the study. From September 2003 to January 2016, 74 patients that underwent radical gastrectomy and lymphadenectomy for locally advanced GRC at Renji Hospital, were enrolled. Clinicopathological characteristics and overall survival were recorded. This retrospective study was approved by the Ethics Committee of Renji Hospital.

Data collection

All histopathological information and tumor-node-metastasis (TNM) stages were assessed and confirmed by implementing the AJCC cancer staging manual 8th edition[13]. Patients were divided into two groups based on initial surgery for peptic ulcer (benign disease) or gastric cancer (malignant disease). Histological types were dichotomized into two categories: differentiated (papillary, moderately or well-differentiated carcinoma) and undifferentiated (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). The lesions were classified into anastomotic, nonanastomotic and total remnant stomach. Serum albumin < 35 g/L was defined as hypoproteinemia. Hemoglobin < 90 g/L was considered to indicate anemia. Serum tumor biomarkers including carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, CA72-4 and CA12-5 were all detected before the surgery.

Definition of LNR

The best cut-off point of LNR is still controversial[7,14]. LNR stages were categorized according to previous published cut-offs or quartiles. In this study, LNR was classified into four groups according to quartiles: LNR0 0.0, LNR1 0.01-0.20, LNR2 0.21-0.69 and LNR3 0.70-1.0.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM, Chicago, IL, USA). Continuous values were analyzed using independent *t* tests or one-way analysis of variance. χ^2 and Fisher's exact probability tests were applied for analysis of categorical variables. For survival analysis, univariate analysis was determined by log-rank test and curves were plotted using the Kaplan-Meier method. Multivariate survival analysis was conducted using Cox proportional hazards regression. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

The mean age of the 74 patients was 66.24 ± 9.057 years, and 66 (89.2%) were male. A total of 64 patients (86.5%) underwent initial surgery for benign disease and 10 (13.5%) underwent initial surgery for gastric cancer. Billroth II anastomosis was performed in most patients (73.0%). The mean interval survival time was 29.32 ± 11.970 years, which was significantly longer in patients affected by a previous benign disease than those who suffered from a previous malignant disease (30.66 ± 11.044 years *vs* 20.80 ± 14.665 years, $P = 0.014$). GRC was most commonly located at the site of anastomosis (47/74, 63.5%). The baseline characteristics of all patients are shown in Table 1.

LN dissection and metastasis

A total of 836 LNs were dissected in 74 patients, and the mean number was 11 (range 1-33). There were 274 metastatic LNs, and the mean was four (range 0-20). The mean number of retrieved LNs was 11 in the initial benign group and 10 in the initial malignant group ($P = 0.607$). Patients with < 15 LNs were predominantly located in the initial malignant group (80.0% *vs* 73.4%, $P = 0.659$).

Different staging system and characteristics

The number of patients classified as N0, N1, N2, and N3 was 27, 13, 18 and 16, respectively. There were 27 patients classified as LNR0, 12 as LNR1, 16 as LNR2 and 19 as LNR3. The number of metastatic LNs, number of LNs dissected, tumor diameter, Borrmann type, depth of tumor invasion, serum tumor biomarkers, combined resection and TNM stage were correlated with N stage (Table 2). LNR stage was significantly associated with vascular or neural invasion, number of metastatic LNs, tumor diameter, depth of tumor invasion, serum tumor biomarkers, Borrmann type, and TNM stage (Table 3).

Survival analysis

The median follow-up of the entire cohort was 26 mo (range 2-129 mo). The median survival time was 31.0 mo. Overall, 1-, 3- and 5-year survival rates were 81.9%, 44.5% and 27.4%, respectively (Figure 1). According to univariate analysis, tumor diameter, anemia, serum tumor biomarkers, vascular or neural invasion, combined resection, N stage, LNR stage and TNM stage were all significant factors ($P < 0.05$) (Table 4). Multivariable analysis revealed that anemia, serum tumor biomarkers and LNR stage were independently associated with prognosis ($P < 0.05$) (Table 5). The median survival time of patients with N0, N1, N2 and N3 stage were 61, 31, 19 and 20 mo, respectively ($P = 0.000$) (Figure 2A). The median survival time for those with LNR0, LNR1, LNR2 and LNR3 stage was 61, 31, 23 and 17 mo, respectively, and the differences were significant ($P = 0.000$) (Figure 2B).

DISCUSSION

GRC was first described in 1922 by Balfour[15]. The prevalence of GRC continues to increase because of the long latency period after prior gastric surgery, including that for peptic ulcer or gastric cancer[16]. However, the clinicopathological characteristics and prognosis of GRC, especially the values of LN metastasis or N stage, are still controversial[3,5,7,8]. Our results showed that, compared with N stage, LNR stage was not related to the number of retrieved LNs and, according to the multivariable analysis, it played an independent role in prognosis.

Some studies have shown that the number of dissected LNs was significantly lower in patients with GRC, especially in patients with initial malignant cancer. This aspect was considered to be related to LN dissection during primary gastrectomy[6,17]. In the present study, the mean number of retrieved LNs and the proportion of patients with < 15 was similar to those reported in previous studies[5-7,9]. Although these values did not differ significantly between the two groups, our series displayed a trend: The patients that underwent initial surgery for benign disease had more retrieved LNs and a lower proportion.

LN metastasis plays an important role in both gastric cancer and GRC. Since N stage seems inaccurate for the evaluation, other studies are suggesting an alternative to N stage, which is dependent on the absolute number of metastatic LNs required for GRC[5,9]. In our study, we found that the new LNR stage is uniquely based on the number of metastatic LNs. Other studies have demonstrated that this new staging system might be more accurate in predicting survival in different cancers, including primary gastric cancer, regardless of the number of retrieved LNs[10,18,19]. Thus, the value of LNR stage in GRC, due to its unique characteristics, is worthy of exploration.

Table 1 Baseline characteristics of all patients, *n* (%)

Variables	Values
Gender	
Male	66 (89.2)
Female	8 (10.8)
Age (yr) (mean $\pm$ SD, range)	66.24 $\pm$ 9.057 (41-86)
Initial surgery	
Benign	64 (86.5)
Malignant	10 (13.5)
Interval (yr) (mean $\pm$ SD, range)	29.32 $\pm$ 11.97 (5-55)
Reconstruction	
Billroth I	20 (27.0)
Billroth II	54 (73.0)
Lesion location	
Anastomosis site	47 (63.5)
Non-anastomotic	22 (29.7)
Total remnant stomach	5 (6.8)
Histological types	
Differentiated	22 (29.7)
Undifferentiated	52 (70.3)
Borrmann	
Borrmann I	7 (9.4)
Borrmann II	13 (17.6)
Borrmann III	46 (62.2)
Borrmann IV	8 (10.8)
Vascular or nerve invasion	
Yes	33 (44.6)
No	41 (55.4)
Tumor diameter (cm) (mean $\pm$ SD, range)	5.59 $\pm$ 2.61 (0.50-12.00)
Combine resection	
Yes	26 (35.1)
No	48 (64.9)
Hypoproteinemia	
Yes	15 (20.3)
No	59 (79.7)
Anemia	
Yes	24 (32.4)
No	50 (67.6)
Serum tumor biomarkers level	
Normal	47 (63.5)
Abnormal	27 (36.5)
Depth of tumor invasion	
T2/T3	13 (17.6)

T4	61 (82.4)
N stage	
N0	27 (36.5)
N1	13 (17.6)
N2	18 (24.3)
N3	16 (21.6)
LNR stage	
LNR0	27 (36.5)
LNR1	12 (16.2)
LNR2	16 (21.6)
LNR3	19 (25.7)
TNM stage	
IB-II	26 (35.1)
III	48 (64.9)

N stage: Lymph node stage; LNR: Lymph node ratio; TNM stage: Tumor-node metastasis stage.

Table 2 Factors correlated with lymph node stage

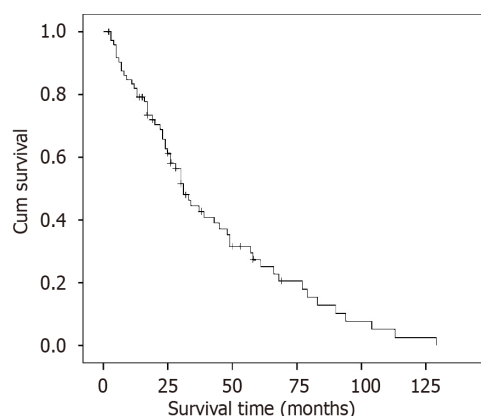
Variables	N0	N1	N2	N3	F/ χ^2	P value
Dissected lymph nodes	9.85 ± 7.32	9.15 ± 5.89	9.83 ± 7.56	17.13 ± 8.22	4.294	0.008
Metastatic lymph nodes	0.00 ± 0.00	1.23 ± 0.44	4.06 ± 1.16	11.56 ± 4.77	91.523	0.000
Tumor diameter	3.96 ± 1.67	5.92 ± 2.56	6.83 ± 2.70	6.66 ± 2.64	7.363	0.000
Borrmann					17.450	0.042
Borrmann I	3	0	2	2		
Borrmann II	9	0	3	1		
Borrmann III	15	12	9	10		
Borrmann IV	0	1	4	3		
Depth of tumor invasion					11.152	0.011
T2/T3	10	1	1	1		
T4	17	12	17	5		
Serum tumor biomarkers level					9.019	0.029
Normal	22	9	7	9		
Abnormal	5	4	11	7		
TNM stage					54.105	0.000
IB-II	24	1	1	0		
III	3	12	17	16		
Combine resection					8.917	0.030
Yes	4	6	10	6		
No	23	7	8	10		

N stage: Lymph node stage; TNM stage: Tumor-node metastasis stage.

Table 3 Factors correlated with lymph node ratio stage

Variables	LNR0	LNR1	LNR2	LNR3	F/ χ^2	P value
Metastatic lymph nodes	0.00 ± 0.00	1.75 ± 1.29	6.63 ± 5.51	7.74 ± 5.12	21.263	0.000
Tumor diameter	3.96 ± 1.67	5.38 ± 2.05	6.66 ± 2.32	7.13 ± 3.01	8.755	0.000
Borrmann					21.878	0.009
Borrmann I	3	0	0	4		
Borrmann II	9	1	3	0		
Borrmann III	15	10	11	10		
Borrmann IV	0	1	2	5		
Depth of tumor invasion					12.470	0.006
T2/T3	10	2	0	1		
T4	17	10	16	18		
Serum tumor biomarkers level					8.654	0.034
Normal	22	6	11	8		
Abnormal	5	6	5	11		
TNM stage					54.986	0.000
IB-II	24	2	0	0		
III	3	10	16	19		
Vascular or nerve invasion					8.616	0.035
Yes	8	8	5	2		
No	19	4	11	7		

LNR: Lymph node ratio; TNM stage: Tumor-node metastasis stage.

**Figure 1** Kaplan-Meier curves of overall survival for all patients.

The prognosis of GRC remains controversial. Some studies have reported that GRC shows similar prognosis to primary gastric cancer[20-22], whereas others have argued that the prognosis for GRC is worse[3,9,23]. In our study, we only enrolled patients with locally advanced GRC and 73.9% (67/74) of the patients were stage II or stage III. The survival rate was similar to that in other reports[5,9].

Other studies have confirmed that tumor size, combined resection, N stage, LNR stage and TNM stage were linked to prognosis, while the number of retrieved LNs had no effect[5-7,9]. GRC has higher rates of combine resection and the prognostic value is highly debated. Some studies have demonstrated that this factor has no influence[5,24], but others have reported a worse outcome[7,20]. In contrast, we were unable to demonstrate the predictive value of T stage, which may be due mainly to two factors: (1) we excluded patients with T1 stage; and (2) patients with T2 and T3 stage were combined as a whole cohort. With respect to the influence of primary disease and histological types on prognosis, we concluded that they do not affect survival. Kung *et al*[16] reported that prognosis was better in patients with initial

Table 4 Prognostic factors of gastric remnant cancer based on univariate log-rank test

Variable	n	Median survival time (months)	P value
Tumor diameter (cm)			0.013
< 5.5	35	48.0	
≥ 5.5	39	25.0	
Anemia (HGB) < 90 g/L			0.034
Yes	24	23.0	
No	50	37.0	
Serum tumor biomarkers level			0.014
Normal	47	37.0	
Abnormal	27	26.0	
Vascular or nerve invasion			0.020
Yes	33	25.0	
No	41	43.0	
Combined resection			0.021
Yes	26	25.0	
No	48	39.0	
N stage			0.000
N0	27	61.0	
N1	13	31.0	
N2	18	19.0	
N3	16	20.0	
LNR stage			0.000
LNR0	27	61.0	
LNR1	12	31.0	
LNR2	16	23.0	
LNR3	19	17.0	
TMN stage			0.000
IB-II	26	79.0	
III	48	25.0	

HGB: Hemoglobin; N stage: Lymph node stage; LNR: Lymph node ratio; TNM stage: Tumor-node metastasis stage.

malignant disease because of the regular follow-up. Son *et al*[5] reported that previous malignant disease meant poor 5-year survival rate. In addition, histological types were considered not to affect survival as their influence was reported as inconsistent in different studies[6,16].

Despite reports of worse outcomes in patients with vascular or neural invasion, this evidence remains unclear, due to the limited number of cases[16,25,26]. Our study demonstrated that anemia was an independent predictor of GRC. The estimated rate of preoperative anemia was 27%-44% in gastric cancer and predicted poor prognosis[27]. Due to lifelong vitamin B₁₂ deficiency and iron absorption disorders due to gastrectomy[28], anemia may be more common in GRC. The rate of anemia was 55.4% in our cohort, being defined as hemoglobin < 90 g/L. This implies the need to improve nutritional status.

The abnormal rate of tumor biomarker level was 36.5% in our study. A correlation has been commonly observed between serum tumor biomarkers and prognosis and diagnosis of gastric cancer[29-31], but no consensus has been reached. Deng *et al*[30] reported that high serum tumor biomarker level was possibly a poor prognostic factor. A recent Chinese study with 92 GRC cases indicated that patients with high CEA level had an equivalent prognosis. Few studies have evaluated the association between serum tumor biomarker levels and GRC; therefore, more data are needed to clarify this aspect.

Table 5 Prognostic factors of gastric remnant cancer based on COX proportional hazards model							
Variable	B	SE	Wald	df	P value	HR	95%CI
LNR stage	0.499	0.122	16.755	1	0.000	1.647	1.297-2.092
Anemia	0.656	0.287	5.216	1	0.022	1.926	1.097-3.381
Serum tumor biomarkers level	0.612	0.293	4.365	1	0.037	1.844	1.039-3.275

B: Beta; SE: Standard error; df: Degree of freedom; HR: Hazard ratio; LNR: Lymph node ratio.

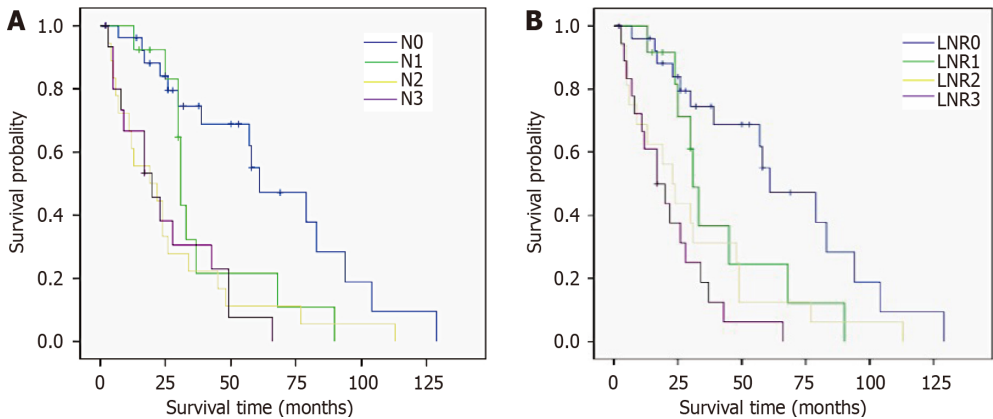


Figure 2 Kaplan-Meier curves according to lymph node stage and lymph node ratio stage. Comparison of survival curves according to the lymph node stages (N stages) and lymph node ratio (LNR) stages (both $P < 0.001$). A: Survival curves of patients with various N stages; B: Survival curves of patients with various LNR stages. N: Lymph node stage; LNR: Lymph node ratio.

In the present cohort, we tried to demonstrate the superiority of LNR stage for GRC. Some studies have demonstrated that the prognostic ability of a new staging system (using the ratio of the number of metastatic LNs to the number of retrieved LNs) has not improved[5,7]. We confirmed some advantage of LNR stage in predicting median survival time in different groups. As shown in Figure 2, patients with N3 stage had a longer median survival time compared to those with N2 stage, while median survival time decreased with the increase of LNR stage. Moreover, LNR stage was still an independent predictive factor considering the multivariable analysis, but N stage and TNM stage (which is largely related to N stage) were not. Notwithstanding the limited number of cases and the diverse entry criteria, our results suggest that LNR stage has a better prognostic performance in all patients and those with different stages of GRC. This suggests that LNR stage is an ideal and effective staging system for patients with GRC, but whether the same staging system is suitable for all patients is still an open question.

There were several limitations to this study. First, GRC is a rare disease, and 74 cases are not sufficient to identify an optimal staging system. Second, it was a retrospective study conducted in single center. Third, overall survival is most significant in evaluating the prognosis of cancer patients[32,33]. Only the 5-year survival rate and median survival time were assessed, and we did not include disease-free survival. Therefore, it is crucial to perform future studies with large sample sizes in multiple institutions.

CONCLUSION

This study showed the limitation of traditional N staging. LNR stage was not correlated with the number of LNs dissected and had a better prognostic value. It might be more reliable than N stage in patients with GRC.

ARTICLE HIGHLIGHTS

Research background

Some studies have shown that the number of dissected lymph nodes (LNs) was significantly lower in patients with gastric remnant cancer (GRC). Since traditional LN stage (N stage) seems inaccurate for the evaluation, other studies have suggested an alternative to N stage, which is dependent on the absolute number of metastatic LNs required for GRC.

Research motivation

To explore a superior predictor in surgically treated locally advanced GRC.

Research objectives

To evaluate the impact of LN ratio (LNR) on clinicopathological characteristics and prognosis in patients with GRC.

Research methods

The relationship between LNR and clinicopathological characteristics was analyzed. The survival analysis was performed using Kaplan-Meier survival curves and Cox regression model.

Research results

The 1-, 3- and 5-year overall survival rates were 81.9%, 44.5% and 27.4%, and the median survival time was 31.0 mo. The median survival time for those with LNR0, LNR1, LNR2 and LNR3 stage was 61, 31, 23 and 17 mo, respectively, and the difference was significant. Univariate analysis revealed that the factors affecting survival included tumor diameter, anemia, serum tumor biomarkers, vascular or neural invasion, combined resection, N stage, LNR stage and TNM stage. Anemia, level of serum tumor biomarkers and LNR stage were independent prognostic factors for survival in multivariable analysis.

Research conclusions

Compared with N stage, the new LNR stage is uniquely based on the number of metastatic LNs. LNR stage has significant prognostic value for patients with locally advanced GRC, and it could better differentiate overall survival in patients than N stage.

Research perspectives

In the future, we will work with other hospitals to increase the number of samples and evaluate whether LNR is better at predicting the need for adjuvant treatment than N stage.

FOOTNOTES

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