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RAPID COMMUNICATION

Prognostic impact of metastatic lymph node ratio in advanced gastric cancer from cardia and fundus

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Abstract

AIM: To investigate the prognostic impact of the metastatic lymph node ratio (MLR) in advanced gastric cancer from the cardia and fundus.

METHODS: Two hundred and thirty-six patients with gastric cancer from the cardia and fundus who underwent D2 curative resection were analyzed retrospectively. The correlations between MLR and the total lymph nodes, positive nodes and the total lymph nodes were analyzed respectively. The influence of MLR on the survival time of patients was determined with univariate Kaplan-Meier survival analysis and multivariate Cox proportional hazard model analysis. And the multiple linear regression was used to identify the relation between MLR and the 5-year survival rate of the patients.

RESULTS: The MLR did not correlate with the total lymph nodes resected (r = -0.093, P = 0.057). The 5-year overall survival rate of the whole cohort was 37.5%. Kaplan-Meier survival analysis identified that the following eight factors influenced the survival time of the patients postoperatively: gender (χ^2 = 4.26, P = 0.0389), tumor size (χ^2 = 18.48, P < 0.001), Borrmann type (χ^2 = 7.41, P = 0.0065), histological grade (χ^2 = 5.07, P = 0.0243), pT category (χ^2 = 49.42, P < 0.001), pN category (χ^2 = 87.7, P < 0.001), total number of retrieved lymph nodes (χ^2 = 8.22, P = 0.0042) and MLR (χ^2 = 34.3, P < 0.001). Cox proportional hazard model showed that tumor size (χ^2 = 7.985, P = 0.018), pT category (χ^2 = 30.82, P < 0.001) and MLR (χ^2 = 69.39, P < 0.001) independently influenced the prognosis. A linear correlation between MLR and the 5-year survival was statistically significant based on the multiple linear regression (β = -0.63, P < 0.001). Hypothetically, the 5-year survival would surpass 50% when MLR was lower than 10%.

CONCLUSION: The MLR is an independent prognostic factor for patients with advanced gastric cancer from the cardia and fundus. The decrease of MLR due to adequate number of total resected lymph nodes can improve the survival.

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Key words: Stomach neoplasms; Lymph node metastasis; Metastatic lymph node ratio; Lymphadenectomy; Prognosis

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INTRODUCTION

At present, patients with advanced gastric cancer from the cardia and fundus still have a poor prognosis despite some therapeutic modalities. Lymph node metastasis is considered one of the most important prognostic factors[1-3]. And lymphadenectomy is fundamentally critical in radical surgery. Its standardization highly depends on the accuracy of prognosis evaluation according to the classification of lymph node metastasis. The current American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM system (1997) has established the classification

system based on the number of metastatic lymph nodes. D2 curative resection, which includes gastrectomy and D2 lymphadenectomy, required dissection of all the Group 1 and Group 2 nodes classified by anatomical location. However, with the development of D2 lymphadenectomy, larger lymph nodes dissected may enable to fine larger metastatic lymph nodes, which induces a migration in the staging system. The ratio of the number of metastatic lymph nodes over the total number of resected lymph nodes is introduced to prognosis evaluation. It was reported that metastatic lymph node ratio (MLR) can minimize the stage migration effect caused by increasing total dissected lymph nodes, also can help refine the current TNM stage system[4,5]. Though many studies on the prognostic significance of MLR in gastric cancer have been carried out, relevant researches on advanced gastric cancer from the cardia and fundus are still rare. Therefore, the aim of this retrospective study was to discuss the clinical impact of MLR in patients with gastric cancer from the cardia and fundus, and provide further evidence for rational lymphadenectomy.

MATERIALS AND METHODS

Materials

Two hundred and thirty-six cases, diagnosed as primary gastric cancer from the cardia and fundus were treated with curative resection at the Department of Oncology, Affiliated Union Hospital of Fujian Medical University, Fuzhou China, between January 1996 and June 2002. The surgical procedure was defined as curative when no grossly visible tumor tissue (metastasis or lymph node involvement) remained after the resection and the resection margins were histologically normal. There were 197 male (83.5%) and 39 female (16.5%) patients aged from 30 to 79 years with a mean of 58.8 ± 9.8 years. All patients received a D2 or more extended dissection of all the Group 1 and Group 2 lymph nodes or more according to the Japanese Classification of Gastric Carcinoma (JCGC)[6]. Among the 236 patients, total gastrectomy (TG) was performed in 190 patients, and proximal subtotal gastrectomy (PSG) in 46. Lymph nodes were meticulously dissected from the en bloc specimens, and the classification of the dissected lymph nodes was determined by specialized surgeons who reviewed the excised specimens after surgery based on the JCGC. Clinical and histopathologic data of each patient were collected and recorded in a specifically designed data collection form. The histopathologic spectrum included papillary adenocarcinomas (47/236, 20%), tubular adenocarcinomas (101/236, 43%), mucinous adenocarcinomas (29/236, 12%), poorly differentiated adenocarcinomas (36/236, 15%), undifferentiated carcinomas (8/236, 3%) and others (15/236, 6%) according to the World Health Organization classification system. Based on the 5th Edition of UICC TNM system[7], T category is defined as follows: T2: tumor invades muscularis propria or submucosa; T3: tumor penetrates serosa without invasion of adjacent structure; T4: tumor invades adjacent structures. N category is defined as follows: N0: no regional lymph node metastasis; N1: metastasis in 1 to 6 regional lymph nodes; N2: metastasis in 7 to 15 regional lymph nodes; N3: metastasis in more than 15 regional lymph nodes. Among our patients, there were 25 at stage pT2, 118 at pT3 and 93 at pT4, respectively, while there were 42 pN0, 97 pN1, 68 pN2 and 29 pN3 respectively. Finally, 48 cases (20%) were categorized as stage Ⅱ, 128 (54%) as stage Ⅲ and 60 (25%) as stage Ⅳ. All the patients received postoperative chemotherapy, using 5-FU as the dominant agent. No patientreceived postoperative radiotherapy. The follow-up was carried out by specialized investigators, who were trained about the follow-up system for clinical observation. The median follow-up for the entire cohort was 44 mo (range: 1-136 mo). A total of 222 cases were followed up with a rate of 94.0%.

Methods

All calculations were performed using the SPSS 11.5 statistical package. Correlation analysis was made to find the relationship between MLR and the total lymph nodes, positive nodes and the total lymph nodes. Cumulative survival was determined *via* the Kaplan-Meier method, with univariate comparisons between groups through the log-rank test. Covariates that remained significant through the univariate analysis were selected for multivariate analysis. Cox regression was used for multivariate analysis, with a forward stepwise elimination model. A multiple linear regression model to correlate MLR with 5-year survival was obtained based on Kaplan-Meier 5-year survival estimates for each MLR interval, using midpoint of MLR interval as the independent variate. Significance of differences was assumed at P values of less than 0.05.

RESULTS

MLR of different pT/pN subcategories

From the 236 cases, a total of 5615 lymph nodes were picked up and histologically examined, with 1610 positive and 4005 negative. The median total LN number was 23 (range 7-74, mean 23.8 ± 8.8 per patient), the median number of positive LNs was 5 (range 0-44, mean 6.8 ± 6.8 per patient), and that of negative LNs was 16 (range 0-48, mean 16.9 ± 9.3 per patient). The MLRs were 12.0%, 26.3% and 36.2% in cases with pT2, pT3and pT4, ($\chi^2 = 138.9$, $P < 0.001$), and 16.8%, 42.7% and 68.9% in cases with pN1, pN2, and pN3, respectively ($\chi^2 = 820.7$, $P < 0.001$). Figure 1 shows a trend of MLR according to different pT/pN subcategories. The MLR ascended as the invasion deepened, or the number of metastatic nodes increased.

Correlation analysis between MLR and total lymph nodes, positive lymph nodes and total lymph nodes

The MLR did not correlate with the total lymph nodes dissected ($r = -0.093$, $P = 0.057$), whereas positive lymph nodes did ($r = 0.173$, $P = 0.008$). Figures 2 and 3 show the scatters of these two groups. The results revealed that, in the same extent of lymphadenectomy, MLR

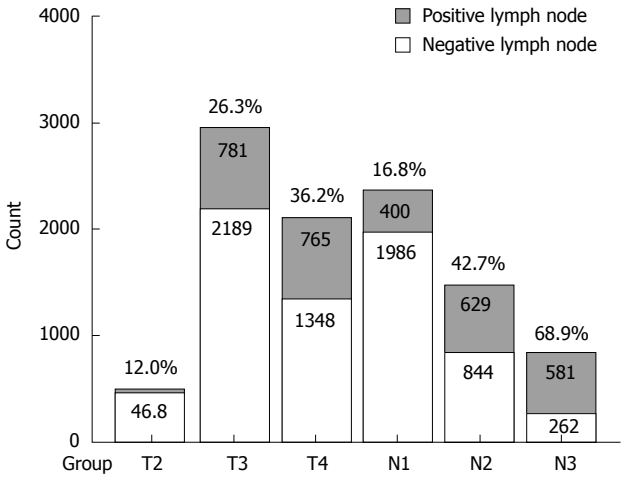

Figure 1 MLR of different pT/pN subcategories.

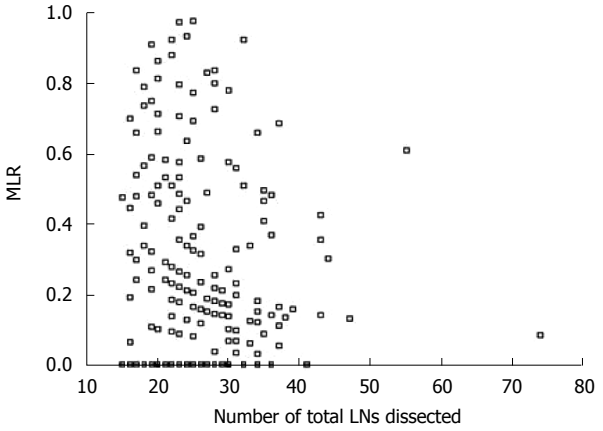

Figure 2 Scatter of MLR and total LNs dissected.

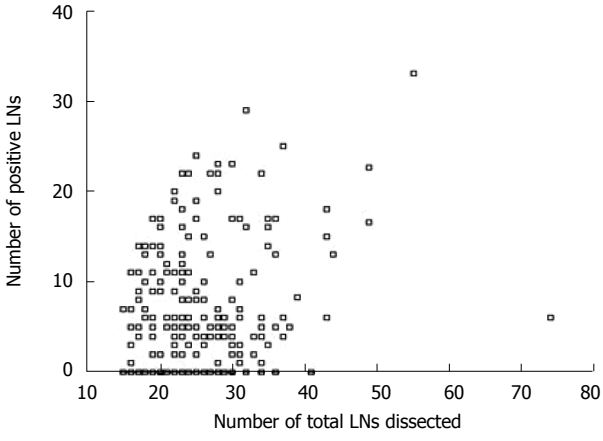

Figure 3 Scatter of positive LNs and total LNs dissected.

would not increase with the number of total lymph nodes, but the number of positive lymph nodes would.

Univariate survival analysis

The 5-year overall survival rate of the entire cohort was 37.5%. The clinicopathological variables tested in the univariate analysis are shown in Table 1. Factors influencing the 5-year survival rate were patient gender ($P = 0.0389$), tumor size ($P < 0.001$), Borrmann type ($P = 0.0065$), histological grade ($P = 0.0243$), pT category ($P < 0.001$), pN category ($P < 0.001$), total number of dissected lymph nodes ($P = 0.0042$) and MLR ($P < 0.001$). Patient age ($P = 0.2777$) and type of gastrectomy ($P = 0.0844$) had no significant influence on the survival.

Table 1 Univariate survival analysis of MLR and clinicopathological characteristics in 236 patients undergoing curative surgery

Characteristics	*n*	Median survival time (mo)	5-yr survival (%)	χ^2	*P*
Gender				4.26	0.0389
Male	197	45	36.3		
Female	39	51	43.6		
Age (yr)				1.18	0.2777
< 60	103	45	39.0		
⩾ 60	133	46	36.6		
Tumor size (cm)				18.48	0.0000
< 3	88	60	45.5		
3-6	97	47	39.7		
> 6	51	32	18.1		
Borrmann's type[1]				7.41	0.0065
Borrmann Ⅰ, Ⅱ	172	50	41.7		
Borrmann Ⅲ, Ⅳ	64	41	26.5		
Histological type				5.07	0.0243
Differentiated	213	47	38.9		
Undifferentiated	23	35	19.9		
pT category				49.42	0.0000
pT2	25	72	84.0		
pT3	118	54	40.2		
pT4	93	29	20.8		
pN category				87.7	0.0000
pN0	42	65	73.2		
pN1	97	55	42.4		
pN2	68	27	19.9		
pN3	29	17	0.0		
Num of dissected LNs				8.22	0.0042
< 15	36	27	22.4		
⩾ 15	200	49	39.1		
MLR				34.3	0.0000
< 10%	59	63	60.5		
~ 20%	58	46	34.1		
~ 30%	33	44	33.5		
> 30%	86	28	21.0		
Type of gastrectomy				2.98	0.0844
TG	190	46	39.3		
PSG	46	45	31.3		

[1]Borrmann's type: Macroscopic appearances of primary tumor, classified as Type Ⅰ: polypoid tumors; Type Ⅱ: ulcerated carcinomas with demarcated and raised margins; Type Ⅲ: ulcerated carcinomas without definite limits, infiltrating into the surrounding wall; Type Ⅳ: diffusely infiltrating carcinomas.

Multivariate survival analysis

Multiple survival analysis was calculated by the Cox's proportional hazard regression model. In order to confirm the influence of MLR, the prognostic factors considered at univariate analysis were analyzed first by stepwise regression, including gender, tumor size, Borrmann type, histological grade, pT category, pN category and total number of dissected lymph nodes except MLR. As a result, there were four independent, statistically significant prognostic parameters: tumor

Table 2 Multiple stepwise regression analysis with Cox proportional hazards model

Characteristics	β	Wald	*P*	RR	95% CI for RR	
					Low	High
MLR excluded						
Tumor size		6.665	0.039			
3-6 cm *vs* < 3 cm	0.222	1.938	0.164	1.249	0.913	1.707
> 6 cm *vs* < 3 cm	0.501	6.636	0.010	1.650	1.127	2.414
pT category		27.747	0.002			
pT3 *vs* pT2	0.761	9.184	0.000	2.140	1.308	3.499
pT4 *vs* pT2	1.286	24.369	0.000	3.617	2.171	6.026
pN category		65.066	0.000			
pN1 *vs* pN0	0.618	9.792	0.002	1.855	1.260	2.733
pN2 *vs* pN0	1.224	30.727	0.000	3.402	2.206	5.244
pN3 *vs* pN0	2.156	57.470	0.000	8.639	4.947	15.090
Num of total LNs	-0.682	10.684	0.001	0.506	0.336	0.761
MLR included						
Tumor size		7.985	0.018			
3-6 cm *vs* < 3 cm	0.307	3.863	0.049	1.359	1.001	1.845
> 6 cm *vs* < 3 cm	0.512	7.353	0.007	1.668	1.152	2.415
pT category		30.821	0.000			
pT3 *vs* pT2	0.772	9.940	0.002	2.165	1.339	3.500
pT4 *vs* pT2	1.343	26.759	0.000	3.832	2.303	6.375
MLR	2.569	69.390	0.000	13.06	7.134	23.900

Table 3 Estimation based on multiple linear regression model (stepwise method)

Parameters	β	*t*	*P*	95% CI for β
Tumor size	-0.11	-1.97	0.051	
MLR	-0.63	-10.4	0.000	-0.71 to -0.51
Intercept (constant)	0.56	19.0	0.000	0.48 to 0.59

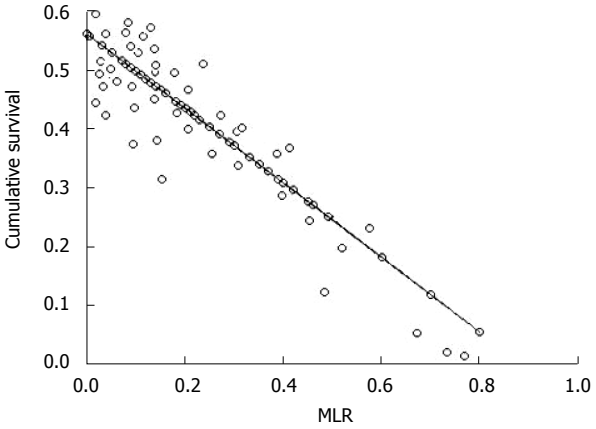

Figure 4 Regression line of MLR impact on the 5-year survival rate.

size (P = 0.039), pT category (P = 0.002), pN category (P < 0.001) and total number of dissected lymph nodes (P = 0.001). When MLR was included in the Cox's regression, the overall fit of the Cox model increased (likelihood ratio test with and without MLR: 397 and 305, respectively). Tumor size (P = 0.018), pT category (P < 0.001) and MLR (P < 0.001) were remained to be independent prognostic factors, with MLR being the most significantly independent factor. The risk ratios and their 95% confident interval are listed in Table 2.

MLR impact on overall survival

Linear trend test found that tumor size and MLR both had a linear correlation to the 5-year overall survival rate, and the correlation coefficients (r) were -0.157 (P = 0.019) and -0.655 (P < 0.0001), respectively. Obviously, MLR showed a much stronger correlation than tumor size. Despite tumor size and overall survival related, only MLR can reach statistically significant differences according to the multiple linear regressions (P < 0.0001). As shown in Table 3, the regression equation of the assumed statistically linearity was y = -0.63x + 0.56. Figure 4 presents a regression line of this calculated MLR effect on the 5-year survival. The hypothetical baseline 5-year survival (based on the y-intercept, i.e. MLR 0%) was 56%. For every 10% added to MLR, the calculated 5-year survival rate decreased by 6.3%. Hypothetically, the 5-year survival would surpass 50% when MLR was lower than 10%.

DISCUSSION

Over the last few decades, the rising trends in incidence rates for upper third gastric cancer have been reported by many investigators around the world[8,9]. Cancer of the gastric cardia and fundus is commonly found in late or the advanced stage at the initial diagnosis[10,11]. It was warranted to link the poor prognosis to lymph node metastases for cancer of this anatomical location reported with a higher frequency of perigastric lymph nodes and higher proportion of overall lymph node metastasis[12,13]. A prospective study conducted by de Manzoni *et al*[14] showed that 56.9% of patients with types Ⅱ and Ⅲ cardia cancer had nodal spread. Di *et al*[15] set up a research on lymph node involvement in gastric cancer for different sites, showing an involvement in 80.4% of cases for upper third cancers. In the present study, 82.2% of cases were found to have lymph node metastasis. And the overall MLR was 28.7%. These data confirmed the cited reports.

Lymph node metastasis is one of the most important prognostic factors for gastric cancer after curative resection. Methods of metastatic lymph nodes evaluation are still under investigation and being continuously improved, including some immunohistochemical methods, in order to predict the prognosis and guide the therapy. But few special proteins expressed in gastric cardia cancer, compared with non-cardia cancer. For example, with regard to the mucin phenotype, MUC1 and MUC5AC expression was less frequent in cardia carcinomas than in non-cardia carcinomas[16]. Therefore, lymph node status mainly depends on routine pathological examinations, previously based on the anatomical station of metastatic lymph nodes, and is classified by the number of metastatic regional lymph nodes[17-19]. The problem of lymph node classification based on number of metastatic ones is the stage migration, induced by larger lymph nodes dissected. Researches on prognostic impact of MLR have been done in patients with colon cancer, pancreatic cancer, breast cancer and other carcinomas[20-23] to find its advantage

in predicting survival outcome after curative resection. MLR was introduced as a more reliable prognostic factor for gastric cancer[24,25]. In our study, a greater MLR was associated with poorer survival by univariate analysis. Multivariate analysis further identified that the MLR was a most important independent prognostic factor among the other factors evaluated, including pN category. This phenomenon was in agreement with those reported by some other investigators. It may be a superior indicator for lymph node classification system. Relevant data were reported about the grouping of patients with gastric cancer with lymph node metastasis ratios. By imitating the pN category of UICC/AJCC, most researchers selected three or four different groups. Different N ratio cutoffs have been proposed[26-29], such as 0%, 1% to 9%, 10% to 25%, > 25%; 0%, < 25%, < 50%, > 50% and so on. Many authors did not describe a specific method for the selection of the reported cutoffs. Hyung *et al*[30] discovered that the cutoff values were 10% for T3N1M0 and 25% for T3N2M0 by analysis of the prognosis according to MLR. In the present study, we found the 5-year survival would surpass 50% when MLR was lower than 0.10.

Our study also showed that MLR can reflect the number of LNs examined and the quality of LN dissection. Curative resection was the determining factor to improve the 5-year survival in this type of tumor[31]. Although D2 radical resection for patients with cancer of gastric cardia and fundus is widely accepted[32], how many lymph nodes should be removed to accurately predict clinical outcome has not been determined. Barbour *et al*[33] suggested patients with Siewert types Ⅱ and Ⅲ adenocarcinoma of the GEJ should undergo adequate lymphadenectomy to permit examination of ⩾ 15 lymph nodes allowing the accurate identification of prognostic variables. Removal of ⩾ 15 lymph nodes is associated with more accurate survival estimates for patients with advanced disease. Gee *et al*[34] stated that preferably 20-25 lymph nodes were necessary for determining prognosis and treatment for tumors of the gastroesophageal junction. In the present study, MLR did not correlate with the total lymph nodes while the number of metastatic LNs did. This finding indicated that the extent of lymphadenectomy was adequate when MLR value did not fluctuate with the resected number of lymph nodes. Obviously, it requires a certain amount of lymph nodes to be dissected. McKee *et al*[35] pointed out, MLR may be confounded by the small number of nodes examined from each patient, it should not be used for prognostic information in patients with fewer than 15 nodes examined. The median total LN number was 23 (mean 23.8 ± 8.8 per patient) in this study, so we suggested D2 lymphadenectomy in order to ensure adequate dissection.

In conclusion, MLR has advantages in providing a more precise prognostic evaluation. We should pay attention to the clinical impact of MLR on prognosis of gastric cancer located in cardia and fundus when performing a D2 radical resection. It is warranted to make efforts to reduce MLR, preferably lower than 10%, in order to achieve better therapeutic efficiency.

COMMENTS

Background

The incidence rates of gastric cancer located in cardia and fundus have increased in recent years. Though the staging system of gastric cancer refines step by step, staging techniques never stop updating. So far, few studies have investigated the relative contribution of metastatic lymph node (LN) ratio to the prognosis evaluation with advanced gastric cancer from cardia and fundus.

Research frontiers

Some researches have shown that metastatic lymph node ratio (MLR) is an excellent predictor for survival outcome in patients with colon cancer, pancreatic cancer, breast cancer and other carcinomas. Some related studies on gastric cancer also found the potential of the MLR on prognostic evaluation, but without a consensus on stratification cutoffs, especially lack of data for advanced gastric cancer located in cardia and fundus.

Innovations and breakthroughs

The authors retrospectively reviewed 236 patients with gastric cancer from cardia and fundus who were treated with D2 radical resection in a hospital in Fujian between 1996 and 2002, to investigate the validity of metastatic LN ratio as a prognostic factor. The study not only divided MLR into some different grades for survival analysis, but also set up a regression to discover the relation between MLR and survival.

Applications

The authors suggest that metastatic LN ratio can provide more dependable and accurate information on the extent of LN metastasis and lymphadenectomy for advanced gastric cancer located in cardia and fundus. Moreover, it is an important prognostic factor and can provide further evidence for rational lymphadenectomy.

Peer review

This is an interesting and well-done study investigating the prognostic role of MLR in cancer of gastric cardia and fundus. This is a well-written and significant paper.

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