

RESEARCH COMMUNICATION

Prognostic Significance of the Metastatic Lymph Node Ratio in T3 Gastric Cancer Patients Undergoing Total Gastrectomy

Jun Feng¹, Yun-Fei Wu^{2*}, Hui-Mian Xu², Shu-Bao Wang², Jun-Qing Chen²

Abstract

Aims and background: The International Union Against Cancer tumor node metastasis classification is routinely applied for evaluating the prognosis of patients with gastric cancer. However, results are still heterogeneous. This study was therefore carried out to evaluate the prognostic significance of the metastatic lymph node (LN) ratio in T3 gastric cancer patients undergoing gastrectomy. **Methods:** Clinical data of 109 LN-positive cases were retrospectively analyzed. Spearman correlation analysis was used to determine the correlation coefficient. Survival time was determined by Kaplan-Meier and Log-rank test. Multivariate analysis was performed using the Cox model. ROC curves were used to compare the accuracy of the number of metastatic LN and metastatic LN ratio. **Results:** The metastatic LN ratio did not correlate with the number of LN when at least 15 nodes were dissected, whereas the number of metastatic LN did. Univariate analysis showed that the metastatic LN ratio influenced significantly the survival time, while multivariate analysis revealed it to be a major independent prognostic factor. **Conclusions:** The metastatic LN ratio can be used as a major independent prognostic factor for the patients with T3 gastric cancer.

Keywords: Gastric cancer - total gastrectomy - lymph node metastasis - staging - prognosis

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Introduction

Early studies had shown that metastatic lymph node (LN) was one of the most critical prognostic factors in gastric carcinoma (Hohenberger and Gretschel, 2003; Yokota et al, 2004; Dicken et al., 2005). Since the International Union Against Cancer tumor node metastasis (UICC TNM) classification for LN staging standard was modified in 1997, LN metastatic sites were replaced by the number of metastatic LN to evaluate the prognosis of patients. However, the number of dissected LN affected the accuracy of N staging, or even led to N staging bias (de Manzoni et al., 2002).

A lot of studies suggested that metastatic LN ratio (MLR), which is the percentage of metastatic LN among the total dissected LN, was considered as a better prognostic factor for patients with gastric cancer than number of metastatic lymph nodes because it overcame the problem of N staging bias (Bando et al., 2002; Inoue et al., 2002; Nitti et al., 2003; Ding et al., 2004). A wider range of LN were removed in total gastrectomy that could better reveal the true rules of LN metastasis. Therefore, this study was carried out to evaluate its prognostic significance in T3 gastric cancer patients who underwent total gastrectomy and evaluated the difference of prognostic value between the MLR staging and the UICC TNM Classification (6th Edition) of gastric tumor.

Materials and Methods

Patient selection

A total of 109 T3 gastric cancer patients who underwent radical total gastrectomy (UICC R0) in the first affiliated hospital of China Medical University between January 1990 and December 2005 were included in this retrospective study. All the patients had complete clinical data and follow-up results. The number of dissected LN in all cases was at least 15. Clinical pathological data was based on UICC TNM Classification of gastric tumor (6th Edition). 82 males and 27 females were included. The average age of selected patients was 54.70± 10.16 years (range 29-72). With respect to tumor location, 26 upper-third (U), 17 middle-third stomach tumors (M) cases, 39 lower third (L) stomach tumors, and 27 two areas or more than stomach tumors were concluded. The total number of dissected LN was 4180 (average 38.34 per case), including 1092 metastatic LN and 91 cases with LN metastasis. All the patients received at least 5 years follow-up or until death. The methods of follow-up included telephone, letters and the access to the medical record after rehospitalization. The results included death, survival or loss. If a patient was died during follow-up, the cause was examined and recorded. If a patient had not died from gastric cancer, the follow-up result was defined as loss.

¹Department of Surgical Oncology, Taizhou Cancer Hospital, Taizhou Branch of Fudan University, Taizhou, Zhejiang Province,

²Department of Surgical Oncology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, China

*For correspondence: xinyuan7811@126.com

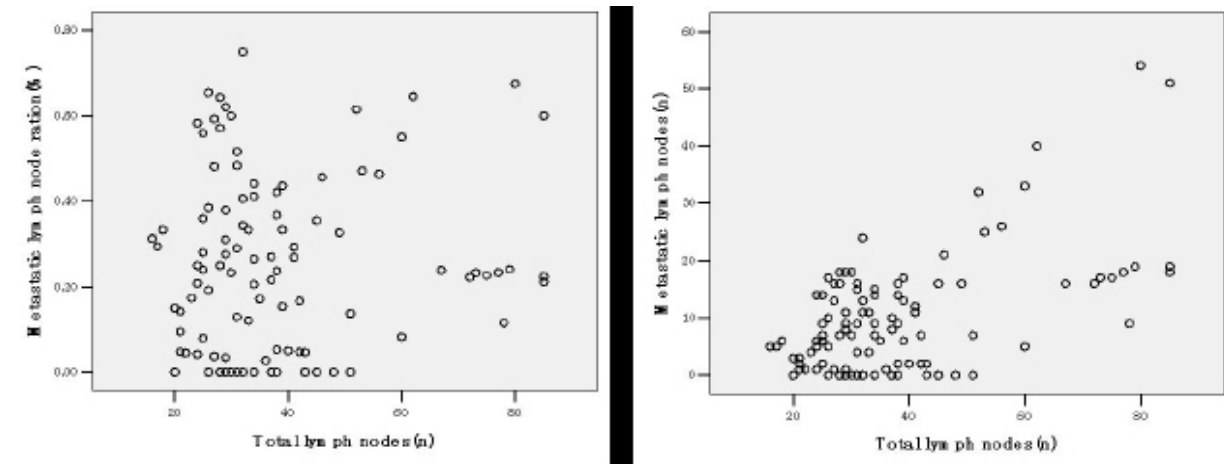


Figure 1. The Correlation Analysis Between Metastatic LN Ratio or the Number of Metastatic LN and the Total Number of LN. A. The correlation analysis between metastatic LN ratio and the total number of LN. B. The correlation analysis between the number of metastatic LN and the total number of LN

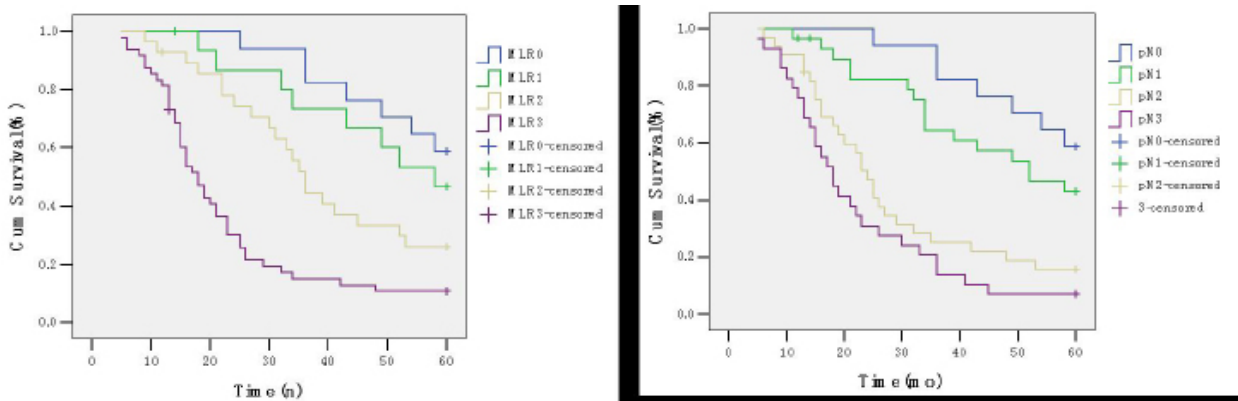


Figure 2. The Comparison of Survival Curves According to the Patients with Different MLR and pN Staging. A. The comparison of survival curves according to the patients with different MLR staging. B. The comparison of survival curves according to the patients with different pN staging

Table 1. The Comparison of Survival Rates Among MLR Groups from the Patients with pN Staging

	MLR1		MLR2		MLR3		χ^2	P
	n	5-yr survival(%)	n	5-yr survival(%)	n	5-yr survival(%)		
p	30	7	11	4	3	1	0.5	0.7
N ₁							72	51
p	33	0	8	2	25	3	1.5	0.2
N ₂							50	13
p	29	0	9	1	20	1	9.3	0.0
N ₃							70	02

Classification of LN

MLR staging(Nitti et al., 2003): MLR₀(no LN metastasis), MLR₁ (metastatic rate 0-10%), MLR₂ (metastatic rate 11-25%), MLR₃ (metastatic rate >25%); pN staging (): pN₀ (no LN metastasis), pN₁ (1-6 LN metastasis), pN₂ (7-15 LN metastasis) and pN₃ (more than 15 LN metastasis).

Statistical analysis

The data were analyzed by SPSS13.0 statistical software. Spearman correlation analysis was used to evaluate the relationship of metastatic rate or number of LN with the total LN. Survival time was estimated by Kaplan-Meier method. Significant comparison was performed by Log-rank test. Cox model was used for the analysis of patient prognosis. MedCalc 11.3 software was used to compare the ROC curves. P <0.05 was considered

statistically significant.

Results

Correlation analysis

The metastatic LN ratio did not correlate with the total number of LN when at least 15 nodes were dissected (r=0.036, P=0.708), whereas the number of metastatic LN did (r =0.562, P=0.000) (Figure 1).

Comparison of survival rates according to the patients with different MLR staging

In 109 patients, there were 17 patients with MLR₀, 16 with MLR₁, 28 with MLR₂, and 48 with MLR₃, while the 5-year survival rate of the patients with different MLR staging was respectively 58.8%, 43.8%, 25.0% and 10.4%. There were significant differences on the 5-year

Table 2. Univariate Analysis of T3 Gastric Cancer by Kaplan-meier Method

Factor	n	5-yr survival	χ^2	P	
Gender	Male	81	19	0.972	0.324
	Female	28	10		
Age(yr)	≤50	36	8	0.596	0.440
	>50	73	21		
Tumor size(cm)	<5	21	11	7.673	0.006
	≥5	88	18		
Tumor location	Upper	26	6	3.606	0.307
	Middle	17	6		
	Lower	39	12		
	≥Two areas	27	5		
Borramann type	I/II	25	9	2.831	0.092
	III/IV	84	20		
Histology	Well differentiated	29	12	8.521	0.014
	Moderately differentiated	63	11		
	Poorly differentiated	17	6		
metastatic LNs ration(%)	0	17	10	39.465	0.000
	1-10	16	7		
	11-25	28	7		
	>25	48	5		
Number of LN	0	17	10	37.327	0.000
	1-6	30	12		
	7-15	33	5		
	>15	29	2		

Table 3. Multivariate Analysis of T3 Gastric Cancer by Cox Model

Risk Factor	B	SE	Wald	P	RR	95.0%CI
Tumor size	0.763	0.357	4.568	0.033	2.145	1.065 4.320
Histology	0.284	0.172	2.737	0.098	1.329	0.949 1.862
MLR staging	0.475	0.167	8.122	0.004	1.608	1.160 2.229
pN staging	0.387	0.162	5.711	0.017	1.473	1.072 2.024

survival rates of the patients with different MLR staging ($\chi^2=39.465, P=0.000$) (Figure 2A).

Comparison of survival rates according to the patients with different pN staging

In 109 patients, there were 17 patients with pN0, 30 with pN1, 33 with pN2, and 29 with pN3. , while the 5-year survival rate of the patients with different MLR staging was respectively 58.8%, 40.0%, 15.2% and 6.9%. There were significant differences on the 5-year survival rates of the patients with different pN staging ($\chi^2=37.327, P=0.000$)(Figure 2B).

Comparison of survival rates among MLR groups from the patients with pN staging

Among the same pN staging group, we divided the patients into three different subgroups according to the MLR staging and compared the 5-year survival rates of the patients on the three subgroups. The results showed that the 5-year survival rates of the patients on the three subgroups were different on the same pN staging group, while there are significant difference on the 5-year survival rate of the patients on between MLR2 and MLR3 staging subgroup in pN3 group (Table 1).

Univariate analysis of T3 gastric cancer

The Univariate analysis of clinical pathological factors

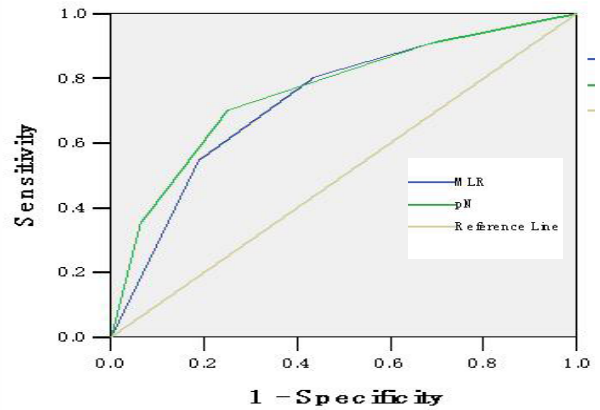


Figure 3. The Comparison of ROC Curve Between Metastatic LN Ratio and Metastatic LN

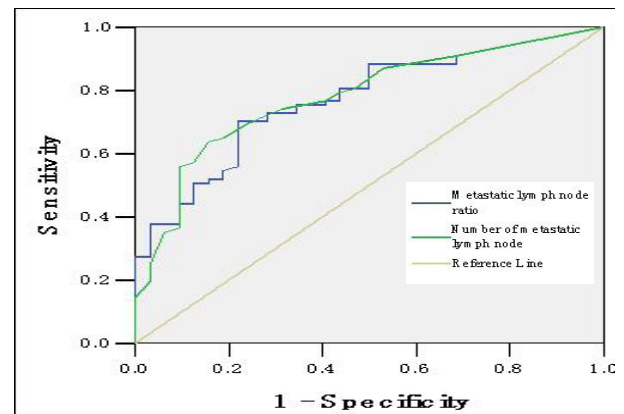


Figure 4. The Comparison of ROC Curve Between MLR and pN Staging

on the prognosis of T3 gastric cancer patients showed that tumor size, histological type, pN staging and MLR staging had correlation with the prognosis of T3 gastric cancer patients, while gender, age, tumor site, Borramann type and total number of LN had not (Table 2)

Multivariate analysis of T3 gastric cancer

The cox proportional hazards regression analysis suggested that tumor size, MLR and pN staging had correlation with the prognosis of T3 gastric cancer patients. By comparing the relative risk, MLR staging was most closely related to the prognosis of T3 gastric cancer patients among all the independent risk factors (Table 3).

Analysis of ROC curves

By 5-year survival rates of T3 gastric patients after surgery as standard, we drew the ROC curve of 109 patients. Using the metastatic LN ratio to determine whether T3 gastric patient die after 5-years of surgery, the ROC area under the curve was 0.770 (95%CI: 0.679~0.845), the area in number of metastatic LN was 0.779 (95%CI: 0.690~0.853); $z=0.378, P=0.7055$. There was no significant difference between the area under the ROC curve of metastatic LN ratio and that of the number of metastatic LNs in predicting the 5-year survival rate (Figure 3).

Using the MLR staging to determine whether T3 gastric patients die after 5 years of surgery, the ROC area under the curve was 0.733 (95% CI: 0.639~0.813), the area in pN staging was 0.760 (95%CI: 0.669~0.837); $z=0.807,$

$P=0.4194$. There was no significant difference between the area under the ROC curve of MLR staging and that of pN staging in predicting the 5-year survival rate (Figure 4).

Discussion

Presently, most gastric cancer patients who undergo surgery are at advanced stage in China, and there were about 40% at T3 staging among them (Kim, 1999). The survival rates of T1 and T2 gastric cancer patients are least affected by metastatic LN, while the survival rates of T4 gastric cancer patients after surgery is mainly dependent on the extension of tumor (Hyung et al., 2002). However, how the metastatic LN ratio affects the survival rates of T3 gastric cancer patients after surgery is still unclear.

Since 1997, the UICC TNM classification of gastric tumor (6th Edition) has redefined the N staging of gastric cancer based on the number of metastatic LN, and proved to be a more reliable and objective method for evaluating the prognosis of gastric cancer patients compared with other staging systems (Hayashi et al., 2000). But in this staging system, the number of dissected LN has an impact on the number of metastatic LN. Therefore, the more the LN is dissected, the more metastatic LN will be found, and this will lead to prognosis bias in case of not enough dissected LN. Cheong et al (Cheong et al., 2006) reported that metastatic LN ratio can reduce bias of UICC N staging. In this study, the number of metastatic LN, rather than the positive rate of metastatic LN, is correlated with the total number of dissected LN. This result is similar to what Cheong et al reported (Cheong et al., 2006). MLR staging can better reflect the biological behavior of gastric cancer patients and predict its clinical prognosis. In clinical settings, if MLR staging was used, it would improve the N staging system of UICC TNM staging system to better guide the treatment and predict the prognosis of gastric cancer patients.

In this study, the metastatic LN ratio is correlated with the prognosis of T3 gastric cancer patients. With the increase of detected metastatic LN, 5-year survival rates of T3 gastric cancer patients were decreased dramatically. According to the UICC N staging, if the pN3 patients were divided to subgroups based on metastatic LN ratio, there is significant difference on 5-year survival rates among the subgroups. This conclusion is similar as what Liu et al reported (Liu et al., 2007). Thus, we think that metastatic LN ratio is more accurate and objective to predict 5-year survival rates of T3N3 gastric cancer patients compared with the number of metastatic LN.

The univariate and multivariate analysis showed that metastatic LN ratio were also correlated with the prognosis of T3 gastric cancer patients. A patient with higher metastatic LN ratio was more likely to die after surgery and more little survival time. Metastatic LN ratio was considered an independent risk factor of the prognosis of T3 gastric cancer patients. This is similar to what Nitti and his team reported (Nitti et al., 2003). ROC curve was a wide used method to detect the accuracy of diagnosis. By drawing the ROC curve, we found that MLR staging can accurately predict the 5-year survival rates of T3 gastric cancer patients. The metastatic LN ratio in T3

gastric cancer patients was not correlated with the total number of dissected LN. The metastatic LN ratio was a major independent prognostic factor for the patients with T3 gastric cancer. The ability of the metastatic LN ratio in predicting 5-year survival rate was the same as that of the number of metastatic LN.

Based on the current study, metastatic LN ratio is an independent risk factor of the prognosis of T3 gastric cancer patients. In the case of dissected LN was at least 15, MLR staging could reduce the bias of the 6th-ed UICC TNM Classification for T3 gastric cancer and add to consummate it. If the dissected LN are less than 15, further research on the metastatic LN ratio to predict the prognosis of T3 gastric cancer patients was warranted.

References

- Bando E, Yonemura Y, Taniguchi K, et al (2002). Outcome of ratio of lymph node metastasis in gastric carcinoma. *Ann Surg Oncol*, **9**, 775-84
- Cheong JH, Hyung WJ, Shen JG, et al (2006). The N ratio predicts recurrence and poor prognosis in patients with node-positive early gastric cancer. *Ann Surg Oncol*, **13**, 377-85
- de Manzoni G, Verlato G, Roviello F, et al (2002). The new TNM classification of lymph node metastasis minimises stage migratio problems in gastric cancer patients. *Br J Cancer*, **87**, 171-4
- Dicken BJ, Bigam DL, Cass C, et al (2005). Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg*, **241**, 27-39
- Ding YB, Chen GY, Xia JG, et al (2004). Correlation of tumor-positive ratio and number of perigastric lymph nodes with prognosis of patients with surgically-removed gastric carcinoma. *World J Gastroenterol*, **10**, 182-5
- Hayashi H, Ochiai T, Suzuki T, et al (2000). Superiority of a new UICC-TNM staging system for gastric carcinoma. *Surgery*, **127**, 129-35
- Hohenberger P, Gretschel S (2004). Gastric cancer. *Lancet*, **362**, 305-15
- Hyung WJ, Noh SH, Yoo CH, et al (2002). (Prognostic significance of metastatic lymph node ratio in T3 gastric cancer. *World J Surg*, **26**, 323-9
- Inoue K, Nakane Y, Iiyama H, et al (2002). The superiority of ratio-based lymph node staging in gastric carcinoma. *Ann Surg Oncol*, **9**, 27-34
- Kim JP (1999). Surgical results in gastric cancer. *Semin Surg Oncol*, **17**, 132-8
- Liu C, Lu P, Lu Y, et al (2007). Clinical implications of metastatic lymph node ratio in gastric cancer. *BMC Cancer*, **7**, 200.
- Nitti D, Marchet A, Olivieri M, et al (2003). Ratio between metastatic and examined lymph nodes is an independent prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. *Ann Surg Oncol*, **10**, 1077-85
- Yokota T, Ishiyama S, Saito T, et al (2004). Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. *Scand J Gastroenterol*, **39**, 380-4