Clinical Influence of the Lymph Node Ratio on Lymph Node Metastasis-positive Gastric Cancer Patients Who Receive Curative Treatment

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Abstract. *Background/Aim:* The present study investigated the clinical impact of the lymph node ratio (LNR) on overall survival (OS) and recurrence-free survival (RFS) in cancer patients with lymph node metastasis who received curative treatment. *Patients and Methods:* Eighty-six patients who received curative surgery for gastric cancer between 2000 and 2015, and in whom lymph node metastasis was pathologically confirmed, were included in this study. The LNR was defined as the ratio of the number of metastatic lymph nodes to the total number of harvested lymph nodes. *Results:* A lymph node ratio of 0.23 was considered the optimal cutoff point for classification according to OS. Statistically significant differences were observed in the 3- and 5-year OS rates and 3- and 5-year RFS rates. The 3-year and 5-year OS rates in the LNR <0.23 group were 57.6% and 57.6%, respectively, whereas those in the LNR ≥0.23 group were 33.0% and 0% ($p<0.001$). The 3-year and 5-year RFS rates in the LNR <0.23 group were 45.9% and 43.6%, respectively, whereas those in the LNR >0.23 group were 25.2% and 0% ($p=0.002$). Regarding the site of first relapse, the incidence rates of peritoneal and lymph node metastasis in the LNR >0.23 group were significantly different in comparison to the LNR <0.23 group. *Conclusion:* A high LNR was associated with significantly

worse OS and RFS in patients who received curative treatment for gastric cancer. The lymph node metastasis status should be utilized in the development of treatment strategies for gastric cancer.

Worldwide, gastric cancer is the third-most common cancer and the second leading cause of cancer-related death (1-3). Gastrectomy with D2 lymph node dissection is the standard procedure for locally advanced gastric cancer. Lymph node metastasis is among the most important prognostic factors for gastric cancer (4-6). In the TNM staging system of the Union for International Cancer Control (UICC), the N factor is determined according to the number of metastatic lymph nodes among harvested lymph nodes (7). For an accurate evaluation of the lymph nodes, the UICC and Japanese Gastric Cancer Association's 15th edition of the general rules for gastric cancer currently recommend the harvesting of ≥16 lymph nodes (8). However, the number of metastatic lymph nodes depends on the number of the harvested lymph nodes. Thus, the number of the lymph nodes that are harvested may have an impact on the evaluation of the lymph nodes and an under and overestimation of stage. For the improvement of survival of patients with gastric cancer, the N factor should be considered.

Recently, the lymph node ratio (LNR) has attracted attention for its value in the evaluation of the N factor in some gastrointestinal malignancies, including gastric cancer (9-12). The LNR is defined as the number of metastatic lymph nodes to the number of harvested lymph nodes. However, the number of studies that have evaluated the clinical influence of LNR in gastric cancer is limited (13-15). Furthermore, the optimal cutoff value for the LNR remains controversial. In the present study, we investigated whether the LNR influences overall survival (OS) and recurrence-free survival (RFS) of patients with lymph node-positive gastric cancer.

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Table I. Comparison of survival rates stratified by patient characteristics.

Characteristics	No. of patients (%)	1-year OS rate (%)	3-year OS rate (%)	5-year OS rate (%)	p-Value
Gender					0.554
Male	56 (65.1)	87.4	48.3	44.6	
Female	30 (34.9)	79.2	49.0	37.3	
Age (years)					0.155
<70	41 (47.7)	85.4	53.7	53.7	
≥70	45 (52.3)	84.0	43.2	31.9	
Pathological type					0.583
Intestinal	44 (51.1)	81.8	48.2	41.5	
Diffuse	42 (48.9)	87.6	48.5	41.6	
Pathological T status					0.003
T1 to T2	23 (26.7)	95.5	75.9	75.9	
T3 to T4	63 (73.3)	80.8	39.0	30.1	
Lymph node ratio					<0.001
<0.23	54 (62.8)	92.5	57.6	57.6	
≥0.23	32 (31.2)	71.4	33.0	0.0	
Lymphatic invasion					0.684
Negative	10 (11.6)	90.0	50.0	50.0	
Positive	76 (84.4)	84.0	48.5	41.6	
Vascular invasion					0.934
Negative	17 (19.8)	88.2	44.6	44.6	
Positive	69 (80.2)	83.8	49.7	41.6	
Postoperative surgical complications					0.149
No	48 (55.8)	89.2	55.8	50.7	
Yes	38 (44.2)	78.9	40.6	32.8	

OS: Overall survival.

Patients and Methods

Patients. This retrospective study targeted 288 gastric cancer patients who received curative gastrectomy with lymphadenectomy at Yokohama City University between 2000 and 2015. Eighty-six patients who met the following inclusion criteria were included in the study: 1) histologically proven gastric adenocarcinoma with lymph node metastasis, 2) R0 curative gastrectomy, and 3) ≥16 harvested lymph nodes. Patients who received preoperative chemotherapy and/or radiation therapy were excluded from the present study.

Surgical procedure and adjuvant treatment. Patients with gastric cancer undergo distal or total gastrectomy with radical lymphadenectomy. In principle, the extent of dissection is determined according to the third edition of the Japanese Gastric Cancer Association's Gastric Cancer Treatment Guidelines (16). Spleen-preserving D2 total gastrectomy was permitted in this study. After surgery, patients with pathological II or III disease received adjuvant chemotherapy for one year. In principle, S-1 monotherapy was administered to patients with pathological stage II disease, and S-1 plus docetaxel or capecitabine+oxaliplatin therapy was administered to patients with pathological stage III disease (17-19).

Harvesting of lymph nodes. During surgery, the stomach and perigastric tissues containing the lymph nodes, fat, and vessels were removed in a single block (so-called *en-bloc* dissection). The perigastric tissues were then separated from the stomach and divided into the following three areas: 1) the area containing the lymph

nodes located along the proper hepatic, common hepatic, celiac, and splenic arteries, 2) the area that was previously attached to the lesser curvature, which contained the lymph nodes along the right and left gastric arteries, and 3) the area that was attached to the greater curvature and which contained the lymph nodes along the right and left gastro-epiploic arteries. Lymph nodes were harvested from each area immediately after surgery. First, all palpable lymph nodes were removed from each area. Usually, most lymph nodes could be harvested from the area along the major branched arteries using this method because the amount of fat tissue in this area was limited. In contrast, the lymph nodes in the lesser and greater curvatures were buried in fatty tissue. Subsequently, the remaining tissues were sliced and stretched for the detection of visible lymph nodes. Thereafter, we fixed the resected stomach and all harvested lymph nodes with 10% buffered formalin for at least 48 h (20).

Follow-up. Hematological tests and physical examinations were performed at least every three months for 5 years after surgery. Carcinoembryonic antigen and CA19-9 tumor marker levels were evaluated at least every 3 months for 5 years. Computed tomography (CT) scans were performed every 6-12 months for 5 years.

Evaluations and statistical analyses. The chi-squared test was used to compare differences between the LNR and clinicopathological parameters. OS and RFS were defined as the period between the date of surgery and death and the period between surgery and the occurrence of an event, recurrence, or death, whichever came first, respectively. OS and RFS curves were drawn using the Kaplan-

Table II. Uni- and Multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	p-Value	OR	95%CI	p-Value
Age (years)				0.159			
<70	41	1.000					
≥70	45	1.542	0.845-2.814				
Gender				0.555			
Woman	30	1.000					
Man	56	1.203	0.650-2.227				
Pathological type				0.584			
Intestinal	44	1.000					
Diffuse	42	1.181	0.651-2.140				
T status				0.006			0.044
T1 to T2	23	1.000			1.000		
T3 to T4	63	3.698	1.454-9.405		2.733	1.029-7.262	
Lymph node ratio				<0.001			0.016
<0.23	54	1.000			1.000		
≥0.23	32	2.849	1.559-5.207		2.172	1.157-4.077	
Lymphatic invasion				0.684			
Negative	10	1.000					
Positive	76	1.213	0.477-3.086				
Vascular invasion				0.934			
Negative	17	1.000					
Positive	69	1.032	0.496-2.147				
Postoperative complications				0.153			
No	48	1.000					
Yes	38	1.542	0.852-2.793				

Meier method. Univariate and multivariate survival analyses were performed using a Cox proportional hazards model. *p*-Values of ≤ 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS (v27.0 J Win; SPSS, Chicago, IL, USA). The present study was approved by the IRB of Yokohama City University.

Results

Patients. A total of 86 patients were evaluated. The median number of harvested lymph nodes was 31 (range=16-82). The median number of metastatic lymph nodes was 7.7 (range=1-52). The cutoff value for the LNR was set at 0.23 based on the 3- and 5-year OS rates and according to the results of previous studies (Table I). The study population was classified into the low-LNR (LNR<0.23; n=54) and high-LNR (LNR≥0.23; n=32) groups. There were no significant differences in the background characteristics of the two groups, including the median age, median operation time, median blood loss, and median number of harvested lymph nodes.

Survival analysis and patterns of recurrence. Clinicopathological factors were categorized and analyzed to evaluate their prognostic significance (Table II). T factor and LNR were identified as significant prognostic factors by the univariate analysis of factors associated with OS. The LNR was therefore

included in the final multivariate analysis model. The OS rate at 3 and 5 years after surgery was 57.6% and 57.6%, respectively, in the low-LNR group and 33.0% and 0% in high-LNR group ($p<0.001$). The LNR was a significant prognostic factor by the univariate analysis of factors associated with RFS. Thus, RFS was therefore included as a significant prognostic factor in the final multivariate analysis model (Table III). The RFS rate at 3 and 5 years after surgery was 45.9% and 43.6%, respectively, in the low-LNR group, and 25.2% and 0% in the high-LNR group ($p=0.002$). The OS and RFS curves are shown in Figure 1 and Figure 2, respectively. Regarding the site of first relapse (Table IV), the incidence rates of peritoneal and lymph node recurrence in the high-LNR group were significantly higher in comparison to the low-LNR group.

Subgroup analysis according to pathological N stage. The clinical impact of the LNR was evaluated in each pathological (p) N stage. In patients with pN1 (1-2 metastatic lymph nodes), the OS rate at 3 and 5 years after surgery was 58.5% and 58.5%, respectively, in the low-LNR group; there were no patients with pN1 disease in the high-LNR group. In the patients with pN2 (3-6 metastatic lymph nodes), the OS rate at 3 and 5 years after surgery was 67.3% and 67.3%, respectively, in the low-LNR group and 75.0% and 0.0% in high-LNR group. In the patients with pN3 (≥8 metastatic

Table III. Uni- and Multi-variate Cox proportional hazards analysis of clinicopathological factors for recurrence free survival.

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	p-Value	OR	95%CI	p-Value
Age (years)				0.522			
<70	41	1.000					
≥70	45	1.195	0.692-2.062				
Gender				0.828			
Woman	30	1.000					
Man	56	1.067	0.597-1.905				
Pathological type				0.688			
Intestinal	44	1.000					
Diffuse	42	1.118	0.648-1.931				
T status				0.006			0.040
T1 to T2	23	1.000			1.000		
T3 to T4	63	2.868	1.345-6.115		2.297	1.038-5.085	
Lymph node ratio				0.002			0.037
<0.23	54	1.000			1.000		
≥0.23	32	2.350	1.354-4.081		1.853	1.039-3.302	
Lymphatic invasion				0.595			
Negative	10	1.000					
Positive	76	1.260	0.537-2.953				
Vascular invasion				0.273			
Negative	17	1.000					
Positive	69	1.495	0.728-3.069				
Postoperative complications				0.101			
No	48	1.000					
Yes	38	1.583	0.915-2.738

Figure 1. Overall survival in patients with lymph node ratios of >0.23 and ≤0.23.

Figure 2. Recurrence-free survival in patients with lymph node ratios >0.23 and ≤ 0.23 .

Table IV. Patterns of recurrence between the patients with lymph node ratio <0.23 and those with count score ≥ 0.23 .

Recurrence site	All cases (n=86)		<0.23 (n=54)		≥ 0.23 (n=32)		p-Value
	Number	%	Number	%	Number	%	
Peritoneal	23	26.7	9	16.7	14	43.8	0.006
Lymph node	13	15.1	4	7.4	9	28.1	0.010
Hematological	18	20.9	8	14.8	10	31.3	0.070
Local site	4	4.7	2	3.7	2	6.3	0.633

lymph nodes), the OS rate at 3 and 5 years after surgery was 50.0% and 25.0%, respectively, in the low-LNR group, and 25.0% and 0.0% in high-LNR group.

Discussion

The present study aimed to investigate whether the LNR is a prognostic factor for lymph node metastasis-positive gastric cancer patients who receive curative treatment. The major finding of the present study was that the LNR was a prognostic factor for these patients. Furthermore, the clinical value of the LNR as a prognostic factor was higher in patients with pN3 disease in comparison to those with pN1 or pN2 disease. The present study therefore suggested that the LNRs should be considered in the development of treatment strategies for gastric cancer, especially for patients with a more advanced N factor.

The hazard ratio (HR) of the LNR was 2.849, [95% confidence interval (CI)=1.559-5.207] for OS and 2.350

(95%CI=1.354-4.081) for RFS. In previous studies, similar findings were reported in patients with gastrointestinal malignancies, including gastric cancer. Nakamura *et al.* evaluated the clinical influence of LNR in 973 gastric cancer patients with lymph node metastasis (21). They set the cutoff value of the LNR at 0.737 and classified 583 patients into low-LNR group and 390 patients into high-LNR group. They found that a high LNR was associated with significantly shorter disease-free survival (DFS) and disease-specific survival (DSS) in comparison to a low LNR group (HR=3.64 for DFS and HR=4.15 for DDS). Kim *et al.* evaluated the influence of the metastatic lymph node ratio in data from the adjuvant chemoradiotherapy in stomach tumor (ARTIST) trial (22). In their retrospective study, they analyzed 458 patients from the ARTIST trial. The patients were divided into 4 groups according to the lymph node ratio (0%, 1-9%, 10-25%, and $\geq 25\%$). The HR was 1.000 for a lymph node ratio of 0%, 1.061 for a lymph node ratio of 1-9%, 1.202 for a lymph node ratio of 10-25%, and 3.571 for a lymph node ratio of $\geq 25\%$. Thus,

the LNR might have some clinical impact in patients with gastric cancer and lymph node metastasis who receive curative treatment. On the other hand, in the present study, the LNR showed higher clinical value as a prognostic factor in patients with pN3 disease in comparison to those with pN1 or pN2 disease. In the subgroup analysis, there were statistically significant survival differences in the survival of the high-LNR and low-LNR groups in patients with pN3 disease, but not in patients with pN1 or pN2 disease. The prognostic value of the LNR may therefore be limited to patients with an advanced tumor stage. Similar results were observed in previous studies. Hung *et al.* evaluated the clinical impact of the LNR in 139 gastric cancer patients with >15 metastatic regional lymph nodes (23). In their study, the cutoff value of the LNR was set at 0.80. They showed that the HR of a high LNR for OS was 1.61 (1.01-2.56) in comparison to a low LNR. In addition, Wu *et al.* evaluated the prognostic value of the metastatic lymph node ratio in 745 gastric cancer patients who received curative surgery and in whom at least 15 lymph nodes were examined (24). They demonstrated that the LNR only had prognostic value in patients with stage III gastric cancer ($p<0.001$); it was not a significant prognostic factor in gastric cancer patients with stage I ($p=0.877$) or II ($p=0.169$) disease. Considering the present study and the previous studies, the clinical value of the LNR as a prognostic factor in gastric cancer patients may be limited to those with an aggressive tumor stage. This issue should be investigated in further studies.

To utilize the LNR as prognostic factor in gastric cancer treatment, it is necessary to set an optimal cutoff value. In the present study, we used a cutoff value of 0.23 based on the 3- and 5-year survival rates. Previous studies have used cutoff values of 0.25-0.80 (21-24). The differences in the cutoff values are explained by differences in patient background factors and in the methods of evaluation. First, with regard to patient background, the present study and the studies of Nakamura *et al.* and Hung *et al.* only evaluated patients with lymph node metastasis, while the study by Deng *et al.* evaluated patients with and without lymph node metastasis (21-24). Second, numbers of harvested lymph nodes and metastasis-positive lymph nodes were different. In our study, the median number of harvested lymph nodes was 31 (range=21-82) and the median number of metastasis-positive lymph nodes was 7.7 (range=1-52). In contrast, Deng *et al.* reported that the mean number of metastasis-positive lymph nodes was 4.84 ± 2.19 and the mean number of metastasis-negative lymph nodes was 13.01 ± 9.65 (24). Hwang *et al.* reported that the median number of harvested lymph nodes was 44 (range=33-55). In addition, the median number of metastasis-positive lymph nodes was 4 (range=1-7) in patients with lymph node metastasis (25). Moreover, Hung *et al.* reported that the median number of harvested lymph nodes was 44 (range=17-135) and the median number of metastatic lymph nodes was 22 (range=16-67) (22). The differences in the numbers of harvested lymph nodes and

metastatic nodes might have affected the LNR. Third, the methods of evaluation were different. In the present study, we set the cutoff value according to the 3- and 5-year survival rates. On the other hand, other studies set their cutoff value according to a receiver operating characteristic curve analysis (21-24). Taken together, further studies are required to determine the optimal cutoff value for the LNR.

In conclusion, the LNR was a prognostic factor for patients with gastric cancer and lymph node metastasis who received curative treatment. The clinical value of the LNR as a prognostic factor was higher in patients with a more advanced N factor. Thus, the present study suggested that the LNR should be considered in the development of treatment strategies for gastric cancer, especially for patients with a more advanced N factor.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TA and MN made substantial contributions to the concept and design. TA, MN, KS, SN, HS, KK, TY, IH, HW, MN, HT, TO, NY, TO and YR made substantial contributions to the acquisition of data and the analysis and interpretation of data. TA, HW, MN, HT, TO, NY and YR were involved in drafting the article or revising it critically for important intellectual content. All Authors gave their final approval of the version to be published.

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