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Clinical Impact of Metastatic Lymph Node Ratio in Advanced Gastric Cancer

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Abstract. *Background: We examined the prognostic value of metastatic lymph node ratio (the ratio of the number of metastatic lymph nodes to the number of lymph nodes removed) after curative resection. Patients and Methods: The results of surgery on 758 patients were assessed by uni-and multi-variate analysis by classifying the metastatic lymph node ratio into 4 categories: 0, <0.1, >0.1 <0.2, >0.2. Furthermore, the rationality and prognostic significance of the lymph node ratio classification as a nodal staging system was compared with the UICC/TNM classification. Results: Univariate analysis showed that operative method, location of tumor, macroscopic appearance, tumor diameter, depth of invasion, metastatic lymph node ratio, lymphatic invasion and venous invasion significantly affected prognosis. A Cox proportional regression hazard model revealed that macroscopic appearance, tumor diameter, depth of invasion and metastatic lymph node ratio independently influenced prognosis. Among patients with pN2 by the UICC/TNM classification, survival in those with a metastatic lymph node ratio less than 0.1 was significantly better than in those with a higher metastatic lymph node ratio. Conclusions: The metastatic lymph node ratio is an independent prognostic factor. Extended lymphadenectomy could increase survival of patients with pN2 gastric cancer by decreasing the metastatic lymph node ratio below 0.1.*

Lymph node metastasis is a promising prognostic factor in gastric cancer irrespective of stage. However, the classification of lymph node metastasis in patients with gastric cancer is controversial. In Japan the anatomical distribution of metastatic lymph nodes is used (1), whereas the number of metastatic lymph nodes is used in the tumor node metastasis (UICC/TNM) classification of the International Union Against Cancer (2). Many reports have emphasized the superiority of the UICC classification, on the grounds of simplicity, reliability and stratification. We have also pointed out the advantages of the UICC classification, as well as mentioning some of the problems associated with it (3). In addition, some authors have discussed the significance of the metastatic lymph node ratio (the number of metastatic lymph nodes/the total number of dissected lymph nodes) in gastric cancer (4-8) and in other malignant diseases (9). This parameter carries the advantage of reflecting the quantity of metastatic lymph nodes as well as the extent of lymph node dissection, and, in theory at least, is the most rational classification. However, the usefulness of the metastatic lymph node ratio has not been evaluated in a substantial number of advanced gastric cancer patients undergoing extended or super-extended (para-aortic) lymphadenectomy. In this study, we assessed the prognostic impact of the metastatic lymph node ratio in advanced gastric cancer with potential curative resection in 758 patients, with tumors that invaded proper muscle or extended even further. The prognostic value of the metastatic lymph node ratio was also compared to that of the number of metastatic lymph nodes (on the basis of the sixth UICC/TNM classification).

Patients and Methods

From a prospectively maintained institutional database, a series of 758 eligible patients with a diagnosis of advanced gastric cancer (the depth of invasion is muscularis propria or deeper) were enrolled in this study. All patients underwent R0 curative gastrectomy, registered between April 1980 and March 2000, in the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Japan. Patient demographic data (age, gender), tumor characteristics (tumor location, tumor diameter, macroscopic appearance, histological classification, lymph

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Key Words: Gastric cancer, metastatic lymph node ratio, lymph node dissection, prognostic factor.

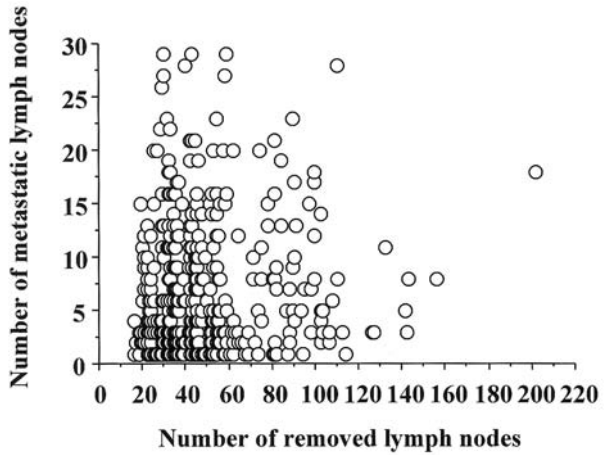

Figure 1. *Correlation between number of metastatic lymph nodes and number of lymph nodes removed in patients with lymph node metastasis.*

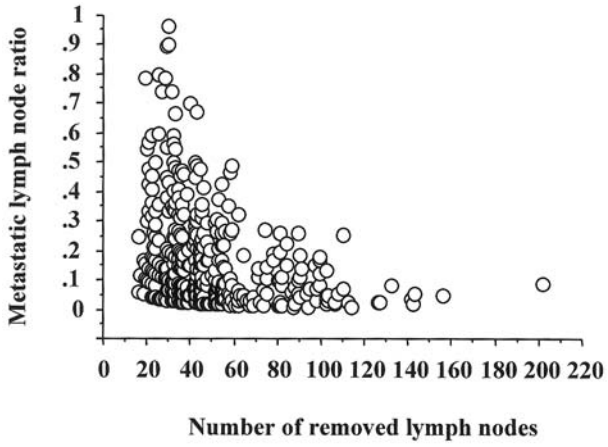

Figure 2. *Correlation between the metastatic lymph node ratio and number of lymph nodes removed in patients with lymph node metastasis.*

node metastasis, depth of invasion, venous invasion, lymphatic invasion) treatment factors (type of gastric resection, extent of lymphadenectomy), and survival data were recorded prospectively. There were 521 males and 237 females, with a mean age of 60.8 years (range 21 to 93 years). Pathological diagnosis and classification were based on the Japanese Classification of Gastric Carcinoma (1), and only lymph node metastasis was evaluated using the UICC/TNM classification (2). Preoperative evaluation was performed by oral barium-meal examination, gastrofiberscopy with biopsy and computed tomography (CT). We diagnosed clinical lymph node metastasis by CT, on the basis of irregular shape of lymph nodes and diameter more than 10 mm.

The macroscopically superficial type of carcinoma was observed in 156 patients, the well-defined type in 234 patients and the ill-defined type in 368. Mean tumor diameter was 56.8±30.0 mm. Histologically, the differentiated type was observed in 322 patients, undifferentiated in 436. Of the patients, 405 (53.4%) had T2 tumors, 291 (38.4%) had T3 tumors and 62 (8.2%) had T4 tumors. At least 15 lymph nodes were dissected pathologically in each patient. Lymph node involvement was detected in 460 patients: pN1 in 284, pN2 in 130 and pN3 in 46 according to the UICC/TNM classification. Lymph node dissection was performed in the Japanese manner. Partial gastrectomy was employed in 438 patients (distal; 435, proximal; 3) and total gastrectomy in 320.

As concerns the extent of lymph node dissection, D3 gastrectomy was employed in patients with subserosa invasion diagnosed by the preoperative imaging modalities and in patients who gave informed consent. D2 gastrectomy was adopted in 583 patients, with 175 D3 gastrectomies.

All patients were followed up according to our standard protocol (every 4-12 weeks, for at least 5 years) including tumor marker studies, gastrofiberscopy, abdominal ultrasonography, computed tomography and chest radiography. Mean follow-up duration was 55.6±33.9 months.

Statistical analysis. Statistical analyses were performed with SPSS statistical software, version 10.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance is defined as $p<0.05$. Disease-specific survival was calculated by the method of Kaplan Meier, and comparisons between groups assessed by the log-rank test. To evaluate the impact of clinicopathological factors on long-term survival, potential prognostic factors were analyzed by univariate analyses, and then assessed by a forward condition Cox proportional hazards regression model. The following variables were inserted: age, gender, location of the tumor, macroscopic appearance, tumor diameter, histological type, depth of invasion, metastatic lymph node ratio, lymphatic invasion, venous invasion, operative method and extent of lymph node dissection. Statistical analysis comparing clinicopathological features used the two-tailed Chi-square test or Student's *t*-test.

Results

Correlation between number of metastatic lymph nodes and number of lymph nodes removed in patients with lymph node metastasis. Numbers of metastatic lymph nodes ranged from 1-29 (mean, 6.6±6.0) and numbers of removed lymph nodes from 16-202 (mean, 46.9±25.1). There was significant correlation between the number of metastatic lymph nodes and number of lymph nodes removed, correlation coefficient = 0.847 (95% Confidence Interval; 0.820 ~ 0.871, $p<0.0001$) (Figure 1).

Correlation between metastatic lymph node ratio and total number of lymph nodes removed. The metastatic lymph node ratio ranged from 0.008-0.966 (mean, 0.165+0.164). There was significant correlation between the metastatic lymph node ratio and total number of lymph nodes removed, correlation coefficient = -0.269 (95% Confidence Interval; -0.351 ~ -0.180, $p<0.0001$) (Figure 2).

Survival. The calculated 5-year and 10-year survival rates in all the registered advanced gastric cancer patients were 65.4%

Table I. *Univariate analysis in 758 registered patients.*

Variable	(n)	Survival time %			*p*-value*	Hazard ratio (95%CI**)
		3y	5y	10y		
Age					0.5863	
<60	336	71.3	64.4	60.9		1
≥60	422	72.2	66.5	58.0		1.0725 (0.8329-1.3811)
Gender					0.3350	
Female	237	75.6	68.1	61.2		1
Male	521	70.2	64.2	58.8		1.1459 (0.8680-1.5126)
Operative method					0.0218	
Partial	444	75.3	70.0	63.0		1
Total	314	66.4	59.0	56.1		1.3427 (1.0423-1.7298)
Lymph node dissection					0.5349	
D2	583	71.7	64.0	58.9		1
D3	175	71.7	70.0	62.0		1.1002 (0.8129-1.4891)
Location of tumor					0.0000	
Lower third	270	70.3	66.2	57.8		1
Middle third	262	81.6	73.5	69.0		0.6677 (0.4860-0.9175)
Upper third	177	66.9	58.6	57.2		1.1260 (0.8115-1.5623)
Whole	49	41.8	38.5	17.9		2.3074 (1.4980-3.5544)
Macroscopic appearance					0.0000	
Superficial	156	93.3	90.4	83.5		1
Well -defined	234	76.3	73.6	68.3		2.6558 (1.5252-4.6246)
Ill-defined	368	60.3	50.4	45.0		5.6757 (3.3890-9.4802)
Tumor diameter (mm)					0.0000	
<50	330	83.4	77.0	70.2		1
≥50, <100	357	67.6	60.8	56.2		1.7798 (1.3369-2.3694)
≥100	71	38.2	33.0	27.5		4.0985 (2.8034-3.9920)
Histological type					0.1064	
Differentiated	322	74.6	69.2	60.2		1
Undifferentiated	436	69.9	62.3	58.6		1.2383 (0.9542-1.6069)
Depth of invasion					0.0000	
T2	405	86.5	81.3	76.7		1
T3,4	353	55.0	47.3	40.2		3.6287 (2.7500-4.7883)
Metastatic lymph node ratio					0.0000	
0	298	87.0	84.1	76.7		1
<0.1	220	75.1	67.2	64.3		1.8830 (1.3005-2.7263)
≥0.1, <0.2	106	58.1	49.0	37.7		3.9655 (2.6751-5.8785)
≥0.2	134	43.0	32.2	28.1		5.7482 (4.0177-8.2240)
Lymphatic invasion					0.0000	
Present	250	81.4	77.0	72.3		1
Absent	508	66.9	59.4	53.2		2.0053 (1.4843-2.7092)
Venous invasion					0.0000	
Present	357	80.5	76.2	70.1		1
Absent	401	63.8	55.3	50.0		2.0915 (1.6037-2.7276)

p-Value*: log-rank test
95%CI**: 95% Confidence interval

and 59.7%, respectively. Those in patients without lymph node metastasis were 84.2% and 76.7%, and in patients with lymph node metastasis, 53.1% and 48.6%, respectively.

Univariate analysis. The prognostic value of each clinicopathological variable was analyzed by univariate analysis. Operative method, location of tumor, macroscopic appearance, tumor diameter, depth of invasion, metastatic lymph node ratio, lymphatic invasion and venous invasion had significant effects on the outcome of surgery (Table I). The differences in survival between each of the 4 categories of metastatic lymph node ratios were all statistically significant ($p<0.0001$, Figure 3).

Multivariate analysis. In a Cox proportional regression hazard model, macroscopic appearance, tumor diameter,

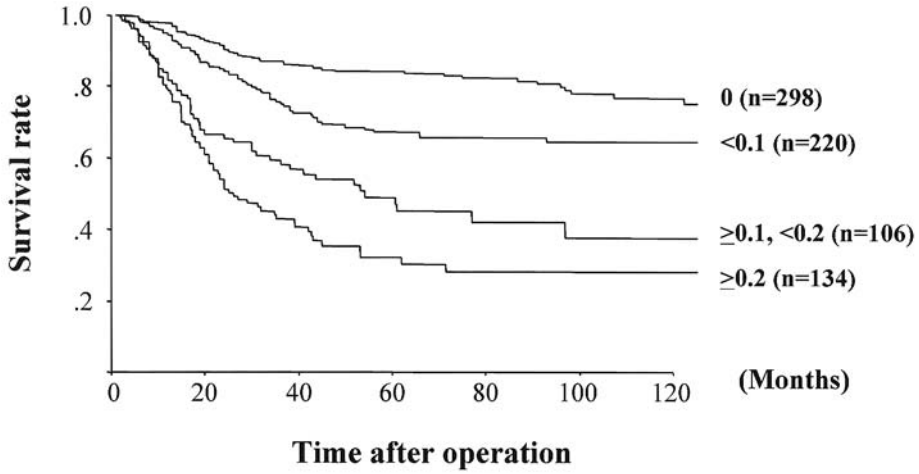

Figure 3. *Survival rate classified by the metastatic lymph node ratio. There was a significant difference in survival between each of the categories of metastatic lymph node ratio (p<0.0001).*

Table II. *A Cox proportional regression hazards model.*

Variable	Coefficient	SE	Hazard ratio (95%CI*)	*p*-value
Macroscopic appearance				0.0003
Well-defined/Superficial	0.5928	0.2916	1.8091 (1.0215-3.2040)	0.0421
Ill-defined/Superficial	1.0067	0.2803	2.7366 (1.5800-4.7399)	0.0003
Tumor diameter (mm)				0.0019
≥50, <100/<50	0.0255	0.1536	1.0258 (0.7591-1.3862)	0.8683
≥100/<50	0.6352	0.2047	1.8875 (1.2637-2.8193)	0.0019
Depth of invasion				
T3,4/T2	0.7053	0.1579	2.0244 (1.4856-2.7587)	0.0000
Lymphatic ratio	0.0000			
<0.1/0	0.4780	0.1904	1.6129 (1.1105-2.3426)	0.0121
≥0.1, <0.2/0	0.8385	0.2095	2.3129 (1.5340-3.4871)	0.0000
≥0.2/0	1.2102	0.1925	3.3540 (2.2997-4.8916)	0.0000

*: 95% Confidence interval

depth of invasion and metastatic lymph node ratio independently influenced the outcome of surgery (Table II).

Relationship between degree of lymph node metastasis and UICC/TNM classification. Of the patients with pN1 according to the UICC/TNM classification, 209 (73.6%) had metastatic lymph node ratios less than 0.1. Of patients with pN2, 81 (62.3%) had metastatic lymph node ratios of 0.1-0.2. Of pN3, 41 (89.1%) belonged to the group with a metastatic ratio 0.2 or more. There was a significant difference in numbers of metastatic lymph nodes between the patients in each of the 4 categories of metastatic lymph node ratio (Table III).

Dependence of survival on metastatic lymph node ratio. There was no significant difference in the cumulative survival of those patients classified as pN1 according to the UICC/TNM classification as a function of metastatic lymph node ratio. However, the survival of patients classified as pN2, who had metastatic lymph node ratios less than 0.1, was significantly better than that of those with higher ratios ($p<0.0001$). Thus, more extensive lymph node dissection significantly improved survival in patients with pN2 (Figure 4).

Comparison of clinicopathological characteristics according to metastatic lymph node ratio in patients with pN2. There were

Table III. *Relationship between degree of lymph node metastasis and different classifications.*

	Metastatic lymph node ratio			
	<0.1	≥0.1, <0.2	≥0.2	*p*-value
Lymph node metastasis*				
pN1	209	63	12	
pN2	10	39	81	
pN3	1	4	41	
Number of metastatic lymph nodes	4.5±2.0	6.5±3.6	13.4±5.9	<0.0001

*: UICC/TNM Classification

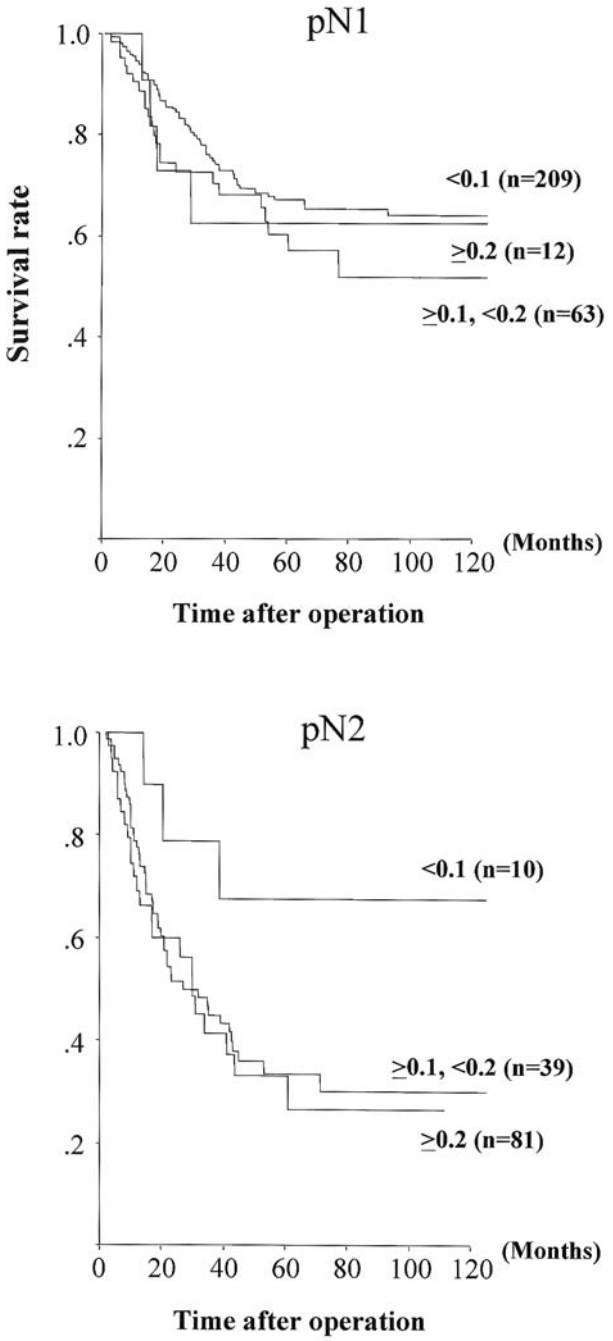

Figure 4. *Survival according to the metastatic lymph node ratio in each lymph node category defined by the UICC/TNM classification. There was no significant difference in cumulative survival in patients with pN1. However, there was a significant difference in survival depending on metastatic lymph node ratio in patients with pN2 (p<0.0001).*

significant differences in the extent of lymph node dissection and the number of dissected lymph nodes, but no differences in other clinicopathological variables between patients with metastatic lymph node ratio <0.1 and those with higher ratios. pN2 patients (those with 6-15 metastatic lymph nodes) with metastatic lymph node ratios of 0.1 or less benefited from extended lymph node dissection (Table IV).

Discussion

The current study revealed that the metastatic lymph node ratio (the number of metastatic lymph nodes/the total number of lymph nodes removed), which reflects the extent of lymph node dissection in addition to the degree of lymph node metastasis, is an important prognostic factor in patients with curatively resected advanced gastric cancer. Furthermore, extended lymph node dissection significantly improved long-term survival in pN2 patients with metastatic lymph node ratios less than 0.1. Hence it might be advisable to restrict D2 or more extended lymph node dissection to this group.

The prognosis of patients with gastric cancer depends not only on clinicopathological variables (*i.e.*, location of tumor, depth of invasion and lymph node metastasis) but also on therapeutic measures (*i.e.*, the extent of resection and lymph node dissection). As concerns lymph node metastasis, both the anatomical distribution of metastatic lymph nodes (Japanese Classification of Gastric Carcinoma) (10, 11) and the number of metastatic lymph nodes (UICC/TNM) have been reported to be independent prognostic factors (12-15). The metastatic lymph node ratio has also been shown previously to be an independent prognostic factor (4-8). Since this parameter reflects both tumor characteristics (number of metastatic lymph nodes) and therapeutic measure (extent of lymph node dissection), it is theoretically the most rational one. Although several authors have asserted the superiority of the criterion of metastatic lymph node ratio in gastric cancer, there is no agreement on the appropriate categories of metastatic lymph node ratio.

Table IV. *Comparison of clinicopathological characteristics according to metastatic lymph node ratio in patients with pN2.*

	Metastatic lymph node ratio		*p*-value
	<0.1 (n=10)	≥ 0.1 (n=120)	
Gender			0.7264
Female	4	38	
Male	6	82	
Age			0.1093
<60	7	51	
≥60	3	69	
Location of tumor			0.1468
Lower third	1	45	
Middle third	5	37	
Upper third	4	26	
Whole	0	12	
Macroscopic appearance			0.9296
Superficial	1	9	
Well-defind	2	29	
Ill-defined	7	82	
Tumor diameter			0.5007
<50	4	28	
≥50, <100	5	76	
≥100	1	16	
Pathologic type			0.9586
Differentiated	4	47	
Undifferentiated	6	73	
Depth of invasion			0.1318
T2	5	30	
T3,4	5	90	
Number of metastatic lymph nodes	8.9±2.2	9.8±2.5	0.0978
Lymph node dissection			<0.0001
D2	0	88	
D3	10	32	
Number of dissected lymph nodes	108.4±26.4	55.1±18.7	<0.0001

Some clinicians favor 3 categories and others 4, and different cut-off values of 0.1, 0.2, 0.25 and 0.5 have been employed (4-8). However, all workers emphasized the clinical value of the ratio in terms of simplicity, convenience, reproducibility, and prognostic importance.

In a previous study, we suggested that the UICC/TNM classification was more effective and rational as a prognostic variable than the Japanese Classification of Gastric Carcinoma (3). Although the metastatic lymph node ratio may be the most reliable of the current forms of classification of lymph node metastasis, the results of surgery in our Institute depend on Japanese surgical procedures in which the extent of lymph node dissection reflects Japanese practice. The number of lymph nodes removed is a function of the extent of the dissected fields and depends on whether D2 or D3 is used. The number of lymph nodes removed by extended lymph node dissection is a great deal larger in Japan than in the institutes of Western countries. Therefore, it is important to take into consideration the influence of the Japanese manner of lymph node dissection on outcomes.

The extent of lymph node dissection that is appropriate is controversial. D1 gastrectomy is widely accepted as a standard procedure and is employed in many hospitals in Western countries in accord with the results of randomized controlled trials (16, 17). However, D2 gastrectomy is common for advanced gastric cancer in Japan. Recently, many Japanese gastroenterological surgeons have followed "The Guidelines for Gastric Cancer", published not only for surgeons but also for patients with gastric cancer in 2001, and have performed more tailored and appropriate treatments for gastric cancer. In these guidelines, D2 is recommended as the standard for advanced gastric cancer and D3 is included as a clinical research entity. The use of the concept of the metastatic lymph node ratio in our present study has revealed that more extensive lymph node dissection would improve the outcome of surgery in patients with pN2 gastric cancer, whereas there would be no benefit of extended lymph node dissection in patients with pN1. This means that D2 or more extended lymph node clearance (*i.e.*, D3) would eliminate the microinvolvement or micrometastases of lymph nodes in patients with moderately disseminated lymph node metastasis. Thus, although extended lymph node dissection does not always improve outcome in patients with advanced gastric cancer, this operation should be considered for patients with gastric cancer with moderately disseminated lymph node metastasis (*i.e.*, pN2). This framework also suggests the appropriate extent of lymph node dissection in each N stage. It will, of course, be necessary to evaluate the long-term results of different extents of lymph node dissection by means of randomized controlled trials in order to justify this therapeutic strategy. However, as it is practically impossible to diagnose precisely the number and the anatomical extent of lymph node metastasis prior to surgery, novel techniques for predicting lymph node metastasis preoperatively, such as imaging modalities or molecular biological analyses, are required.

In conclusion, the lymph node ratio has prognostic value after curative resection of advanced gastric cancer. This parameter enables surgeons to assess objectively, and to compare, the surgical outcomes of gastric cancer throughout the world. In the subgroup of patients with pN2 gastric cancers, extended lymphadenectomy that reduces the metastatic lymph node ratio to below 0.1 would provide a prognostic gain. However, it is essential that we develop new technology for diagnosing lymph node metastasis prior to surgery.

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