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Outcome of Ratio of Lymph Node Metastasis in Gastric Carcinoma

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Background: The purpose of this study was to clarify the outcome of the ratio of the metastatic lymph nodes (RML) in gastric cancer patients.

Methods: The postoperative survival of 650 patients with gastric cancer who underwent D2 curative gastrectomy was analyzed with regard to the RML. The location, number, and RML in the N1 station and in all (N1 and N2) stations were analyzed. These data were compared from the viewpoints of staging accuracy and patient survival.

Results: The RML was classified as follows: RML 0, no involvement; RML 1, 0 to .1; RML 2, .1 to .25; and RML 3, ≥.25. The 5-year survival rates stratified by RML were RML 0, 86%; RML 1, 68%; RML 2, 35%; and RML 3, 16%. Cox model identified all methods of classifying lymph node metastases as independent prognostic indicators in each calculation. However, a second Cox regression revealed that RML was the only independent prognostic factor among the three methods ($P < .001$). Stage migration was present in 35 cases (15%) when the number was considered. However, only 15 cases (7%) were underdiagnosed when RML was used.

Conclusions: RML is a useful classification of patients with gastric cancer. It may prevent the phenomenon of stage migration.

Key Words: Gastric cancer—Ratio of lymph node metastasis—"Will Rogers" phenomenon—Multivariate analysis.

The classification of lymph node metastasis in patients with gastric carcinoma is controversial. In Japan, classification based on the anatomical location of nodal involvement has been established and used.[1,2] However, recent studies indicate that quantitative evaluation based on the number of lymph node metastases is more predictive of patient survival than evaluation based on anatomical lymphatic spread.[3–6] Several articles have emphasized the clinical significance of a new quantitative classification, the ratio of positive nodes (RML), in stomach carcinoma and other malignant neoplasms.[7–10] However, no previous report has identified the RML as an independent prognostic factor analyzed by a second-step multivariate model in a sufficient number of patients who had undergone D2 dissection.

In addition, this study is the first to show the prognostic value of the incidence of invaded nodes from the viewpoint of the number of dissected lymph nodes (NDL). In this retrospective study of lymph nodes sampled from 650 patients with gastric cancer who underwent R0 resection, we compared the prognostic value of the RML with the location of positive nodes (on the basis of the new Japanese rule[11]) and the number of positive nodes (on the basis of the new tumor-node-metastasis classification[12]).

Furthermore, this article discusses the possibility of preventing the phenomenon of stage migration[13] by using RML. Japanese surgeons routinely perform extended D2 lymph node dissection for gastric cancer without distant metastasis. In contrast, most surgeons in Western countries do not perform aggressive lymphadenectomy because of uncertainty regarding improvement in survival and a high operative risk.[14,15] Limited dissection

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TABLE 1. *Results of 5-year survival rates of each clinical and pathologic variable calculated by univariate analysis (log-rank test)*

Clinicopathologic factor	5-y survival (%)	χ^2	*P* value	RR	95% CI
Tumor size (cm)					
≤2	92			1	
<2 and ≥6	78	61.136	<.001	2.045	1.234–3.391
<6 and ≥10	58			3.207	1.776–5.481
<10	27			7.894	4.406–14.142
Depth of tumor invasion					
T1	89			1	
T2	60	129.904	<.001	3.723	2.635–5.261
T3	33			7.839	4.981–12.335
T4	21			17.93	9.796–32.831
Macroscopic type					
Early	90			1	
Borrmann 1 or 2	65	103.899	<.001	3.558	2.472–5.123
Borrmann 3	41			5.257	3.514–7.863
Borrmann 4	38			9.644	5.836–15.938
Tumor infiltrating patterns					
α	82			1	
β	77	38.367	<.001	1.905	1.258–2.884
γ	53			3.774	2.429–5.859
Histologic type					
Well differentiated	80			1	
Moderately differentiated	63	2.815	.245	1.217	0.821–1.805
Undifferentiated	51			1.331	0.952–1.861
Lymphatic invasion					
Negative	87			1	
Minimal (ly1)	72	61.723	<.001	2.709	1.876–3.913
Marked (ly2, 3)	54			4.315	2.991–6.228
Venous invasion					
Negative	82			1	
Minimal (v1)	53	42.153	<.001	2.367	1.693–3.309
Severe (v2, 3)	52			3.299	2.075–5.248
Location of nodal status					
N0	86			1	
N1	66	95.806	<.001	2.856	2.014–4.049
N2	43			5.162	3.692–7.217
No. of positive nodes					
0 (N0)	88			1	
1–6	69	160.043	<.001	2.613	1.871–3.649
7–15	39			5.858	3.872–8.863
≥16	5			17.71	10.784–29.087
Ratio of metastatic lymph nodes (RML)					
0 (RML 0)	88			1	
0–.1 (RML 1)	75	153.364	<.001	2.195	1.526–3.159
0.1–.25 (RML 2)	38			5.944	4.034–8.757
.25 (RML 3)	19			10.6	6.929–16.215

CI, confidence interval.

yields no information regarding metastasis in N2 lymph nodes. Extensive lymphadenectomy can result in stage migration whether anatomical level or the number of metastatic lymph nodes is used. Our research suggests that RML is the best method to prevent stage migration and has the most prognostic value.

PATIENTS AND METHODS

This study consisted of 650 consecutive patients who underwent D2 gastrectomy with R0 resection at the Department of Surgery II, Kanazawa University Hospital, between April 1974 and December 1995. Clinical and histopathologic factors of patients were evaluated according to the 2nd English edition of the general rules for gastric carcinoma study established by the Japanese Research Society for Gastric Cancer.[11] The definition of the number of metastatic lymph nodes was based on the 5th edition of the tumor-node-metastasis classification.[12] Patients with hepatic metastasis, peritoneal dissemination, or distant lymph node involvement were excluded from the study. Furthermore, no patient was included with 15 or fewer dissected lymph nodes. The criteria were also based on the tumor-node-metastasis system.[12] All the

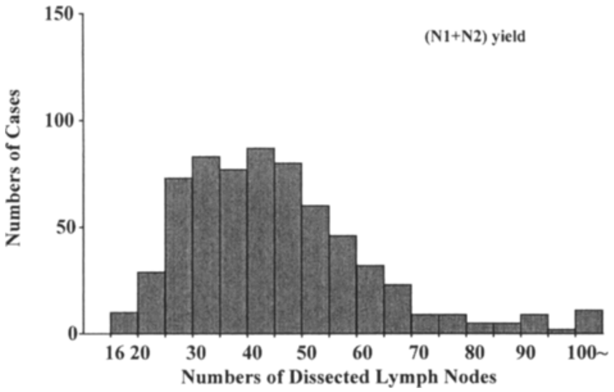

FIG. 1. Histogram of the number of dissected nodes in the N1 plus N2 nodal yield.

resected lymph nodes were examined by hematoxylin-eosin staining for metastasis.

Lymph nodes were meticulously dissected from en-bloc specimens. A lymphadenectomy map was created precisely for each patient, including the numbers of positive and negative lymph nodes at specific stations. Dissection and mapping were performed by experienced surgeons.

The ratio between the positive nodes and the dissected nodes was calculated. The classification of the RML was established according to the following criteria: RML 0, no lymph node metastasis (n = 422); RML 1, 0 to .1 (n = 130); RML 2, .1 to .25 (n = 60); and RML 3, ≥.25 (n = 38).

The SPSS (SPSS, Inc., Chicago, IL) statistical software was used for multivariate analysis. Survival rates were calculated from the time of operation by using the Kaplan-Meier product-limit method.[16] Univariate comparisons of time-dependent events were performed with the log-rank test.[17] The following factors were analyzed

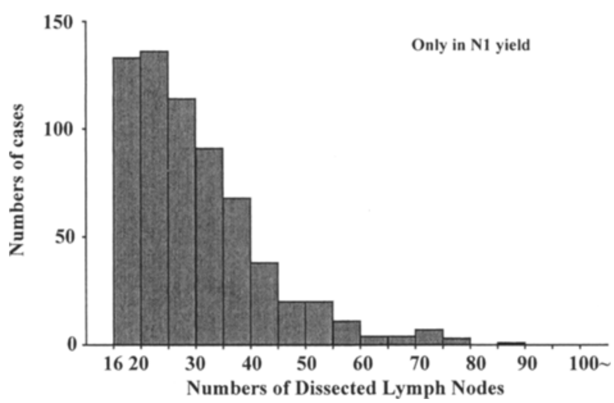

FIG. 2. Histogram of the number of dissected nodes in N1 nodal yield only.

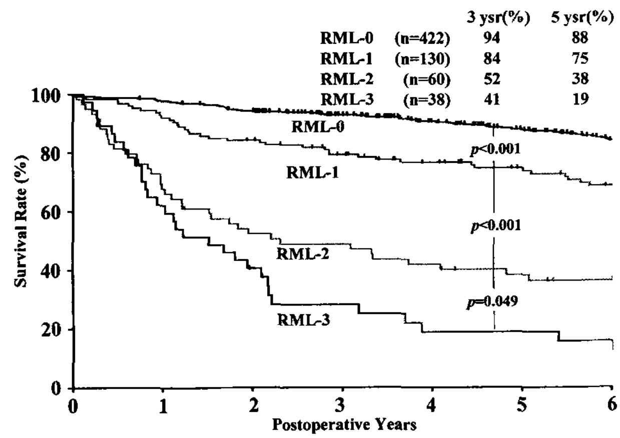

FIG. 3. Survival curves subdivided according to the ratio of metastatic lymph nodes (RML).

for prognostic value by using the Cox stepwise regression model[18]: tumor size, depth of tumor invasion, macroscopic type, tumor infiltrating pattern, histopathologic findings, lymphatic involvement, vessel invasion, location of nodal status, number of metastatic lymph nodes, and RML. A significance level of .10 was used for entry and retention of variables in the stepwise multivariate model. Each prognostic factor was subdivided into three or four categories (Table 1). *P* values <.05 were considered significant.

RESULTS

In the total N1 and N2 nodal yield, the median number of resected nodes per patient was 47 (mean, 45; range, 16–132) (Fig. 1). To elucidate the influence of the NDL on prognosis, we established three categories: NDL 1 (n = 129), 16 to 30 nodes; NDL 2 (n = 245), 31 to 50 nodes; and NDL 3 (n = 276), ≥51 or more nodes. Figure 2 shows the NDLs in the N1 station (median, 27; mean, 30; range, 16–87).

Survival curves stratified by RML in the patients who underwent curative resection are shown in Fig. 3. There were statistical differences between each RML category. The 3- and 5-year survival rates in patients with RML 3 were 41% and 19%, respectively, the poorest in the four categories. An excellent prognosis (94% and 88% 3- and 5-year survival rates, respectively) was seen in node-negative patients (RML 0) compared with the RML 1 or RML 2 groups (both $P < .001$). The 3- and 5-year survival rates in the RML 1 group were 84% and 75%, respectively, and in the RML 2 group they were 52% and 38%, respectively; there was a significant difference between these groups ($P < .001$). As shown in Table 2, among patients with positive nodes in the N1 node

TABLE 2. *Survival curves according to RML in N1-positive and N2-positive patients*

Ratio of metastatic lymph nodes (RML)	N1-positive			N2-positive		
	3-y survival (%)	5-y survival (%)		3-y survival (%)	5-y survival (%)	
0–.1 (RML1)	87	77	$P < .001$; $P < .001$	76	66	$P = .026$; $P < .001$
.1–.25 (RML2)	46	33	$P < .001$	57	41	$P = .026$
≥.25 (RML3)	17	17	$P < .001$	45	19	$P < .001$

station, patients with RML 1 had a significantly better prognosis (3-year, 87%; 5- year, 77%) than did those with RML 2 (3-year, 46%; 5-year, 33%) or RML 3 (3-year, 17%; 5-year, 17%) (both $P < .001$). Also, in the patients with positive nodes at the N2 level, RML 2 (3-year, 57%; 5-year, 41%) and RML 3 (3-year, 45%; 5-year, 19%) patients had a significantly poorer prognosis than RML 1 patients (3-year, 76%; 5-year, 66%) ($P = .026$ and $P < .001$, respectively) (Table 2).

To clarify the prognostic independence of RML from the number of metastatic lymph nodes, this study stratified patients with same number of positive nodes by RML. Table 3 depicts the survival distribution in patients with three or four positive nodes. The survival rate in the RML 2 group (3-year, 46%; 5-year, 38%) was statistically higher than that in the RML 1 group (3-year, 79%; 5-year, 70%) ($P = .026$). In patients with five or six positive nodes, there also was a difference in prognosis between the RML 1 group (3-year, 100%; 5-year, 100%) and the RML 2 group (3-year, 47; 5-year, 29%; $P = .067$) (Table 3).

The prognostic value of each clinicopathologic factor analyzed by univariate analysis is listed in Table 1. Histopathologic differentiation did not have prognostic significance. Multivariate analysis using the stepwise Cox proportional hazards regression model was performed to evaluate each prognostic parameter determined by univariate log-rank test (Tables 4–6). Each classification for lymph node metastasis demonstrated independent significance for survival as compared with the other seven clinicopathologic indicators: tumor size, macroscopic type, depth of invasion, tumor infiltrating patterns, histologic type, lymphatic invasion, and vessel involvement. Table 4 shows that anatomical nodal status demonstrated an independent influence on survival ($P < .001$; $\chi^2 = 18.807$). In particular, the relative risk (RR) of mortality was 1.508 (95% confidence interval [CI], 1.102–2.235) for patients with N1 disease and 2.408 (95% CI, 1.615–3.589) for patients with N2 disease, versus patients with N0 disease (RR = 1). As shown in Table 5, the number of metastatic lymph nodes was an independent predictor for patient prognosis ($P < .001$; $\chi^2 = 46.649$). Patients with ≥16 positive nodes had a RR of death of 5.98 (95% CI, 3.364–10.628) compared with patients with no positive node; patients with 1 to 6 positive nodes had an RR of 1.403 (95% CI, .954–2.063), and those with 7 to 15 metastatic nodes had an RR of 2.922 (95% CI, 1.823–4.684). The classification according to RML also revealed significance for survival in the multivariate stepwise model ($P < .001$; $\chi^2 = 52.403$). The RR was 1.403 (95% CI, .954–2.063) for patients with RML 1, 2.922 (95% CI, 1.823–4.684) for patients with RML 2, and 5.981 (95% CI, 3.365–10.628) for patients with RML 3, compared with those with RML 0 (RR = 1). In addition, patients with RML 1 had a 2.35 times lower RR (1.403 vs. 5.981) than those with RML 3 (Table 6).

Furthermore, the second multivariate stepwise Cox regression analysis, in which all lymph node classifications were analyzed in the same calculation, revealed that RML was the strongest prognostic variable ($P < .001$; $\chi^2 = 47.867$), followed by depth of tumor invasion ($P < .001$; $\chi^2 = 22.475$), macroscopic type ($P = .037$; $\chi^2 = 9.118$), venous invasion ($P = .059$; $\chi^2 = 6.129$), and lymphatic invasion ($P = .084$; $\chi^2 = 5.038$). Compared with the RR of death for patients with RML 0 (RR = 1), the RR of death was 3.002 (95% CI, .961–9.383) for patients with RML 1, 8.078 (95% CI, 2.919–22.353) for patients with RML 2, and 7.463 (95% CI, 4.078–13.639) for patients with RML 3. The RR of death was, therefore, 2.69 times greater (8.078 vs. 3.002) for patients with RML 2 than for patients with RML 1. The location

TABLE 3. *Survival curves according to RML for three to six positive nodes*

Ratio of metastatic lymph nodes (RML)	3 or 4 positive nodes			5 or 6 positive nodes		
	3-y survival (%)	5-y survival (%)		3-y survival (%)	5-y survival (%)	
0–.1 (RML1)	79	70	$P = .026$	100	100	$P = .067$
.1–.25 (RML2)	46	38	$P = .026$	29	29	$P = .067$

TABLE 4. *First multivariate analyses using Cox stepwise proportional hazard model: each classification of lymph node metastasis was analyzed separately as independent covariate: Location of nodal status*

Clinicopathologic factor	χ^2	*P* value	Relative risk	95% CI
Depth of tumor invasion	24.136	<.001		
T1			1	
T2	.229	.632	1.287	.459–3.613
T3	1.429	.232	1.969	.648–5.987
T4	7.887	.005	5.329	1.658–17.136
Macroscopic type	13.053	.007		
Early			1	
Borrmann 1 or 2	.873	.351	1.633	.584–4.566
Borrmann 3	2.163	.141	2.246	.764–6.599
Borrmann 4	5.564	.018	3.869	1.257–11.911
Venous invasion	6.307	.059		
Negative			1	
Minimal (v1)	.777	.378	1.176	.821–1.685
Severe (v2, 3)	6.267	.012	1.853	1.143–3.001
Location of nodal status	18.807	<.001		
N0			1	
N1	4.193	.041	1.508	1.018–2.235
N2	18.617	<.001	2.408	1.615–3.589

CI, confidence interval.

(excluded in the first stepwise retention) and number of the metastatic nodes (excluded in the fourth stepwise retention) did not have an independent influence on survival (Table 7). Survival curves according to NDL are shown in Fig. 4. There were no significant differences between the groups (3- and 5-year survival rates: NDL 1; 86% and 76%; NDL 2, 85% and 79%; and NDL 3, 85% and 75%, respectively). Table 8 shows the survival distributions according to RML in patients with NDL 1. RML 3 patients had the worst prognosis, with a 5-year survival of 25%. In NDL 2, patients with RML 1 showed a significantly better prognosis than patients with RML 2 or RML 3 ($P = .024$ and $P = .019$, respectively) and a significantly worse prognosis than patients with RML 0 ($P < .001$). As shown in patients with NDL 3, there were significant differences between each category of RML.

TABLE 5. *Numbers of metastatic lymph nodes*

Clinicopathologic factor	χ^2	*P* value	Relative risk	95% CI
Depth of tumor invasion	23.936	<.001		
T1			1	
T2	.193	.661	1.267	.441–3.643
T3	1.184	.277	1.877	.604–5.831
T4	7.441	.006	5.239	1.594–17.222
Macroscopic type	8.103	.059		
Early			1	
Borrmann 1 or 2	1.066	.302	1.739	.608–4.973
Borrmann 3	1.571	.211	2.024	.672–6.095
Borrmann 4	4.372	.037	3.401	1.079–10.709
Venous invasion	5.279	.093		
Negative			1	
Minimal (v1)	.402	.526	1.124	.783–1.614
Severe (v2, 3)	5.279	.022	1.771	1.088–2.884
No. of positive nodes	46.649	<.001		
0 (N0)			1	
1–6	2.958	.085	1.403	.954–2.063
7–15	19.835	<.001	2.922	1.823–4.684
≥16	37.167	<.001	5.981	3.365–10.628

CI, confidence interval.

TABLE 6. *Ratio of metastatic lymph nodes (RML)*

Clinicopathologic factor	χ^2	*P* value	Relative risk	95% CI
Depth of tumor invasion	22.286	<.001		
T1			1	
T2	.141	.707	1.215	.439–3.357
T3	1.226	.268	1.856	.621–5.547
T4	6.851	.009	4.692	1.474–14.933
Macroscopic type	10.213	.024		
Early			1	
Borrmann 1 or 2	1.812	.178	2.001	.729–5.489
Borrmann 3	2.461	.117	2.337	.809–6.753
Borrmann 4	6.176	.013	4.046	1.344–12.183
RML	52.403	<.001		
0 (RML 0)			1	
0–.1 (RML 1)	.881	.348	1.217	.807–1.835
.1–.25 (RML 2)	23.294	<.001	2.989	1.916–4.663
≥.25 (RML 3)	37.759	<.001	4.546	2.805–7.369

CI, confidence interval.

If D1 limited dissection had been performed, 10 patients would have been diagnosed as N0 with metastasis in the N2 lymph node station. Ninety-three of 103 cases, which were actually positive in the N2 lymph node station, would have been diagnosed N1 if D1 surgery had been performed. Therefore, the Will Rogers phenomenon occurred in 103 (45%) of 228 patients with lymph node metastases (Table 9). Grouping lymph node metastases by the number of positive nodes, 36 patients (16%) would be underdiagnosed by a D1 limited lymph node dissection (Table 10). If the RML classification were used, only 52 cases (23%) would demonstrate stage migration, of which 15 (29%) would be underdiagnosed and 37 (71%) would be overdiagnosed if D1 limited lymphadenectomy had been performed (Table 11).

Table 12 shows the results of the stepwise Cox proportional hazard analysis to identify the prognostic index

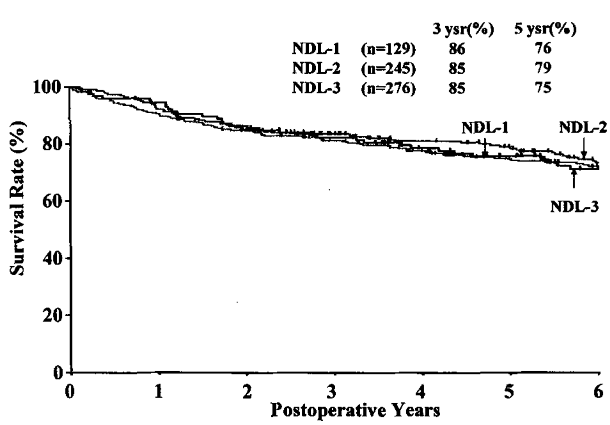

FIG. 4. Survival curves according to the number of dissected lymph nodes (NDL).

considering the N1 node station only. RML again was identified to be an independent prognosticator ($P = .037$; $\chi^2 = 9.701$), as was macroscopic type ($P < .001$; $\chi^2 = 24.798$). RML 2 and RML 3 had RR values of 10.1 (95% CI, 1.307–78.914) and 7.4 (95% CI, .881–62.635) when compared with RML 0 patients, respectively.

DISCUSSION

The depth of wall invasion and the anatomical spread of lymph node metastases are the important prognostic indicators in patients with stomach carcinoma without distant metastases,[19,20] and they constitute the basis in the Japanese classification and tumor-node-metastasis classification. A new Japanese classification has been developed from the results obtained from vast numbers of studies based on the physiologic lymphatic flow and anatomical lymphatic spread, confined by meticulous sampling and histologic study. The Japanese rules about the grouping of lymph node metastases allow categorization of different locations of lymph nodes into so-called lymph node stations. Under the Japanese rule, the lymph nodes of the stomach are numbered from station 1 to 20 and 110 to 112 and subsequently are grouped into three groups, N1 to N3, resulting in the establishment of the D number (D0–D3).[11] Recently, the validity of the Japanese classification has been discussed as to whether or not extended lymph node dissection (D2) is superior to limited dissection (D1).[21–24] A randomized controlled trial in the Netherlands, with approximately 1000 cases, revealed that a D2 extended lymphadenectomy did not contribute to better survival.[23] In addition, a randomized controlled trial in England also reported the same re-

TABLE 7. *Second multivariate analysis using a Cox stepwise regression model: all systems of grouping for nodal involvement were analyzed in the same calculation*

Clinicopathologic factor	χ^2	*P* value	Relative risk	95% CI
Depth of tumor invasion	22.475	<.001		
T1			1	
T2	.052	.819	1.126	.724–5.611
T3	.794	.373	1.651	.784–6.719
T4	6.532	.011	4.552	1.302–12.567
Macroscopic type	9.118	.037		
Early			1	
Borrmann 1 or 2	1.798	.179	2.015	.724–5.611
Borrmann 3	2.295	.129	2.294	.783–6.719
Borrmann 4	5.835	.016	4.044	1.302–12.567
Lymphatic invasion	5.038	.084		
Negative			1	
Minimal (ly1)	.892	.345	1.236	.797–1.916
Marked (ly2, 3)	.719	.397	0.788	.455–1.366
Venous invasion	6.129	.059		
Negative			1	
Minimal (v1)	.913	.339	1.208	.819–1.781
Severe (v2, 3)	6.127	.013	1.959	1.151–3.339
Ratio of metastatic lymph nodes (RML)	47.867	<.001		
0 (RML 0)			1	
0–.1 (RML 1)	3.574	.059	3.002	.961–9.383
.1–.25 (RML 2)	16.183	<.001	8.078	2.919–22.353
≥.25 (RML 3)	42.481	<.001	7.463	4.078–13.659

CI, confidence interval.

sults.[24] However, Sasako et al.[25] reported a new method to evaluate the therapeutic value of lymph node dissection by multiplying the incidence of metastases and the percentage 5-year survival rate of patients with metastases in each node station. They stressed that D2 dissection can improve patient prognosis. A classification based on this theory was established in the 2nd English edition of the Japanese rules for gastric cancer.[11,26] However, this classification may cause stage migration because of the different extents of lymphadenectomy, regardless of its prognostic superiority. In fact, our study revealed that 103 (45%) of 228 patients with lymph node metastasis would have been understaged by a D1 dissection.

Conversely, the classification of nodal metastases according to the tumor-node-metastasis classification is subdivided into four groups according to the number of positive lymph nodes. Several articles have emphasized the prognostic value of the number of nodes involved in patients with stomach carcinoma. Shiu et al.[4] reported that four or more positive nodes adversely influenced survival, and Jaehne et al.[5] showed that the number of metastatic lymph nodes in curative resection was an independent prognostic factor. In Japan, Adachi et al.[6]

TABLE 8. *Survival curves according to RML in NDL (number of dissected lymph nodes) 1, 2, or 3 patients*

Ratio of metastatic lymph nodes (RML)	NDL 1		NDL 2		NDL 3	
	3-y survival (%)	5-y survival (%)	3-y survival (%)	5-y survival (%)	3-y survival (%)	5-y survival (%)
0 (RML 0)	90	84	87	77	94	87
				P < .001		*P* = .031
0–.1 (RML 1)	75	63	67	51	77	75
		P = .051		*P* = .024		*P* < .001
.1–.25 (RML 2)	30	30	48	31	55	36
		P = .012		*P* = .019		*P* = .020
≥.25 (RML 3)	38	25	13	13	6	6

TABLE 9. *Stage migration caused by different extents of lymph node dissection in 228 cases with lymph node metastasis: location of nodal status*

N1 station	(N1 + N2) station 1	2
0	0	10[a]
1	125	93[a]

[a] Underdiagnosed cases.

TABLE 11. *Ratio of metastatic lymph nodes*

Ratio in N1 station	Ratio in (N1 + N2) station 0–.1	.1–.25	≥.25
0	9[a]	0	0
0–.1	95	3[a]	1[a]
.1–.25	25[b]	46	2[a]
≥.25	1[b]	11[b]	35

[a] Underdiagnosed cases.
[b] Overdiagnosed cases.

reported that the level of positive nodes was inferior as a prognostic factor to quantitative evaluation. This study also showed the prognostic significance of the number of metastatic lymph nodes on the basis of the new tumor-node-metastasis rule. The 5-year survival rate in patients with ≥16 positive nodes was only 13%, similar to that with distant metastasis. In addition, there were significant survival distributions for each category. These results may indicate the accuracy of the tumor-node-metastasis classification according to the number of nodes involved. Furthermore, the Will Rogers phenomenon was seen in only 5% of all patients.

A few articles have described the clinical value of the RML. Yu et al.[7] emphasized that the classification of nodal metastasis to the regional lymph nodes as N0 (no nodal metastasis), N1 (metastasis in 1%–25% of dissected nodes), and N2 (metastasis in >25% of dissected nodes) would be a simple, convenient, and reproducible system with an ability to predict surgical results. Msika et al.[27] reported that multivariate analysis identified the presence of residual tumor after resection as the most important independent prognostic factor, followed by the ratio of invaded to removed lymph nodes, in 186 squamous cell carcinomas of the esophagus. Siewert et al.[9] reported that the lymph node ratio and the number of lymph node metastases were important prognostic factors in patients with resected gastric cancer. Furthermore, Kwon and Kim[10] clarified that the RML was the most meaningful prognostic factor analyzed by a multivariate Cox regression model.

However, no article has demonstrated the prognostic significance of the RML by second-step multivariate analysis compared with anatomical node level (Japanese rule) and the number of nodes involved (tumor-node-metastasis rule). In this study, all systems for grouping nodal involvement were independent prognostic factors when analyzed by the Cox proportional hazard model, in which each category was calculated separately and compared with the other seven clinicopathologic covariates. However, when each classification of lymph node metastasis was enrolled in the same analysis, stepwise Cox regression analysis revealed that RML was the most important prognostic indicator. The reason why the present study is using the two step Cox model is to prevent the misunderstanding that Japanese classification of nodal status had no influence on prognosis. Adachi et al.[6] reported that the location of positive nodes was not prognostic of survival compared with the number of metastatic nodes. However, if the two categories were analyzed separately, anatomical evaluation would be significant for survival. In fact, many previous articles[19,20,27,28] showed that nodal status based on lymphatic spread was an independent prognostic factor. Our multivariate models with two-step methods should be the new standard analysis to identify the RR for death when comparing the different categories of lymph node metastases.

TABLE 10. *Numbers of metastatic lymph nodes*

No. in N1 station	No. in (N1 + N2) station 1–6	7–15	≥16
0	10[a]	0	0
1–6	146	18[a]	1[a]
7–15	0	31	7[a]
≥16	0	0	15

[a] Underdiagnosed cases.

Furthermore, this study is the first to show the prognostic value of the incidence of positive nodes in the restricted NDLs. Our results also show that the NDL has no influence on patient prognosis. These results suggest that the RML is independent of the number of lymph node metastases and the extent of dissection performed.

Generally, the stage migration phenomenon is caused by a difference in the extent of lymph node dissection.[29,30] This study aimed to reveal the utility of RML from the aspect of the Will Rogers phenomenon. Fifty-two of 228 patients with lymph node metastasis would have been assigned to an other nodal stage (15 underdiagnosed and 37 overdiagnosed). All patients who exhibited stage migration with the Japanese or tumor-node-metastasis rules were underdiagnosed, so the surgeon could not choose the appropriate regimen for adjuvant

TABLE 12. *Multivariate analysis using the Cox stepwise regression model: All systems of grouping for nodal involvement were analyzed in the same calculation in N1 limited nodal yield only*

Clinicopathologic factor	χ^2	P value	Relative risk	95% CI
Tumor size (cm)	7.336	.069		
≤2cm			1	
<2 and ≥6	.263	.608	1.161	.656–2.058
<6 and ≥10	.032	.858	.942	.489–1.813
<10	2.937	.087	1.925	.911–4.072
Macroscopic type	24.798	<.001		
Early			1	
Borrmann 1 or 2	19.569	<.001	2.675	1.729–4.136
Borrmann 3	19.017	<.001	3.059	1.851–5.055
Borrmann 4	14.901	<.001	3.782	1.925–7.429
Ratio of metastatic lymph nodes (RML) (N1 station only)	9.701	.037		
0 (RML 0)			1	
0–.1 (RML 1)	2.762	.096	5.432	.738–39.956
.1–.25 (RML 2)	4.911	.027	10.157	1.307–78.914
≥.25 (RML 3)	3.398	.065	7.428	.881–62.635

CI, confidence interval.

chemotherapy. We also believe the superiority of category of RML from the viewpoint of stage immigration. Finally, this study calculated the prognostic index of each nodal category by using only the N1 lymph node yield. RML also showed the strongest value for patient prognosis if D1 limited dissection had been performed.

To standardize treatment results, Bunt et al.[31] recommended histologic examination of a fixed number of nodes per anatomically defined N level (20 in N1 and 15 in N2). In the Western world, D1 limited lymph node dissection is generally performed, and only approximately 10 to 15 nodes are histologically examined in the majority of institutions. In Japan and some other Eastern countries, D2 extensive lymph node dissection is standard procedure, and ≥30 lymph nodes are routinely histologically examined.[7,32] This study identified that RML has prognostic significance regardless of the extent of lymphadenectomy and prevents stage migration.

The reason the RML is an independent prognostic factor is unknown. Siewert et al.[9,33] reported a new concept of grading lymphadenectomy on the basis of the NDL (D1, ≤25 dissected nodes; D2, ≥26 dissected nodes). They emphasized that D2 extended gastrectomy markedly improved long-term survival in patients with tumor-node-metastasis stage II tumors, showing the significance of the ratio between positive nodes and removed nodes. However, our study clearly shows that the number of lymph nodes from the stomach is different in each person. Wagner et al.[34] reported that striking individual differences in the total number of lymph nodes and the number of single stations were observed in gastric cancer in 30 cadavers. Their data showed that within N2, an average of 27 nodes (range, 17–44 nodes) was found, whereas within N3, an average of 43 nodes (range, 25–64 nodes) was found. Accordingly, the grading of Siewert et al. for lymph node dissection is not theoretical. We suspect that the number of lymph nodes may reflect the potential of the defense mechanism against cancer invasion through the lymphatic pathway, resulting in the same outcome even in cases with different numbers of metastatic lymph nodes. Furthermore, patients with the same grade of RML have the same outcome regardless of the different NDL.

These findings suggest that quantitative evaluation of lymph nodes according to RML yields the best classification from the viewpoint of patient survival and the prevention of stage migration. Consequently, if classification of nodal status were established by a combination category of anatomical level and RML, it could be the best grouping to decide both accurate lymph node dissection and the regimen for adjuvant chemotherapy and predict the prognosis of patients with carcinoma of the stomach who have undergone curative resection.

Of course, this category should be used only in patients who are staged by diligent pathologic examination. Hammond and Henson[35] emphasized the important role of pathologists in the management of patients with cancer. Noda et al.,[36] histologically analyzing 23,233 lymph nodes from gastric cancer, clarified that all lymph nodes ≥4 mm in size (5 mm when fresh) should be retrieved and examined to keep the rate of stage migration caused by this factor <5%. Furthermore, proper conduct of clinical trials requires a reliable means of standardizing the performance of the surgical-pathologic team.[37] If the surgeon or pathologist expended a little effort to pick up lymph nodes from the resected specimen, RML would be an invaluable parameter. Furthermore, if only lymph nodes of large size or those macroscopically suspected to be involved were examined, the value of RML would decrease, resulting in the induction of stage migration.

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