J Gastrointest Surg (2016) 20:1565–1571
DOI 10.1007/s11605-016-3197-9

ORIGINAL ARTICLE

Positive Lymph Node Ratio as an Indicator of Prognosis and Local Tumor Clearance in N3 Gastric Cancer

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Received: 31 March 2016 / Accepted: 22 June 2016 / Published online: 28 June 2016

Abstract

Background Nodal metastasis is an important clinical issue in gastric cancer patients. This study was designed to investigate the clinical usefulness of the positive lymph node ratio (PLNR), which reflects both metastatic and retrieved lymph node numbers, in patients with pN3 gastric cancer.

Methods We retrospectively analyzed the records of 138 consecutive pN3 patients who underwent curative gastrectomy with lymphadenectomy from 2000 to 2012.

Results A PLNR of 0.4 was proved to be the best cutoff value to stratify the prognosis of patients with pN3 gastric cancer ($P < 0.001$). Univariate and multivariate analyses revealed that older age, larger tumor size (≥10 cm), and PLNR ≥ 0.4 [$P < 0.001$, HR 3.1 (95 % CI 1.7–5.4)] were independent prognostic factors in pN3 gastric cancer. Regarding the recurrence, patients with PLNR <0.4 had a significantly lower rate of lymph node recurrence than those with PLNR ≥0.4 ($P = 0.020$). There was no significant difference in the lymph node recurrence rate between N3a and N3b patients in the PLNR <0.4 group [$P = 0.546$, 11.6 % (7/60) vs. 12.5 (1/8)], indicating a better local control regardless of pN3 subgroups.

Conclusions PLNR is useful to stratify the prognosis and evaluate the extent of local tumor clearance in pN3 gastric cancer.

Keywords Positive lymph node ratio · Prognosis · Curability · Stage migration · Gastric cancer

Introduction

Recent advances in diagnosis, less invasive treatments, surgical techniques, perioperative management, and chemotherapy have improved the early and long-time outcomes of gastric cancer.[1] Nonetheless, patients with advanced stage disease have a high incidence of lymph node metastasis and still have a poor prognosis. Nodal status is the strongest predictor of the prognosis of gastric cancer patients, and the treatment strategy against metastatic lymph nodes is the most important clinical issue.[2,3]

Although the enthusiasm for optimal lymphadenectomy is different between Eastern and Western countries because of the incidence of obese patients, for whom a surgical approach is difficult in Western countries, and because of differences in the management strategy for resection and the epidemiologic characteristics of gastric cancer,[4–6] radical lymphadenectomy is currently recognized as the crucial strategy for macroscopic tumor clearance for gastric cancer.[7–10] In various cancers, the positive lymph node ratio (PLNR), which is obtained by dividing the metastatic lymph node counts by the retrieved lymph node counts, has been reported to be a promising prognostic indicator,[11–13] in particular in Western countries because some patients cannot be adequately staged due to the small number of retrieved lymph nodes after gastrectomy for gastric cancer.[14,15]

In this study, we investigated whether the PLNR could stratify the prognosis and reflect the extent of local tumor clearance in patients with pN3 gastric cancer. pN3 gastric cancer has been recognized as a highly advanced gastric

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cancer with nodal metastases, which consists of two subgroups such as pN3a with 7 to 15 metastatic lymph nodes and pN3b with more than 15 metastatic lymph nodes. The results of our study may provide evidence that the PLNR is a better system of characterizing the prognosis and local tumor clearance in patients with pN3 gastric cancer.

Methods

Patients and surgical procedures

Between 2000 and 2012, 1146 consecutive gastric cancer patients underwent curative gastrectomy with radical lymphadenectomy at the Department of Digestive Surgery, Kyoto Prefectural University of Medicine. Of all patients, 138 patients, who were pathologically categorized as having pN3 gastric cancer, were analyzed retrospectively. Patients underwent preoperative assessments including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. Based on the preoperative diagnosis, total or distal gastrectomy and sufficient lymphadenectomy was performed, mainly according to the Japanese guidelines for the treatment of gastric cancer.[16,17] All enrolled pN3 patients underwent D2 or D2+ lymphadenectomy. In the D2 dissection, the perigastric lymph nodes and all second-tier lymph nodes were completely retrieved. Depending on the location of the tumor, lymphadenectomy was added along the distal side of the splenic artery (No. 11d) and at the splenic hilum (No. 10), together with splenectomy or splenectomy with distal pancreatectomy.[17]

All lymph nodes from the resected specimens were completely retrieved by experienced surgeons. Resected tumor specimens and retrieved lymph nodes were examined and evaluated by at least two pathologists based on classifications of the 14th JCGC[18] and the 7th TNM staging manual.[19] As a result, 138 patients were pathologically categorized as having pN3 gastric cancer, which consisted of 90 patients in N3a and 48 patients in N3b. All enrolled patients underwent macroscopic and pathologically curative resection (R0) and had a negative result for peritoneal washing cytology. Histological types were classified as differentiated (papillary adenocarcinoma or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma or mucinous adenocarcinoma) based on the 14th JCGC.[18]

Treatments following curative gastrectomy

Of all pN3 patients, 119 patients (86.2 %) received adjuvant chemotherapy, while 19 patients (13.8 %) did not. One hundred and eleven patients received S-1 alone or an S-1 based chemotherapy such as S-1 plus cisplatin, S-1 plus taxane or S-1 plus irinotecan; six patients received methotrexate plus 5-fluorouracil, and two patients received uracil-tegafur as adjuvant chemotherapy. None of the patients received neoadjuvant chemotherapy, adjuvant radiotherapy, or chemoradiotherapy. All patients were examined in the outpatient clinic, in which abdominal ultrasound, computed tomography (CT), and measurements of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were performed every 3–6 months after surgery.

Evaluation of clinical impact of PLNR

To evaluate the clinical usefulness of the PLNR in pN3 gastric cancer, firstly, the PLNR was calculated by the following formula: PLNR = total pathological metastatic lymph node numbers / total retrieved lymph node numbers. To detect the best cutoff value, we examined the ability to stratify the prognosis in each cutoff value of the PLNR (Fig. 1). Secondly, we performed a multivariate analysis using the Cox's proportional hazard model (Table 1) and examined whether the best cutoff value of the PLNR could specifically stratify the prognosis in patients of each N3a or N3b subgroup following radical lymphadenectomy (Fig. 2a, b). Finally, we investigated the related clinicopathological factors and the related types of recurrence according to the best cutoff value of the PLNR (Tables 2 and 3) and examined whether the best cutoff value of the PLNR could reflect the local tumor clearance (Table 4).

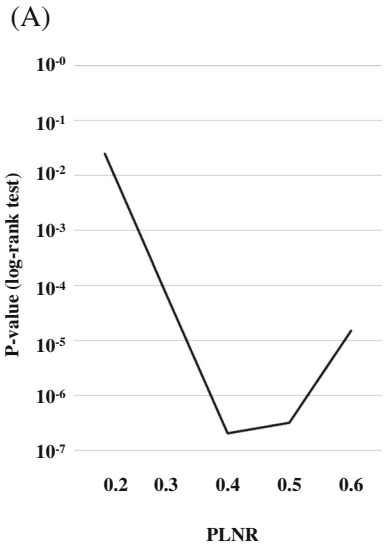
Statistical analysis

The χ^2 test and Fisher's exact probability test were performed for categorical variables, while the Student's t test and Mann–Whitney U test for unpaired data of continuous variables were performed to compare the clinicopathological characteristics between the two groups. Survival curves were estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. The data were stratified for multivariate analysis using both forward and backward stepwise Cox regression procedures. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics of pN3 gastric cancer patients

The clinical characteristics in 138 patients with pN3 gastric cancer were as follows. Of 138 patients, seven patients were staged as pStage IIB, seven patients as pStage IIIA, 39 patients as pStage IIIB, and 85 patients as pStage IIIC. The study group consisted of 83 male and 55 female patients with a



(B)

Cut-off value		n	Survival rate (%) 1yrs	3yrs	5yrs	*P*-value
0.2	<0.2	8	100	85.7	85.7	2.43 x 10^{-2}
	≥0.2	130	78.3	39.2	26.1	
0.3	<0.3	40	94.7	70.1	58.4	6.60 x 10^{-5}
	≥0.3	98	73.4	31.1	18.2	
0.4	<0.4	68	96.9	63.5	49.6	2.00 x 10^{-7}
	≥0.4	70	63.7	23.3	12.8	
0.5	<0.5	89	91.5	54.6	42.6	3.17 x 10^{-7}
	≥0.5	49	58.3	20.8	8.3	
0.6	<0.6	105	86.8	48.3	37.4	1.47 x 10^{-5}
	≥0.6	33	56.3	18.4	4.9	

Fig. 1 Cutoff value of the PLNR to stratify the prognosis in pN3 gastric cancer. **a** Survival analyses using various cutoff values such as 0.2, 0.3, 0.4, 0.5, and 0.6, and **b** demonstrated that the cutoff value 0.4 could most significantly stratify the prognosis of gastric cancer patients into two groups ($P = 2.0 \times 10^{-7}$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 49.6 vs. 12.8 %)

median age of 66 years (range 27–88 years). The median number of metastatic and retrieved lymph nodes was 12.5 (range 7–67) and 36 (range 9–91). Of 138 patients, 129 patients [93.5 % (129/138)] had more than 15 retrieved lymph nodes. The median PLNR was 0.4 (range 0.12–0.98). The median number of retrieved lymph nodes in each sub-stage was 27 in pStage IIB, 27 in pStage IIIA, 38 in pStage IIIB, and 36 in pStage IIIC. The average number of retrieved lymph nodes was sufficient in all stages of our cohort. There was no significant prognostic difference between the 119 patients with adjuvant chemotherapy and the 19 patients without ($P = 0.459$).

Cutoff value of the PLNR to stratify the prognosis

As shown in Fig. 1a, we performed survival analyses using various cutoff values such as 0.2, 0.3, 0.4, 0.5, and 0.6 and demonstrated that the cutoff value of 0.4 could most significantly stratify the prognosis of gastric cancer patients into two groups ($P = 2.0 \times 10^{-7}$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 49.6 vs. 12.8 %; Fig. 1b). Specifically, all pN3 patients were distributed as 68 patients in PLNR < 0.4 and 70 patients in PLNR ≥ 0.4, respectively.

In each final pathologic stage, the cutoff value of 0.4 could stratify the prognosis of patients with pN3 gastric cancer in

Table 1 Univariate and multivariate analyses using the Cox's proportional hazard model in pN3 gastric cancer

Variables		*n*	Univariate[b]	Multivariate analysis[c]		
			P value	HR	(95 % CI)	*P* value
Age	≥70 vs. <70	52 vs. 86	**0.031**	2.5	1.5–4.1	**<0.001**
Gender	Male vs. female	83 vs. 55	0.423		–	
Gross type	Infiltrative vs. localized	45 vs. 93	0.526		–	
Histological type	Undifferentiated vs. differentiated	94 vs. 44	0.224		–	
Tumor size[a]	≥100 vs. <100 mm	41 vs. 97	**<0.001**	2.2	1.3–3.6	**0.003**
pT[a]	T4 vs. T1–T3	85 vs. 53	**<0.001**		–	
ly[a]	ly2–ly3 vs. ly0–ly1	108 vs. 30	**0.036**		–	
v[a]	v1–v3 vs. v0	76 vs. 62	**0.002**		–	
pN	N3b vs. N3a	48 vs. 90	**0.001**		–	
PLNR[a]	≥0.4 vs. < 0.4	70 vs. 68	**<0.001**	3.1	1.7–5.4	**<0.001**

Significant values are in bold

HR hazard ratio, *CI* confidence interval, *ly* lymphatic invasion, *v* venous invasion

[a] Cutoff values were decided by the minimum *p* value method

[b] log-rank test

[c] Multivariate survival analysis was performed using the Cox's proportional hazard model

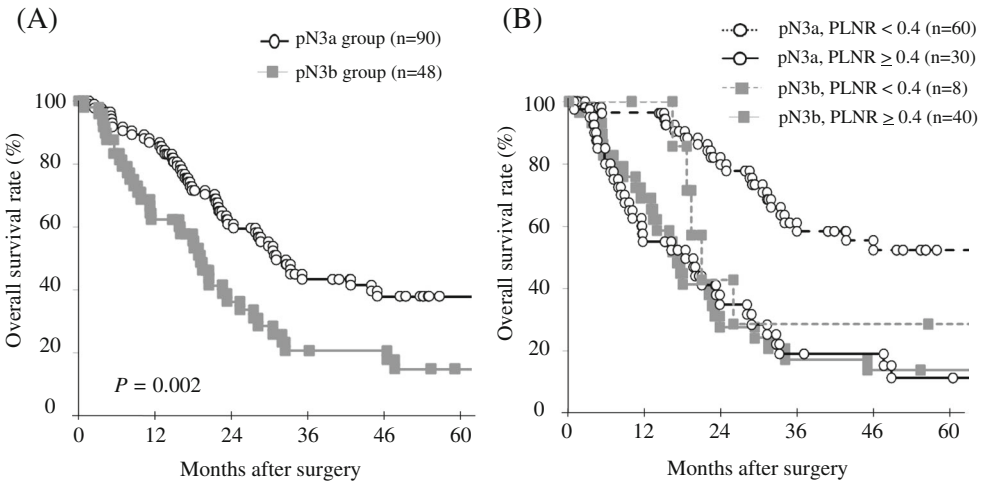


Fig. 2 Comparison of survival curves according to pN3 subgroups (**a**) and pN3 subgroups using the PLNR cutoff value of 0.4 (**b**)

pStage IIB ($P = 0.086$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 49.6 vs. 12.8 %), pStage IIIA (not evaluated due to a small number of patients), pStage IIIB ($P = 0.060$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 56.2 vs. 27.3 %), and pStage IIIC ($P < 0.001$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 41.5 vs. 7.9 %). Therefore, we used the cutoff value of 0.4 for further analyses in pN3 gastric cancer.

Univariate and multivariate analyses using the Cox's proportional hazard model in pN3 gastric cancer

As a prognostic factor in pN3 gastric cancer, univariate and multivariate analyses using the Cox's proportional hazard model demonstrated that older age, larger tumor size (≥10 cm), and a PLNR ≥ 0.4 [$P < 0.001$, HR 3.1 (95 % CI 1.7–5.4)] were independent poor prognostic factors in pN3 gastric cancer (Table 1).

Evaluation of the utility to stratify the pN3 subgroups using the PLNR

Figure 2 shows survival curves according to pN3 subgroups and pN3 subgroups using the PLNR cutoff value of 0.4. Patients with N3a had a significantly better survival than those with N3b ($P = 0.002$; Fig. 2a). Moreover, a PLNR cutoff value <0.4 could significantly discriminate a better prognostic subgroup in N3a patients ($P < 0.001$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 52.3 vs. 13.8 %) but not in N3b patients ($P = 0.270$, 5-year survival rate; PLNR < 0.4 vs. PLNR ≥ 0.4; 28.6 vs. 11.4 %; Fig. 2b).

Table 2 Comparison of clinicopathological factors between patients with a PLNR <0.4 and a PLNR ≥0.4 in pN3 gastric cancer

		Positive lymph node ratio (PLNR)		
Variables		≥0.4 ($n = 70$)	<0.4 ($n = 68$)	P value
Age	Median (range)	65 (27–87)	67 (30–88)	0.745
Gender	Male/female	44/26	39/29	0.509
Gross type	0–2/3–5	14/56	31/37	**0.001**[a]
Histological type	Undifferentiated/differentiated	49/21	23/45	**<0.001**[a]
Tumor size (mm)	Median (range)	92.5 (10–215)	65 (20–162)	**<0.001**[b]
T-stage	T1a/T1b/T2/T3/T4a/T4b	1/2/1/12/48/6	0/4/6/27/30/1	**0.020**[c]
Lymphatic invasion (ly)	0/1/2/3	3/7/16/44	5/15/11/37	0.339
Venous invasion (v)	0/1/2/3	30/21/10/9	32/20/10/6	0.978
Number of metastatic lymph nodes	Median (range)	17 (7–67)	10 (7–20)	**<0.001**[b]
Number of retrieved lymph nodes	Median (range)	30.5 (9–75)	38.5 (18–91)	**0.002**[b]

Significant values are in bold

[a] Fisher's exact probability test

[b] Mann–Whitney U test

[c] Yates mxn chi square test

Table 3 Comparison of the recurrence between patients with a PLNR < 0.4 and 0.4 ≤ PLNR ≥ 0.4 in pN3 gastric cancer

	Positive lymph node ratio (PLNR)		
Recurrence	PLNR ≥ 0.4	PLNR < 0.4	*P* value[a]
Total patients	58 (82.8 %)	31 (47.0 %)	<0.001
Types of recurrence			
Local	1 (1.4 %)	1 (1.4 %)	0.489
Peritoneum	27 (38.5 %)	18 (26.4 %)	0.129
Lymph node	19 (27.1 %)	8 (11.7 %)	**0.020**
Hematogenous	13 (18.6 %)	7 (10.2 %)	0.254
Others	5 (7.1 %)	2 (2.9 %)	0.461

Significant values are in bold

[a] Fisher's exact probability test

Comparison of clinicopathological factors between patients with PLNR < 0.4 and PLNR ≥ 0.4

We next compared the clinicopathological factors between patients with the PLNR < 0.4 and PLNR ≥ 0.4. Compared with patients in the PLNR ≥ 0.4 group, those in the PLNR < 0.4 group had a significantly lower incidence of infiltrate type in macroscopic appearance ($P = 0.001$), undifferentiated type of the histological type ($P < 0.001$), large tumor size ($P < 0.001$), and deep tumor depth ($P < 0.001$) in pN3 gastric cancer (Table 2). Regarding the recurrence, patients with a PLNR < 0.4 had a significantly lower rate of total recurrence ($P < 0.001$) and lymph node recurrence ($P = 0.020$) than those with a PLNR ≥ 0.4 (Table 3). Specifically, there was a significant difference in the lymph node recurrence rate between N3a and N3b patients [$P = 0.037$, N3a vs. N3b; 14.4 (13/90) vs. 29.2 % (14/48)] in all patients, whereas there was no significant difference in the lymph node recurrence rate between N3a and N3b patients in the PLNR < 0.4 group [$P = 0.546$, N3a vs. N3b; 11.6 % (7/60) vs. 12.5 (1/8)], indicating a better local control in the PLNR < 0.4 group regardless of pN3 subgroup (Table 4).

Discussion

The PLNR system can reflect the retrieved lymph nodes. The number of retrieved lymph nodes might be affected by various clinical factors: the extent to which lymph nodes are examined pathologically, the extent of lymphadenectomy, the surgical situation such as fat volume, and the difference in the number of innate lymph nodes among individuals. Therefore, even in same nodal stage, a lack of retrieved lymph nodes derived from these clinical factors may be closely related with the stage migration and prevent us from understanding an accurate prognosis of each patient in order to make a decision of further treatment strategy. In this study, we clearly demonstrated that the PLNR of 0.4 was proved to be the best cutoff value to stratify the prognosis of pN3 patients into two groups ($P < 0.001$). A PLNR ≥0.4 was an independent prognostic factor in patients with pN3 gastric cancer [$P < 0.001$, HR 3.1 (95 % CI 1.7–5.4)]. Specifically, a PLNR <0.4 could significantly discriminate a better prognostic subgroup in N3a patients but not in N3b patients. Moreover, a PLNR <0.4 could indicate a better local control for lymphadenectomy regardless of pN3 subgroup.

The most striking finding in this study was that pN3 patients with a PLNR <0.4 had a significantly lower rate of lymph node recurrence than those with a PLNR ≥0.4. Because patients with pN3 gastric cancer were already regarded as being at an extremely advanced stage of the disease, we decided prematurely that the PLNR, which reflects the number of retrieved lymph nodes in addition to metastatic lymph node number, did not reflect the extent of local tumor clearance in pN3 gastric cancer. However, the PLNR ≥ 0.4 group was more frequently correlated with the lymph node recurrence than the PLNR < 0.4 group ($P = 0.020$), although there was no significant difference in other types of recurrence between both groups. Moreover, the rates of lymph node recurrence of N3a and N3b patients in the PLNR <0.4 group were almost the same at 11.6 % (7/60) and 12.5 % (1/8), respectively, and there was no significant difference between both subgroups ($P = 0.546$). In our cohort, the lymph node recurrence included both lymph node recurrence around the site of lymphadenectomy and distant lymph node recurrence. The rates of lymph node recurrence in patients with pN0, pN1-2, and pN3 were 0.9, 5.0, and 19.5 %, respectively. The rates of lymph node recurrence of N3a and N3b patients in the PLNR < 0.4 group might be comparatively low, suggesting a better local control in pN3 gastric cancer.

Table 4 Lymph node recurrence rates in each pN3 subgroup according to PLNR

	Lymph node recurrence rate			Other recurrence rates		
	Total	PLNR ≥ 0.4	PLNR < 0.4	Total	PLNR ≥ 0.4	PLNR < 0.4
pN3a (*n* = 90)	14.4 % (13/90)	20.0 % (6/30)	11.6 % (7/60)	42.2 % (38/90)	56.3 % (17/30)	35.0 % (21/60)
pN3b (*n* = 48)	29.2 % (14/48)	32.5 % (13/40)	12.5 % (1/8)	68.7 % (33/48)	70.0 % (28/40)	62.5 % (5/8)

[a] Fisher's exact probability test

These results strongly suggested that a low PLNR may reflect a better local tumor clearance leading to a better prognosis regardless of pN3 subgroup. However, concerning the comparison of prognosis between N3a and N3b patients in the PLNR < 0.4 group, the prognosis in N3b patients tended to be poorer than that in N3a patients (Figure 2; $P = 0.108$, 5-year survival rate; N3a PLNR < 0.4 vs. N3b PLNR < 0.4; 52.3 vs. 28.6 %). This result indicated that the prognosis of N3b patients might be poorer than that of N3a patients despite of a better local tumor clearance by radical lymphadenectomy because of other recurrences excluding lymph node recurrence [other recurrence rates: N3a PLNR < 0.4 vs. N3b PLNR < 0.4; 35.0 (21/60) vs. 62.5 % (5/8)]. Accordingly, N3b patients need further intensive chemotherapy such as neoadjuvant and/or adjuvant chemotherapy in addition to surgical exploration.

The different enthusiasm for optimal lymphadenectomy between Eastern and Western countries may have existed essentially due to inevitable differences in the number of obese patients and the epidemiologic characteristics of gastric cancer.[4–6] However, we recently reported that the number of retrieved lymph nodes could affect the prognosis of patients with pStage II–III gastric cancer after curative gastrectomy in a Japanese institute because some patients had a small number of retrieved lymph nodes in Japan.[20] In that study, appropriate nodal staging using the 14th JCGC[18] and 7th TNM[19] classifications needed more than 25 lymph nodes. Therefore, we believe that both conventional nodal staging system and the new PLNR system may be necessary for appropriate nodal staging in order to evaluate the prognosis and make the decision making more efficient for further treatments in Eastern countries as well as Western countries.

Recently, the therapeutic value of D2 lymphadenectomy has started to be re-evaluated in Western countries[7,8] because a 15-year Dutch trial recently demonstrated fewer locoregional recurrences of gastric cancer and better long-term survival benefit in patients with D2 lymphadenectomy compared with those with D1 lymphadenectomy.[9] Despite a large number of obese patients, Western surgeons who perform D2 lymphadenectomy face and overcome greater technical challenges. Thereby, patients with higher nodal metastasis such as pN3 may be increasingly common after D2 lymphadenectomy in Western countries and need their prognosis to be more accurately evaluated. Therefore, the PLNR system, which reflects both the prognosis and local tumor clearance, may be needed as an additional indicator of a nodal staging system.

PLNR may thus be useful to stratify the prognosis and evaluate the effect of local tumor clearance. Indeed, the utility of the cutoff PLNR value of 0.4 for nodal staging has already been reported.[14,21] Namely, various PLNR cutoff values for the new nodal staging system have been suggested: 0.1, 0.2;[22] 0.1, 0.25;[23] 0.1, 0.4;[14] 0.2, 0.5;[24–27] 0.2, 0.6;[28] 0.3, 0.6;[29]; and 0.4,0.8.[21] Nevertheless, many issues must be addressed before the PLNR can be translated into a clinically useful nodal staging system in gastric cancer patients.[30] Our study has a limitation because the results of this study were retrospectively demonstrated. The long accrual period of the retrospective analysis at a single institute may reflect possible variations of the treatment. Namely, until definitive clinical guidelines for surgery and adjuvant chemotherapy were established in Japan,[16,17] confounding treatment effects may not have been completely negligible. Therefore, a prospective observational study using several large cohorts and/or a nation-wide clinical database study may be needed to validate the significance of the PLNR for pN3 gastric cancer. In conclusion, the PLNR could stratify the prognosis and reflect the local tumor clearance in pN3 gastric cancer.

Authors' contributions Shuhei Komatsu, Daisuke Ichikawa, Mahito Miyamae, Toshiyuki Kosuga, Kazuma Okamoto, Tomohiro Arita, Hirotaka Konishi, Ryo Morimura, Yasutoshi Murayama, Atsushi Shiozaki, Yoshiaki Kuriu, Hisashi Ikoma, Masayoshi Nakanishi, Hitoshi Fujiwara, and Eigo Otsuji performed the research and analyzed data, and Shuhei Komatsu wrote the paper.

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