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Prognostic Impact of Lymph Node Ratio in Patients Undergoing Preoperative Chemoradiotherapy Followed by Curative Resection for Locally Advanced Rectal Cancer

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Abstract. *Background/Aim: To analyze the prognostic significance of nodal status in patients undergoing preoperative chemoradiotherapy (CRT) followed by curative resection for locally advanced rectal cancer. Patients and Methods: Between 2000 and 2015, 80 consecutive patients with rectal cancer underwent preoperative CRT followed by curative resection. The lymph node ratio (LNR) was defined as the number of positive lymph nodes (LNs) divided by the examined LNs, and log odds of positive lymph nodes (LODDS) was the log of the ratio between positive and negative LNs. The prognostic value of these indicators was evaluated in terms of overall (OS) and disease-free (DFS) survival. Results: The median follow-up period for patients overall was 59 months (range=11-190 months). The median number of examined LNs and number of positive LNs were 10 (range=1-29) and 2 (range=1-27), respectively, and the median LNR and LODDS values were 0.0 (range=0.0-0.96) and −1.0 (range=−1.7-1.3), respectively. The 5-year OS and DFS were 83% and 64%, respectively. In multivariate analysis, LNR was an independent prognostic factor in terms OS (p=0.041) but not for DFS (p=0.075). LODDS was not significantly associated with OS or DFS. In patients with clinical stage III rectal cancer, LNR was significantly associated with OS and DFS when the number of evaluated LNs was greater than 12 (p=0.038 for OS, p=0.006 for DFS). Conclusion: Our study suggests that LNR is a more effective prognostic factor than LODDS in terms of predicting survival. LNR was a significant predictor for survival for patients with clinical stage III rectal cancer with >12 harvested LNs.*

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Key Words: Rectal cancer, lymph node ratio, log odds of positive lymph nodes, lymph node, chemoradiotherapy, prognosis.

Colorectal cancer is the third most common type of cancer among men and women in the United States and Korea (1, 2). Preoperative concurrent chemoradiotherapy (CRT) has been the standard treatment for rectal cancer since the publication of a landmark randomized trial which demonstrated reduced treatment-related toxicity and improved local control in association with this intervention (3).

Previous studies have shown that nodal status is the strongest predictor of recurrence and survival among patients with rectal cancer (4-7). The lymph node ratio (LNR) is a well-known prognostic factor for breast and stomach cancer (8, 9) as well as colorectal cancer (10). However, the LNR has limitations when it comes to revealing heterogeneous survival outcomes. Log odds of positive lymph nodes (LODDS) is a novel prognostic indicator that has been reported to reduce the risk of staging migration in gastric, breast, and colon cancer (11-13). To date, only a few studies have reported LODDS as a predictor of survival among patients with colon and colorectal cancer (14-16). A recent study on the prognostic value of LNR and LODDS for rectal cancer treated with preoperative radiotherapy demonstrated that LODDS was more discriminatory than LNR for cancer-specific survival (17). This study aimed to assess the prognostic value of LNR and LODDS in terms of predicting survival and recurrence among patients with rectal cancer treated with preoperative CRT.

Patients and Methods

Patients. From April 2000 to May 2015, 80 patients with consecutive rectal cancer who underwent preoperative CRT followed by curative resection were included in the present study. Tumors were staged using the eighth edition of the American Joint Committee on Cancer

Table I. *Patient and tumor characteristics.*

Variable		Value
Age, years	Median (range)	57 (26-82%)
Gender, n (%)	Male	59 (73.8%)
	Female	21 (26.2%)
Distance from anal verge, n (%)	≤5 cm	45 (56.3%)
	>5 cm	35 (43.8%)
Histological differentiation, n (%)	WD	17 (21.3%)
	MD, PD	51 (63.8%)
	Unknown	12 (15.0%)
Clinical stage, n (%)	II	17 (21.2%)
	III	63 (78.8%)
Resection margin, n (%)	Negative	77 (96.3%)
	Positive	3 (3.7%)
Vascular invasion, n (%)	Negative	58 (72.5%)
	Positive	10 (12.5%)
	Unknown	12 (15.0%)
Lymphatic invasion, n (%)	Negative	55 (68.8%)
	Positive	13 (16.2%)
	Unknown	12 (15.0%)
Perineural invasion, n (%)	Negative	53 (66.3%)
	Positive	15 (18.7%)
	Unknown	12 (15.0%)
ypT stage, n (%)	T0	8 (10.0%)
	Tis, T1-2	27 (33.8%)
	T3-4	45 (56.3%)
ypN stage, n (%)	N0	53 (66.3%)
	N1	22 (27.5%)
	N2	5 (6.5%)
Pathological complete remission, n (%)	No	73 (91.3%)
	Yes	7 (8.7%)
Downstaging, n (%)	No	43 (53.8%)
	Yes	37 (46.2%)

WD: Well-differentiated; MD: moderately differentiated; PD: poorly differentiated.

(AJCC) guidelines (6). Inclusion criteria were as follows: patients with histologically confirmed rectal adenocarcinoma, with clinical stage II or III rectal cancer, and who underwent surgery after preoperative CRT. Patients were excluded if they had received prior treatment for rectal cancer, had a history of other malignancies, had evidence of distant metastasis, or had received preoperative radiotherapy alone. The present study received Institutional Review Board approval (approval number: 2016-03-058).

Clinicopathological characteristics. Pathological factors considered in the analysis included tumor differentiation, lymphatic invasion, vascular invasion, perineural invasion, resection margin status, and the number of lymph nodes (LNs) with and without metastasis. The LNR was defined as the ratio of the number of positive LNs to the total number of LNs examined. The LODDS was defined as the log of the ratio between positive and negative LNs. The optimal cut-off values for LNR, LODDS, pre-treatment carcinoembryonic antigen (CEA), and postoperative CEA were determined using Maxstat, a maximal chi-square method in R 3.5.1 (R Development Core Team, Vienna, Austria, http://www.R-project.org). Patients were divided into two groups based on the number of dissected LNs (>12 *vs.* ≤12), which is recommended for nodal sampling accuracy in the AJCC guidelines (6). Downstaging of rectal cancer was defined as a reduction of the final pathological T- or N-stage by comparing with the preoperative clinical T- or N-stage. Pathological complete remission was defined as the absence of tumor cells in the primary lesion and LNs (ypT0N0).

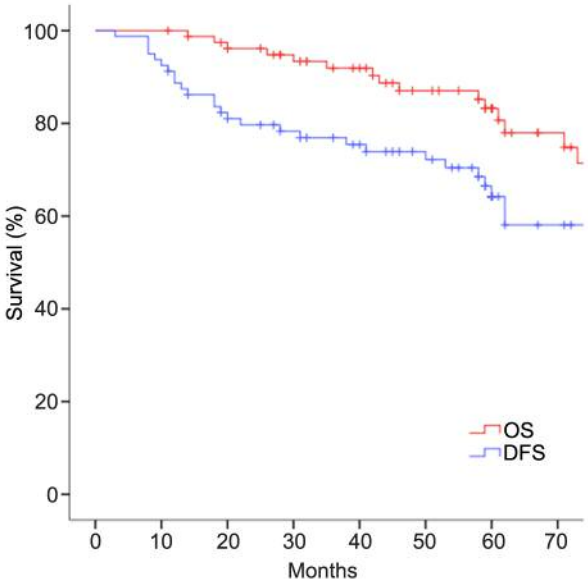

Figure 1. *Kaplan-Meier curves for overall (OS) and disease-free (DFS) survival for patients overall.*

Treatment. A radiation dose of 45.0-50.4 Gy was delivered to the whole pelvis, followed by a boost dose of 0 to 5.4 Gy to the primary tumor. Neoadjuvant chemotherapy consisted of 5-fluorouracil (5-FU, 400 mg/m^2) and leucovorin (20 mg/m^2) for 5 days in the first and fifth weeks of radiotherapy (n=73, 91.2%) or capecitabine (1,650 mg/m^2) daily (n=7, 8.8%). Curative surgery was performed 6-8 weeks after the completion of CRT. Adjuvant chemotherapy was administered for 70 (87.5%) patients. The regimens for adjuvant chemotherapy were 5-FU and LV in 53 (66.2%); doxifluridine or tegafur-uracil in 11 (13.8%); capecitabine in three (3.8%); 5-FU, LV and oxaliplatin (FOLFOX) in two (2.5%); and 5-FU, LV, and irinotecan (FOLFIRI) in one (1.2%).

Follow-up. Locoregional recurrence was defined as recurrent disease detected within the pelvis. Recurrent disease outside the pelvis was considered distant failure. Overall survival (OS) was defined as the interval from the date of diagnosis of rectal cancer until death from any cause or the date of last follow-up. Disease-free survival (DFS) was defined as the interval from the date of diagnosis to the last follow-up, disease recurrence, or death. Patients without recurrence or death were censored at the date of last follow-up.

Statistical analysis. Statistical analysis was performed using SPSS software version 18.0.0 (SPSS Inc., Chicago, IL, USA). OS and DFS rates were calculated using the Kaplan-Meier method. A log-rank test was performed to compare the survival curves. Cox

Table II. *Univariate analyses for 5-year overall (OS) and disease-free (DFS) survival according to clinicopathological factors.*

Variable	No.	OS (%)	*p*-Value	DFS (%)	*p*-Value
Age					
≤57 Years	44	83.8	0.390	62.8	0.719
>57 Years	36	82.6		66.7	
Distance from anal verge					
≤5 cm	45	87.6	0.412	71.4	0.108
>5 cm	35	77.4		55.1	
Histological differentiation					
WD	17	77.1	0.782	59.5	0.996
MD, PD	51	84.5		65.1	
Clinical stage					
II	17	77.0	0.763	75.3	0.220
III	63	85.1		60.8	
Pre-treatment CEA					
≤15.1 ng/ml	69	89.3	<0.001	69.6	0.004
>15.1 ng/ml	9	45.7		20.8	
Postoperative CEA					
≤3 ng/ml	68	90.6	<0.001	68.9	0.032
>3 ng/ml	11	51.1		43.6	
Surgery type					
LAR	64	86.0	0.045	69.7	0.048
APR	16	71.1		38.7	
Resection margin					
Negative	77	84.1	0.105	65.6	0.055
Positive	3	66.7		33.3	
Vascular invasion					
Negative	58	85.2	0.667	63.5	0.742
Positive	10	65.6		56.0	
Lymphatic invasion					
Negative	55	90.8	0.020	68.9	0.011
Positive	13	49.9		36.9	
Perineural invasion					
Negative	53	89.1	0.003	72.0	0.002
Positive	15	49.0		14.7	
ypT stage					
ypT0-2	35	92.4	0.036	79.8	0.015
ypT3-4	45	76.3		52.6	
ypN stage					
ypN0	53	87.2	0.148	73.8	0.017
ypN1-2	27	75.5		46.0	
No. of dissected LNs					
≤12	52	85.3	0.255	67.8	0.830
>12	28	78.8		64.7	
LNR					
≤0.1	59	88.7	0.038	71.9	0.006
>0.1	21	68.9		43.3	
LODDS					
≤1.28	23	93.3	0.196	82.2	0.135
>1.28	57	80.0		58.5	

WD: Well-differentiated; MD: moderately differentiated; PD: poorly differentiated; CEA: carcinoembryonic antigen; LAR: low anterior resection; APR: abdominoperineal resection; LNs: lymph nodes; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes.

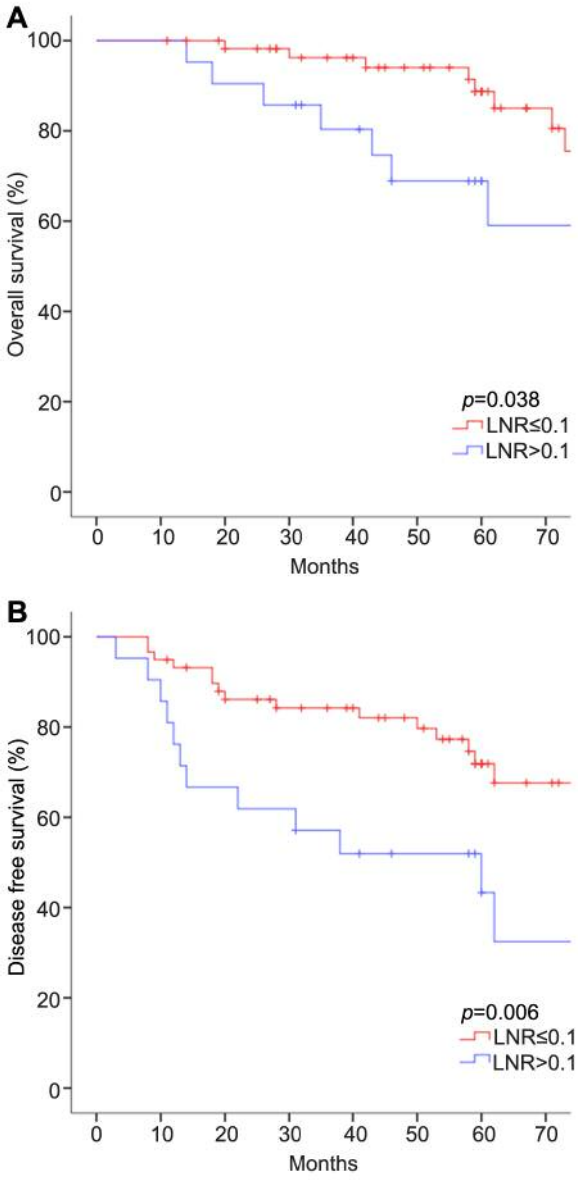

Figure 2. *Kaplan-Meier curves for overall (A) and disease-free (B) survival according to the lymph node ratio (LNR).*

proportional hazard regression modeling was used for univariate and multivariate analyses. Variables with a value of $p<0.2$ in the univariate analysis were included in the multivariate analysis. We performed two different analyses for LODDS and LNR to reduce interference and avoid collinearity during analysis within the same multivariate model. All statistical tests used in this study were two-sided, and values of $p<0.05$ were considered statistically significant.

Results

Characteristics. Patient and tumor characteristics are summarized in Table I. The median age at diagnosis was 57

Table III. *Multivariate analyses for overall (OS) and disease-free (DFS) survival according to lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS).*

	OS				DFS			
	With LNR		With LODDS		With LNR		With LODDS	
Variable	HR (95% CI)	*p*-Value	HR	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Pre-treatment CEA >15.1 ng/ml	3.745 (0.590-23.759)	0.161	2.642 (0.414-16.879)	0.305	1.496 (0.372-6.009)	0.570	1.190 (0.272-5.207)	0.817
Postoperative CEA >3 ng/ml	7.004 (1.207-40.647)	0.030	8.943 (1.322-60.495)	0.025	3.179 (0.877-11.519)	0.078	3.704 (0.886-15.492)	0.073
APR	1.115 (0.307-4.053)	0.869	0.784 (0.208-2.945)	0.718	1.432 (0.520-3.948)	0.487	1.061 (0.387-2.914)	0.908
Positive resection margin	19.335 (1.182-316.321)	0.038	15.687 (1.367-180.043)	0.027	2.406 (0.355-16.303)	0.369	2.773 (0.498-15.448)	0.244
Lymphatic invasion	3.508 (1.103-11.157)	0.033	5.946 (1.727-20.467)	0.005	1.710 (0.661-4.422)	0.269	2.447 (0.909-6.587)	0.077
Perineural invasion	0.677 (0.120-3.812)	0.659	0.596 (0.107-3.338)	0.556	1.698 (0.507-5.692)	0.391	1.714 (0.501-5.870)	0.391
Clinical stage III	0.369 (0.114-1.196)	0.097	0.690 (0.207-2.302)	0.546	1.367 (0.441-4.234)	0.588	2.052 (0.616-6.836)	0.242
LNR >0.1	3.361 (1.050-10.757)	0.041			2.406 (0.915-6.326)	0.075		
LODDS >1.28			4.507 (0.808-25.151)	0.086			2.621 (0.766-8.968)	0.125

APR: Abdominoperineal resection; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio.

years (range, 26-82). The median examined LN and positive LN counts were 10 (range=1-29) and 2 (range=1-27), respectively. The median LNR and LODDS values were 0.0 (range=0.0-0.96) and −1.0 (range=−1.7-1.3), respectively. The median pre-treatment and postoperative CEA levels were 4.1 (range=0.6-364.6) ng/ml and 1.5 (range=1-13) ng/ml, respectively. Clinical stage II and III disease were noted in 21.2% and 78.8% of patients, respectively. Sixty-four patients (80%) underwent low anterior resection, and 16 (20%) underwent abdominoperineal resection. Complete remission was observed in seven patients (8.7%).

Survival outcomes. The median follow-up duration was 59 (range=11-190) months for patients overall. Eight patients (10%) developed locoregional recurrence, 24% developed distant recurrence, and 23% had died by the end of the study. Median OS and DFS were not reached. The 5-year OS and DFS rates were 83% and 64%, respectively. Survival curves for OS and DFS are shown in Figure 1.

Prognostic factor analysis. In the univariate analysis, seven variables were statistically significantly associated with OS and DFS: Pre-treatment CEA, postoperative CEA, surgery type, lymphatic invasion, perineural invasion, ypT stage, and LNR (Table II). ypN stage was significantly associated with DFS but not OS. The 5-year survival rate according to the number of dissected LNs was 85.3% in the group with ≤12 dissected LNs compared with 78.8% in the group with >12 (p=0.255). The 5-year OS and DFS rates were 88.7% and 71.9% for patients with LNR ≤0.1, and 68.9% and 43.3% for patients with LNR >0.1, respectively, and were significantly different (OS: p=0.038) and (DFS: p=0.006) (Figure 2). In multivariate analyses (Table III), LNR [hazard ratio (HR)=3.361, 95% confidence interval (CI)=1.050-10.757, p=0.041], postoperative CEA (HR=7.004, 95% CI=1.207-40.647, p=0.030), resection margin status (HR=19.335, 95% CI=1.182-316.321, p=0.038), and lymphatic invasion (HR=3.508, 95% CI=1.103-11.157, p=0.033) were independent predictors of OS but LODDS was not (HR=4.507, 95% CI=0.808-25.151, p=0.086). Regarding DFS, neither LNR nor LODDS were a significant prognostic factor (HR=2.406, 95% CI=0.915-6.326, p=0.075 for LNR; HR=2.621, 95% CI=0.766-8.968, p=0.125 for LODDS).

Subgroup analysis. Subgroup analyses were performed to determine whether survival differences according to LNR were associated with the number of dissected LNs among patients with clinical stage III disease (Figure 3). LNR>0.1 was a significant predictor of worse OS and DFS among 25 patients with >12 dissected LNs (5-year OS: 90.9% *vs.* 56.0%, p=0.020; 5-year DFS: 76.0% *vs.* 40.0%, p=0.034; Figure 3A). Among 38 patients with ≤12 dissected LNs,

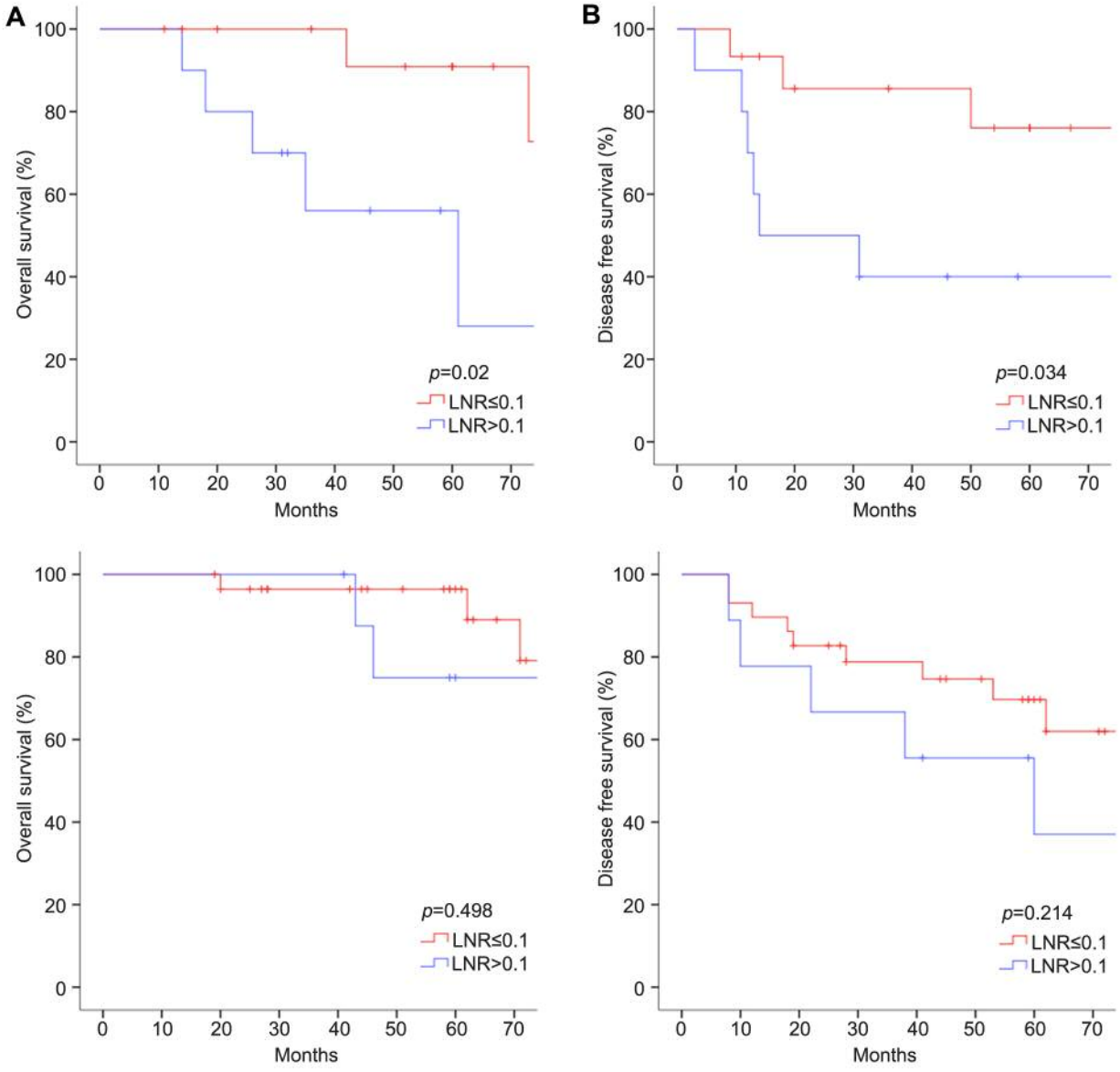

Figure 3. *Kaplan-Meier curves for overall (A) and disease-free (B) survival in patients with clinical stage III according to lymph node ratio (LNR) and the number of dissected lymph nodes (LNs): Upper panel, >12 dissected LNs; lower panel, ≤12 dissected LNs.*

LNR>0.1 was not significantly associated with OS and DFS (5-year OS: 96.4% *vs*. 75.0%, p=0.498; 5-year DFS: 69.7% *vs*. 37.0%, p=0.214; Figure 3B).

Discussion

In this study, we confirmed that LNR>0.1 was significantly associated with poor 5-year survival outcomes among patients who underwent preoperative CRT followed by curative surgery for locally advanced rectal cancer.

Various methods can be used to assess nodal status in rectal cancer, including the AJCC pN staging, LNR, and LODDS. Currently, the most widely used LN staging system is the AJCC eighth edition N-stage, based on the absolute number of metastatic LNs (6). However, with the numeric-based N-staging system for rectal cancer, it is difficult to represent the extent of LN dissection despite radical LN dissection being performed, and the impact associated with the total number of harvested LNs is ignored. Our results showed that the ypN category had no impact on OS. This

result may have been affected by the differences in the number of harvested LNs at the same ypN stage. Johnson *et al*. reported that the number of negative LNs is an important prognostic indicator for patients with stage IIIB and IIIC colon cancer, and having 13 or more negative LNs was found to be independently associated with improved disease-specific survival (18). Several studies have reported an association between the number of LNs evaluated and survival among patients with colorectal cancer (7, 19, 20). Swanson *et al*. examined 35,787 patients with T3N0 colon cancer and demonstrated that three categories of LN harvest (1-7, 8-12, and >12) were associated with different 5-year survival rates (50%, 56%, and 63%, respectively) (7).

LNR and LODDS were developed to consider the prognostic effect of LN status by analyzing both the total number of LNs harvested and the total number affected. Previous studies have reported LNR to be of higher prognostic value than N-stage for rectal cancer (10, 21). Additionally, Huang *et al*. reported that LODDS was a better prognostic factor than LNR for patients with stage III rectal cancer (17). On the other hand, the present study demonstrated that LNR>0.1 was significantly associated with poor survival outcomes, whereas LODDS had no association with survival. The lack of statistical significance associated with LODDS was probably related to the different neoadjuvant treatments. Previous reports do not mention whether or not chemotherapy was concurrently administered with radiotherapy, but in the present study all patients were treated with neoadjuvant CRT. For patients with locally advanced rectal cancer, preoperative CRT can induce nodal downstaging by tumor regression (3) and affect yp-LNR and yp-LODDS values. LNR reflects the proportion of evaluated LNs found to be positive, while LODDS is determined by dividing harvested LNs into positive and negative LNs. Thus, when there are no involved LNs, LNR is zero regardless of the total number of harvested LN but LODDS is heterogeneous, making it difficult to determine the optimal cut-off value.

We found that LNR>0.1 was a statistically significant predictor of shorter survival in the subgroup with >12 dissected LNs among patients with clinical stage III disease. Although there is debate regarding the number of LNs needed for accurate staging, the assessment of more than 12 LNs following colorectal surgery is recommended in clinical guidelines (6, 22). Lee *et al*. reported that low LN harvests (<12) were predictive of poor OS and DFS in stage III colon cancer (23). If the number of metastatic LNs is the same, the higher the number of harvested LNs, the smaller the LNR value. Further investigation is required to confirm whether the same cut-off LNR value can be applied to each subgroup according to the number of dissected LNs.

The present study had a number of limitations. Firstly, the method of determining the cut-off LNR value was different from those of other studies. There are various methods used for determining the cut-off LNR value for rectal cancer investigations, including the mean value (24), median value (25), or quartiles reclassified on the basis of Kaplan-Meier plots (21). Therefore, caution should be taken when interpreting the comparisons of survival outcomes according to LNR in the present study with those of previous studies. Secondly, because there were 53 patients (66.3%) with ypN0 disease, there was a limitation in reflecting nodal status by analyzing LNR. However, there are few published rectal cancer studies that have reported yp-LNR and yp-LODDS data, therefore this study may be useful as a reference. A further prospective study is required to evaluate the prognostic value of LNR and determine its optimal cut-off point among patients who have received preoperative CRT for rectal cancer.

In conclusion, we demonstrated that LNR was a more valuable predictor of survival outcomes than LODDS. Among patients with clinical stage III disease with >12 harvested LNs, LNR was a significant predictor for survival.

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