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Effect of Responsiveness of Lymph Nodes to Preoperative Chemoradiotherapy in Patients With Rectal Cancer on Prognosis After Radical Resection

Hyun Gu Lee,[1] Sung Joo Kim,[2] In Ja Park,[3] Seung Mo Hong,[2] Seok-Byung Lim,[3] Jung Bok Lee,[4] Chang Sik Yu,[3] Jin Cheon Kim[3]

Abstract

Metastatic lymph node status after preoperative chemoradiotherapy can be evaluated using the lymph node regression grade (LRG). In this study, the LRG was shown to discriminate prognostic groups, even within the same ypN stage, indicating that LRG can be considered a prognostic determinant in rectal cancer patients with metastatic lymph nodes after preoperative chemoradiotherapy.

Background: The influence of lymph node (LN) response to preoperative chemoradiotherapy (PCRT) has not been well evaluated for prognosis and additional use of adjuvant treatment after PCRT in rectal cancer patients. The aim of this study was to evaluate the prognostic effect of LN regression grade (LRG) in rectal cancer after PCRT and radical resection. **Patients and Methods:** From 2008 to 2011, 389 patients with rectal cancer treated with PCRT followed by radical resection were identified. The pathologic LRG (pLRG) score was determined on the basis of the proportion of tumor cells and fibrosis. The sum of the pLRG of each evaluated LN was used as the final LRG score, LRG-sum. Cox regression analysis was used to evaluate the association of LRG-sum and recurrence-free survival (RFS). **Results:** The distribution of LRG-sum was significantly associated with tumor regression grade of the primary tumor ($P < .001$). LRG-sum showed different values even in patients with the same number of metastatic LNs. LRG-sum was confirmed as the most relevant associated factor among LN-related variables with RFS along with ypT stage in multivariate analysis. Patients were categorized according to the cutoff points of LRG-sum distribution: LRG1 (LRG-sum 0 to $\leq$3), LRG2 (LRG-sum 3 to $\leq$21), and LRG3 (LRG-sum $>$21). RFS showed a significant difference according to LRG group ($P < .001$) and showed more effective difference in RFS in the same ypN stage subgroup on the basis of the number of metastatic LNs. **Conclusion:** LRG was a prognostic factor of oncologic outcomes of rectal cancer. LN response to PCRT might help in prognostication and determination of treatments after PCRT.

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Keywords: Lymph nodes, Preoperative chemoradiotherapy, Prognosis, Response, Rectal neoplasm

Introduction

The existence of metastatic lymph nodes (LNs) has been well known as one of the most important prognostic factors of rectal cancer. The current staging system uses the number of metastatic LNs as a pathologic nodal staging system. In addition, many clinicians have tried other methods including number of retrieved LNs, metastatic LN ratio (LNR), and location of metastatic LNs to evaluate the prognostic effect of metastatic LNs in rectal cancer.[1-3]

Preoperative chemoradiotherapy (PCRT) followed by radical resection is the treatment of choice in patients with locally advanced

H.-G.L. and S.-J.K. contributed equally to this work as first authors.

[1]Department of Surgery
[2]Department of Pathology
[3]Department of Colon and Rectal Surgery
[4]Departments of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

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Address for correspondence: In-Ja Park, MD, PhD, Department of Colon and Rectal Surgery, University of Ulsan College of Medicine and Asan Medical Center, 86 Asanbyeongwon-gil, Songpa-gu, Seoul, Korea 138-736
Fax: +82-2-474-9027; e-mail contact: ipark@amc.seoul.kr

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rectal cancer.[4,5] The prognostic importance of metastatic LNs is also well established in a PCRT setting for patients with rectal cancer. However, the prognostic importance of metastatic LNs is more complicated to evaluate for patients who undergo PCRT. PCRT is known to decrease the number of retrieved LNs.[6,7] This decrease might be caused by the effect of radiation therapy on lymph nodal status. Therefore, a number-based LN staging system would need to be applied in a different manner after PCRT. In addition, the influence of PCRT on tumor regression in the LN should be considered in combination with its influence on primary tumor regression.

The importance of the pathologic response grade of a primary tumor on a patient's prognosis has been widely studied.[8-10] Metastatic LN status is important for recurrence or survival, as well as primary tumor status. Therefore, the response level of metastatic LNs should be considered for prognostication as well as primary tumor regression grade (TRG). There are, however, limited studies on the effects of PCRT on the histopathology of LNs in rectal cancer and its correlations with prognosis.[11,12]

The correlation between primary tumor and LN regression level should be evaluated because the clinical diagnosis of the primary tumor regression level is used for surgical strategy decision after PCRT, such as local excision, or wait-and-watch strategies. The presence of regional metastatic LNs is a determinant for avoiding organ-preserving strategies; however, accuracy of imaging modality to diagnose LN metastasis is limited. Therefore, the available evidence that LN metastasis rate increased according to the advancement of primary tumor was applied to resolve ambiguous imaging diagnosis of LN metastasis. But, because the results were from patients who did not receive PCRT, they were not included in the consideration of regression of LN metastasis due to PCRT.

The aim of this study was to examine the regression grade of metastatic LNs, after PCRT, using a pathological regression grading system. Further, in this study we aimed to evaluate the prognostic effect of the LN regression grade (LRG) in rectal cancer patients treated with PCRT followed by radical resection.

Patients and Methods

Study Population

We retrospectively analyzed 389 patients with locally advanced, mid- and low-rectal cancer (located within 10 cm from the anal verge) treated with PCRT followed by radical resection between January 2008 and November 2011 at Asan Medical Center, Seoul, Korea. Locally advanced rectal cancer was defined as a tumor clinically diagnosed as T3/4 and/or N+ using magnetic resonance imaging without evidence of distant metastasis. Patients who underwent local excision and who could not be assessed for LN status were excluded from this study.

This study was approved by the institutional review board of Asan Medical Center (Registration number 2017-1022).

Preoperative Chemoradiotherapy and Surgery

The median radiation dose was 50.0 (range, 43.2-51.0) Gy and the most common dose scheme was 44.0 Gy to the whole pelvis with a 6.0-Gy boost to the tumor bed in 1.8- to 2.0-Gy daily fractions. The primary tumor, perirectal adipose tissue, obturator, internal iliac, and presacral nodes were included for the clinical target volume. The superior border of the clinical target volume was the lower margin of the L5 spine, and the inferior border was 2 cm distal to the primary tumor. 5-Fluorouracil with leucovorin or capecitabine was used as concurrent chemotherapy during the treatment period for PCRT. Oral capecitabine (825 mg/m^2) was administered twice daily during radiation therapy, or alternatively, 2 cycles of a bolus 5-fluorouracil (375 mg/m^2/d for 3 days) with leucovorin during the first and fifth week of radiation therapy was used. Surgical resection was performed after 6-8 weeks after completion of radiation therapy, and radical surgical resection was performed according to the principle of total mesorectal excision.

Histopathological Evaluation and Determination of the LN Regression Level

Routine hematoxylin and eosin sections were used for pathologic evaluation of the primary tumor and metastatic LNs. Pathologic responses to PCRT were evaluated in the resected specimens using the TRG system suggested by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists[13]: no evidence of irradiation change (fibrosis, necrosis, or vascular change) was defined as "no regression," dominant tumor mass with obvious irradiation change as "minimal regression," dominant irradiation change with residual tumor (easy to find) as "moderate regression," microscopic residual (difficult to find) tumor in fibrotic tissue as "near total regression," and no residual tumor cells, only fibrotic mass, as "total regression." The regression level of the metastatic LNs to PCRT was determined on the basis of the proportion of tumor cells as well as fibrosis and were classified into a 6-tier grading system[11]: pathologic LRG (pLRG). LN-preserving normal nodal architecture without evidence of cancer cells or fibrosis was scored as pLRG0, LN with 100% fibrosis as pLRG1, LN with <25% cancer cells as pLRG2, scattered glandular elements with fibrosis as pLRG3, LN with >50% cancer cells as pLRG4, and complete replacement with cancer cells as pLRG5. All retrieved LNs were evaluated, and each LN was scored according to the pLRG system. The perirectal and intermediate LNs within radiation fields were evaluated using the pLRG system. We also assessed the number of pathologic metastatic LNs and the LNR (metastatic LN/harvested LN) in patients who had metastatic LNs.

Because variable LN responses were identified in patients, we used the sum of pLRG of each evaluated LN as the final LRG score, identified as LRG-sum, to evaluate the LRG of each patient. TRG and LRG of all specimens were assessed by 2 pathologists (S.J.-K. and S.M.-H.), who specialize in colorectal cancer pathology. They reviewed all specimens together and discussed the results to reach a consensus on TRG and LRG.

Surveillance and Oncologic Outcomes

All patients were followed up every 3 to 6 months after surgery, and the surveillance included detailed history, physical examination, serum carcinoembryonic antigen measurement, abdominal, pelvic, and chest computed tomography (CT), and colonoscopy. Abdominal, pelvic, and chest CT scans were checked every 6 months. Colonoscopy was performed every 2 to 3 years. When multiple polyps or polyps larger than 1 cm were identified, a colonoscopy was performed annually. Local recurrence was defined as the presence of a lesion indicative of cancer in the site of anastomosis, or the bed of

the primary resection, upon postoperative colonoscopy or pelvic imaging (CT, magnetic resonance imaging, and/or positron emission tomography). Distant metastasis was defined as the presence of recurrence beyond the surgical fields, including distant organs, detected using CT or positron emission tomography. These were diagnosed using biopsy and serial change on imaging diagnosis. Recurrence-free survival (RFS) was counted from the date of surgery to the date of the first recurrence event.

Statistical Analysis

Independent sample *t* test and analysis of variance were used to evaluate the distribution of the LRG-sum according to TRG and tumor stage. Cox proportional hazard regression analysis was used to determine the association between clinical variables and RFS. The K-adaptive partitioning for survival data method was applied to find the best split set of cut points for the LRG-sum to find the most suitable prognostic subgroup in the survival data. Statistical data are expressed as mean ± SD. Survival curves were constructed using the Kaplan–Meier method and compared using the log rank test. Data analysis was performed using SPSS software (version 21.0; IBM Corp, Armonk, NY).

Results

Clinicopathological Characteristics of Patients

Among 389 enrolled patients, 135 male patients (65.3%) were more common than female patients. The median number of harvested LNs was 17. Fifty patients (12.9%) with total regression of the primary tumor were identified, and 75 patients (19.3%) had minimal or no regression. ypT3 231 (59.4%) and ypN0 117 (30.1%) were the most common. Among patients, 69.9% had metastatic LNs in the tumor specimen, and the mean number of tumor-involved LNs (±SD) was 2.3 ± 2.9. Among the patients who had metastatic LNs, the mean LNR (±SD) was 0.20 ± 0.18 (Table 1). The median follow-up period was 58 months.

Table 1 Clinicopathological Characteristics of Patients

Variable	Value
Median Age (Range), Years	57 (25-79)
Sex	
Male	254 (65.3)
Female	135 (34.7)
Median Follow-up Time (Range), Months	58 (3-108)
Tumor Regression Grade of Primary Tumor	
Total	50 (12.9)
Near total	77 (19.8)
Moderate	187 (48.1)
Minimal and no	75 (19.3)
ypT stage	
ypT0	53 (13.6)
ypT1	13 (3.3)
ypT2	86 (22.1)
ypT3	231 (59.4)
ypT4	6 (1.5)
ypN stage	
ypN0	117 (30.1)
ypN1a	96 (24.7)
ypN1b	81 (20.8)
ypN2a	59 (15.2)
ypN2b	36 (9.3)
Harvested Lymph Nodes	17.44 ± 7.10
Lymph Node Ratio, %	0.20 ± 0.18
LRG-Sum	6.9 ± 9.2
Lymphovascular Invasion	54 (13.9)
Perineural Invasion	76 (19.5)
CRM Involvement	22 (5.7)

Data are presented as n (%) or mean ± SD, except where otherwise noted.
Abbreviations: CRM = circumferential resection margin; LRG = lymph node regression grade.

Association Between Metastatic LRG and Primary Tumor Regression

Among the enrolled patients, the number of patients who had LN metastasis was 272. Among 50 patients with total regression of primary tumor, 19 had metastatic LNs. The pLRG was evaluated for metastatic LNs and the distribution of pLRG of each LN was quite variable even in the same patient (Supplemental Figure 1) The average of LRG-sum (±SD) was 6.9 ± 9.2 which increased significantly according to advancement of ypN stage (3.45 ± 0.26 for ypN1, 11.25 ± 1.25 for ypN2; $P < .001$). The pLRG-sum differed according to the TRG of the primary tumor. The distribution of pLRG-sum was strongly associated with total regression of the primary tumor, but it did not differ among near total, moderate, and minimal regression (Figure 1). The mean pLRG-sum was quite low, and the amount of variation in total regression compared with regression of other primary tumors was small ($P < .001$).

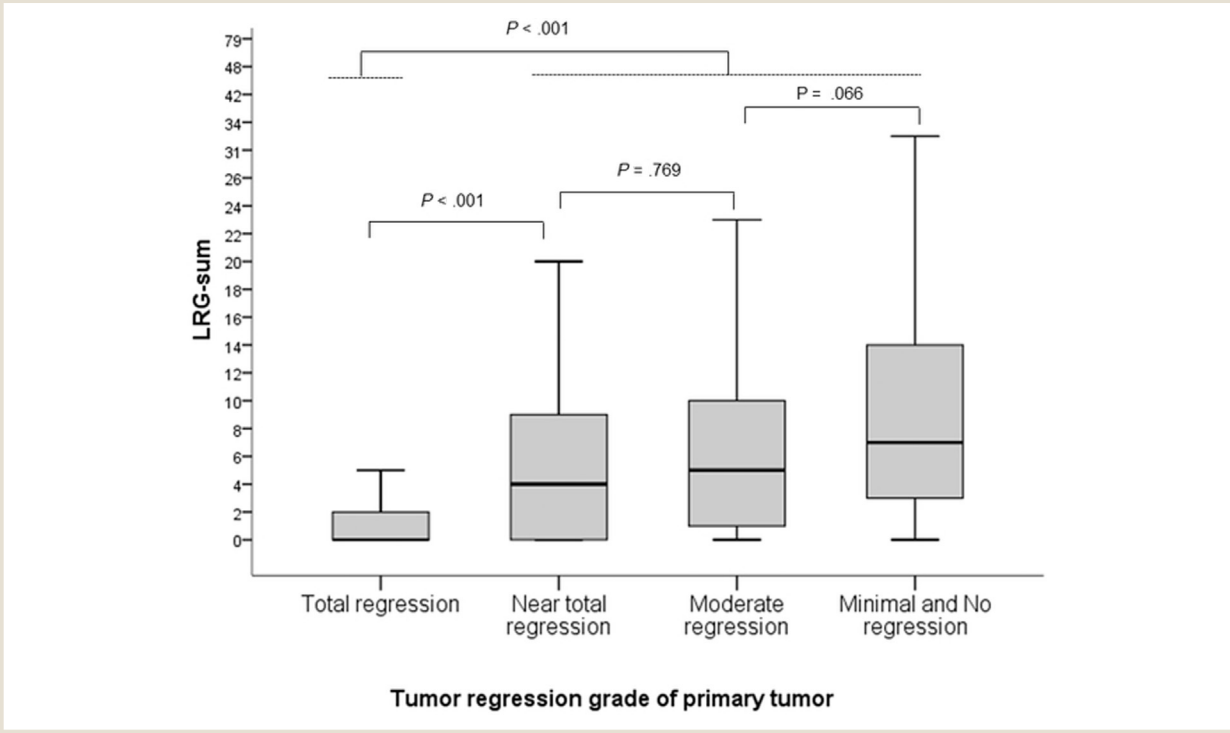
Association Between LRG-Sum and RFS

Overall, LRG-sum, ypN stage, and LNR were associated with RFS in univariate analysis along with TRG of primary tumor, circumferential resection margin involvement, lymphovascular invasion, and perineural invasion in all patients. We performed leave-one-out analysis to determine the most predictive LN-associated variable (LRG-sum, ypN stage, and LNR) that could enter multivariate analysis with other clinicopathologic variables. LRG-sum was found to be the most significantly associated factor with RFS among LN status-associated variables. In multivariate analysis including LRG-sum and other clinical factors, LRG-sum and TRG of primary tumor were the factors associated with RFS (Table 2). Among patients with metastatic LNs (n = 272), LRG-sum was confirmed to be associated with RFS in multivariate analysis (odds ratio, 1.026; 95% confidence interval, 1.007-1.044; $P = .006$).

Determination of the Risk Groups of Oncologic Outcomes According to LRG-sum

The cutoff value of the LRG-sum, which discriminated the best risk subgroups on the basis of survival curves, was determined using the K-adaptive partitioning method. Cutoff points of 3, and 21 of the LRG-sum were selected, and the patients were categorized into 3 groups: LRG1 (LRG-sum 0 to ≤3), LRG2 (LRG-sum 3 to ≤21), and LRG3 (LRG-sum >21) for RFS. Patients with same ypN stage

Figure 1 The Mean LRG-Sum According to Tumor Regression Grade of the Primary Tumor. LRG-Sum Was Correlated With TRG of Primary Tumor; LRG-Sum of Total Regression Was Significantly Different From That of Other Regression Groups



Abbreviations: LRG = lymph node regression grade; TRG = tumor regression grade.

were discriminated within LRG groups. All ypN0 patients belonged to the LRG1 group. All ypN1 patients belonged to either of the 2 groups; LRG1 (n = 66) and LRG2 (n = 111). Among them, the LRG2 group had less total regression of primary tumor (n = 28, 15.2% for LRG1 vs. n = 10, 5.4% for LRG2; $P = .029$), more lymphovascular invasion (n = 11, 6.1% for LRG1 vs. n = 30, 16.2% for LRG2; $P = .048$), and higher LNR (0.08 ± 0.04 for LRG1 vs. 0.13 ± 0.10 for LRG2; $P < .001$). However, the number of harvested LNs did not differ according to LRG group.

Of the 95 patients with ypN2 stage, 75 were included in the LRG2 group, and 20 in the LRG3 group (Table 3). Among them, the LRG3 group showed significantly more lymphovascular invasion (18.7% for LRG2 vs. 70.0% for LRG 3; $P < .001$), more perineural invasion (25.3% for LRG2 vs. 50.0% for LRG 3; $P = .001$), and higher LNR (0.35 ± 0.19 for LRG2 vs. 0.46 ± 0.17; $P = .026$). However, in the same LRG group, clinicopathologic factors such as lymphovascular invasion, perineural invasion, total regression of primary tumor, and total number of harvested LNs did not differ between the ypN stages.

Recurrence-free survival showed significant differences according to the LRG groups as well as ypN stage (Figure 2A and B). However, in the same ypN stage, ypN substages such as ypN1a, ypN1b, ypN2a, and ypN2b did not show a difference in RFS (Figure 2D and F). However, RFS was discriminated according to LRG group in the same ypN stage (Figure 2C and E).

Discussion

In this study, a correlation was identified between pathologic regression grade of metastatic LNs and total regression of a primary tumor among patients with metastatic LNs. LRG was also confirmed as a significant factor associated with RFS.

We suggested the prognostic importance of pathologic regression levels of metastatic LNs after PCRT in patients with ypN1 disease in a previous report.[11] We extended the patient cohort to evaluate the prognostic effect of LRG overall in patients in the current study.

In advanced rectal cancer patients treated with PCRT, it has been constantly questioned whether primary tumors and metastatic LNs respond similarly to PCRT. Some studies have reported that metastatic LNs usually respond similarly as primary tumors.[14,15] In contrast, others have indicated a response difference between the primary lesion and LNs.[11,16-18] The present study showed that LRG had a correlation with TRG, although it was not found to be a stepwise correlation. The distribution of LRG-sum was strongly associated with total regression of the primary tumor. However, this association was not observed in patients with near total, moderate, minimal, and no regression of the primary tumor. It might be helpful to decide on a treatment strategy after PCRT. The primary tumor response after PCRT is typically assessed to decide surgical strategies because LN metastasis rates have been known to increase with advancement of a primary tumor,[19,20] and the diagnostic

Table 2 Factors Associated With Recurrence-Free Survival in All Patients

Variable	Univariate Analysis		Multivariate Analysis[a]	
	Hazard Ratio (95%CI)	*P*	Hazard Ratio (95%CI)	*P*
LRG-Sum	1.04 (1.026-1.054)	<.001	1.025 (1.008-1.042)	.005
Harvested LNs, n	0.999 (0.976-1.022)	.912		
LN Ratio	8.265 (3.833-17.824)	<.001		
ypN		.001		
ypN0	1			
ypN1	1.305 (0.856-1.989)			
ypN2	2.516 (1.622-3.902)			
TRG		.001		.005
Total regression	1		1	
Other regression	4.217 (1.862-9.550)		3.259 (1.424-7.460)	
CRM Involvement	2.46 (1.415-4.274)	.001	1.293 (0.685-2.443)	.428
Lymphovascular Invasion	2.263 (1.528-3.354)	<.001	1.417(0.896-2.241)	.136
Perineural Invasion	1.71 (1.188-2.463)	.004	1.208 (0.817-1.785)	.344
Sex				
Male	1			
Female	1.043 (0.744-1.463)	.807		
Age	0.999 (0.983-1.015)	.880		

Abbreviations: CRM = circumferential resection margin; LN = lymph node; LRG = lymph node regression grade; TRG = tumor regression grade.
[a]Multivariate analysis with metastatic LN-related variables such as LRG-sum, LN ratio, and ypN.

accuracy for metastatic LN evaluation was limited.[21,22] If TRG can allow us to anticipate the response of LNs to PCRT, it could support the local excision or "wait-and-watch" approach in treating clinically totally regressed tumors after PCRT. According to the results of this study, 10 of the 19 patients with total primary tumor regression showed no recurrence during the entire follow-up duration even with metastatic LNs. Therefore, half of the patients with total primary tumor regression and metastatic LNs would have a theoretical chance of rectum preservation. However, preoperative prediction of LN regression level after PCRT is quite limited because of the current diagnostic imaging system and because it is impossible, because this was a pathologic evaluation-based diagnosis. We need to be very careful in suggesting management strategies knowing that half of these patients had recurrence even after radical resection.

Currently, the widely used staging system is solely on the basis of the number of metastatic LNs. After PCRT, evaluation of nodal status using a traditional staging system is more complicated because radiation therapy is known to influence retrieved LNs.[6,7] Although the current staging system recommends harvesting more than 12 LNs,[23,24] the adequate number of harvested LNs for proper staging of rectal cancer after PCRT is not well established. Han et al[25] showed that the retrieval of LNs $\geq$ 12 and LNs $\geq$ 8 should be achieved to obtain accurate staging and optimal treatment for the non-PCRT and PCRT groups in rectal cancer, respectively. Another report stated that the retrieval of fewer than 12 LNs in surgical specimens of rectal cancer patients who underwent PCRT should be considered a good indicator of tumor response with better local disease control. Further, this is a good prognostic factor, rather than as an indicator of poor diligence of the surgical and pathological assessment.[26] LNRs have been studied for identifying prognostic subgroups to complement for number-based staging.[27,28] However, it could not reflect the response of LNs to PCRT and change of tumor status within LNs. We also analyzed the effect of LNRs on RFS, and they were associated with RFS. However, "leave-one-out" analysis of LN status-related variables showed that LRG, which reflects response level to PCRT, was the most predictive factor of RFS and was confirmed as a factor associated with RFS in multivariate analysis with other clinicopathological variables.

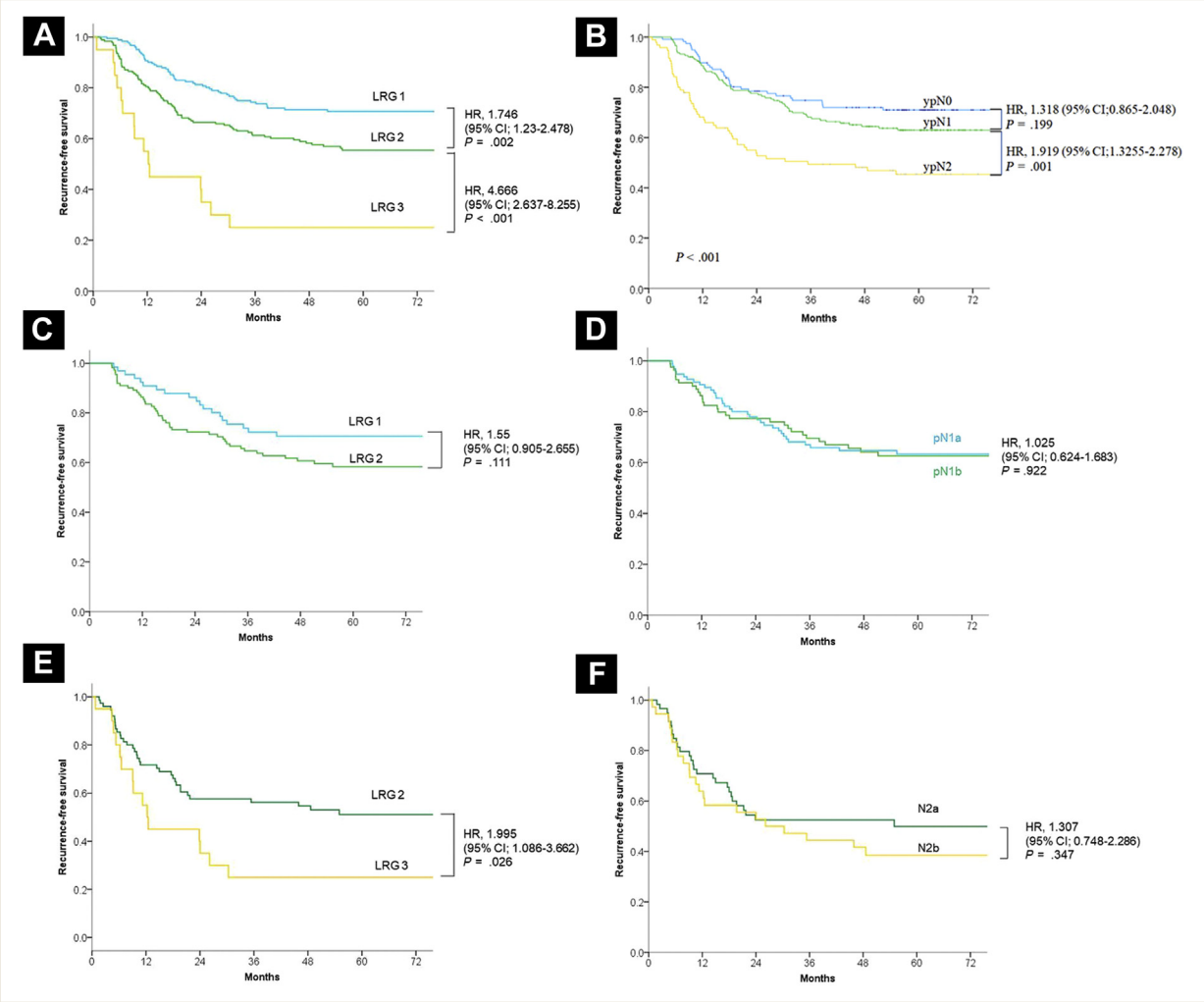
Table 3 Comparison of the Distribution According to LRG Groups and ypN Stage

LRG Group	ypN Stage, n (%)			Total, n
	ypN0	ypN1	ypN2	
1	117 (100)	66 (37.3)	0	183
2	0	111 (62.7)	75 (78.9)	186
3	0	0	20 (21.1)	20
Total	117	177	95	389

Abbreviation: LRG = lymph node regression grade.

As in the primary tumor, the metastatic foci within LN change or even resolve after PCRT. It has been constantly questioned whether to consider resolved metastatic LNs as metastatic LNs. Likewise, it is unclear if a LN with only 10% cancer cells after PCRT and a LN that fully comprises cancer cells have the same prognostic significance. The LRG after PCRT was evaluated using the TRG system of Mandard, which is on the basis of the ratio of residual tumor to fibrosis at first.[29] The first study suggesting LRG after PCRT, however, was limited by a small sample size and did not evaluate the prognostic value of LRG despite reporting complete pathologic regression of LNs in 51% of patients. The oncologic effect of the

Figure 2 Recurrence-Free Survival According to LRG Group and ypN Stage. (A) LRG group; (B) ypN Stage Overall in Patients; (C) LRG Group in Patients With ypN1 (1-3 Metastatic LNs); (D) ypN Substage in Patients With ypN1; and (E) LRG Group in Patients With ypN2 (≥4 Metastatic LNs). (F) ypN Substage in Patients With ypN2. In the Same Subgroup According to the Number of Metastatic LNs, LRG Would Discriminate the Prognostic Group More Effectively Than ypN Substage



Abbreviations: HR = hazard ratio; LN = lymph node; LRG = lymph node regression grade.

pLRG was first reported by Mirbagheri et al.[12] They also examined LN status after PCRT using a scoring system and reported that LRG score was a significant predictor of tumor recurrence. Further, a lower LRG score was correlated with an improved survival curve. In the present study, we also applied the response grade of LNs and tested its prognostic implications. We tested the mean, highest, and lowest value of LRG as well as LRG-sum (because LRG-sum would be influenced by total number of examined LNs). However, the highest and lowest value of LRG would not represent the regression level of entire LNs. The mean value of LRG could not be used to stratify the prognostic group. Therefore, among LN regression-related variables, we used LRG-sum for representing LRG after PCRT. In all patients, including patients with metastatic LNs, LRG was confirmed as a good predictor of prognosis.

The response level of each LN to PCRT can be variable even in a single resection specimen. We identified that the pLRG score of each LN showed various distributions within the same patient. As such, the LRG-sum should be assigned to represent various responses of metastatic LNs in one patient. We tested various methods to evaluate the regression level of LNs to PCRT, such as LRG-mean and LRG-sum; LRG-mean is the average of LRG score of each LN and LRG-sum is the sum of LRG score of each LN. In this study, LRG-sum was chosen because it takes the number of metastatic LNs into account. Therefore, LRG-sum would be used as an appropriate indicator for considering the regression level and the number of metastatic LNs together. We found that patients with the same ypN stage showed varying distributions for LRG-sum, even in ypN1a disease, although LRG-sum showed linear correlation with the ypN stage. Therefore, LRG-sum would discriminate patients according to tumor burden in the LNs.

We found that the LRG-sum grading system using percentile values was a more effective prognostic indicator than the currently

used ypN stage for RFS. Even in patients with one metastatic LN, the LRG-sum was quite variable. The ypN stage would not take the tumor burden within LNs into account and would not discriminate RFS well. However, cutoff values of LRG-sum discriminating prognostic subgroups effectively have to be determined with further studies involving a larger cohort.

This study has some limitations. Because it was a retrospective study, there might be selection bias. Patients who received local excision or a nonsurgical approach were not included because they did not have assessable LNs or primary tumor. This might have influenced the analysis of association between regression grade of primary tumor and LNs. Moreover, the heterogeneity of the surgical techniques and pathologic preparation and evaluation of LNs might have affected the oncologic outcomes. However, a highly trained pathologist repeatedly reviewed the specimens to overcome this limitation. Further, LNs scoring out of the radiation fields (such as inferior mesenteric LN) were not considered for LRG. In this study, there were no metastatic LNs out of the radiation fields. In addition, the determination of prognostic subgroup using LRG should be validated in an extended cohort.

Conclusion

On the basis of the results of this study, LRG was a prognostic factor of oncologic outcomes in rectal cancer patients treated with PCRT followed by radical resection. We confirmed previous results through an investigation of a larger patient cohort including all kinds of metastatic LN statuses. LRG showed association with total regression of primary tumor; therefore, it would be helpful to predict regression of LNs on the basis of the totally regressed primary tumor, particularly in patients in whom nonsurgical approaches are being considered after PCRT.

Before application of LRG in a clinical setting, such as in selection of patients with poor prognoses for more intensive adjuvant treatment or tailored surveillance schedule according to risk group, there is a need for further and more extensive validation.

Clinical Practice Points

- Pathologic TRG of primary tumor is known to be associated with prognosis of rectal cancer patients who were treated with PCRT.
- Extent and influence of LN response to PCRT has not been evaluated enough.
- Lymph node regression grade is various among LNs respectively and sum of each LRG is different even in same ypN category.
- Sum of LRG of each evaluated LN is associated with RFS.
- Lymph node regression grade would be useful for risk group stratification for adjuvant chemotherapy or surveillance.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.03.001.

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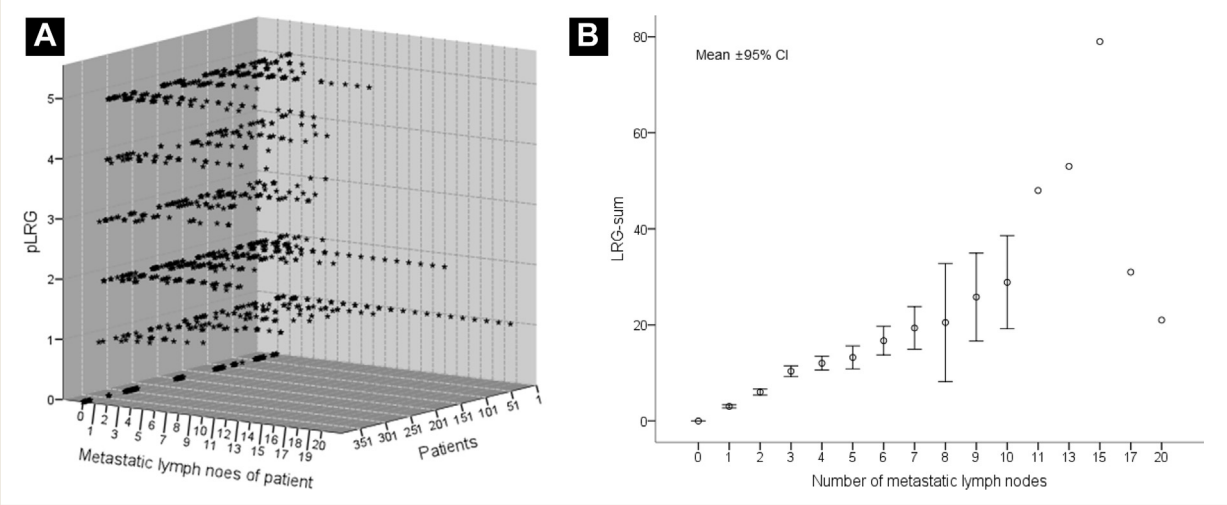
Supplemental Figure 1 **Distribution of Lymph Node (LN) Regression Grade (LRG). (A) Each Metastatic LN Showed a Different LRG in Each Patient. (B) LRG-Sum Also Showed Various Distributions in the Same Number of Metastatic LNs**



Abbreviation: pLRG = pathologic lymph node regression grade.