의학석사 학위논문

수술 전 항암방사선 치료 후 절제를 시행 받은 직장암 환자에서 병리학적 림프절 반응 정도가 예후에 미치는 영향

Prognostic Implication of Pathologic Lymph Node Response Level in Rectal Cancer treated with Preoperative Chemoradiotherapy followed by Radical Resection

울산대학교 대학원

의 학 과

이 현 구

수술 전 항암방사선 치료 후 절제를 시행 받은 직장암 환자에서 병리학적 림프절 반응 정도가 예후에 미치는 영향

지도교수 박 인 자

이 논문을 의학석사 학위 논문으로 제출함

2018년 2월

울산대학교 대학원
의 학 과
이 현 구

이현구의 의학석사학위 논문을 인준함

심사위원장 임 석 병 (인)

심사위원　박 인 자 (인)

심사위원　홍 승 모 (인)

울 산 대 학 교 대 학 원

2018 년 2 월

Abstracts

Prognostic Implication of Pathologic Lymph Node Response Level in Rectal Cancer treated with Preoperative Chemoradiotherapy followed by Radical Resection

Background and Objectives: The response level of metastatic lymph nodes (LN) following preoperative chemoradiotherapy (PCRT) has not been considered in the current staging system in rectal cancer. The aim of this study was to evaluate the prognostic impact of the lymph node regression grade (LRG) in rectal cancer patients treated with PCRT followed by radical resection.

Materials and methods: From 2008 to 2011, 389 patients with rectal cancer treated with PCRT followed by radical resection were identified. The pathologic lymph node regression grade (pLRG) score was determined based on the proportion of tumor cells and fibrosis. Non-tumorous LN with normal architecture was scored as pLRG0; LN with 100% fibrosis as pLRG1, LN with <25% cancer cells as pLRG2, LN with 25-50% cancer cells as pLRG3, LN with >50% cancer cells as pLRG4, complete replacement with cancer cells as pLRG5. The sum of the pLRG of each evaluated LNs was used as the final LRG score, LRG-sum.

Results: The distribution of LRG-sum was significantly associated with tumor regression grade (TRG) of the primary tumor ($p<0.001$). Patients were categorized into 3 groups according to the cut-off points determined by using percentiles of LRG-sum distribution; LRG1 ($0\leq$LRG-sum≤1), LRG2 ($1<$LRG-sum<15) and LRG3 (LRG-sum≥15). Recurrence free survival (RFS) demonstrated significant difference according to LRG groups, and median survival of LRG1, LRG2, and LRG3 was 56.7, 49.3, 21.2 months each ($p<0.001$). Overall survival (OS) was also significantly different according to LRG groups; median survival of LRG1, LRG2, and LRG3 was 60.0, 60.0, 47.0 months each ($p<0.001$). In addition, LRG-sum was confirmed as associated factor with RFS along with ypT stage in multivariate analysis. For OS, LRG-sum was the only associated factor in multivariate analysis. **Conclusion**: LRG was an important prognostic factor of oncologic outcomes in patients with rectal cancer treated with PCRT followed by radical resection.

Key words: rectal cancer, preoperative chemoradiotherapy, lymph node regression

Contents

Lists of figures and tables

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 pathologic nodal staging system.[1, 2] In addition many clinicians have tried to find the other methods including the number of retrieved lymph nodes, metastatic lymph node ratio, and location of metastatic lymph nodes to evaluate the prognostic impact of metastatic LNs in rectal cancer.[3-5] Multiple studies have indicated the relationship between the number of lymph nodes isolated from the surgical specimen and oncologic outcome. [6, 7, 8, 9, 10] They demonstrated that the prognosis of colorectal cancer was dependent on the number of lymph nodes examined[6, 9, 10] and low lymph node count indicated adverse outcome in patients with locally advanced (T3/T4) disease.[7,10] Lymph node ratio (LNR), defined as the ratio of metastatic LNs to all retrieved LNs, has also shown to be a useful prognostic indicator in colorectal cancer.[11, 12]

Preoperative chemoradiotherapy (PCRT) followed by radical resection is the treatment of choice in the patients with locally advanced rectal cancer.[13, 14] The prognostic importance of metastatic lymph nodes is also established under PCRT setting in rectal cancer. Several studies reported that LN positivity is associated with shorter survival and time to recurrence.[15, 16, 17] In addition, some authors reported that positive ypN status had a poor prognosis even after total regression of primary tumor.[18, 19] However, prognostic importance of metastatic LNs is more complicated to evaluated under PCRT setting. PCRT is also known to decrease the number of retrieved LNs. It is suggested that LN size is decreased following apoptosis and involution induced by radiation and the reduction in LN size may decrease the likelihood of smaller LNs to be detected in the resected specimen.[20, 21] Despite these changes in LNs after PCRT, LNR has also been indicated as an important prognostic factor under PCRT setting.[22, 23, 24] Moreover, some studies demonstrated that LNR was more effective prognostic marker than ypN stage for ypN-positive rectal cancer patients.[22, 25]

The response level to PCRT should also be considered to assess the prognosis in rectal cancer patients treated with PCRT. The importance of pathologic response grade of primary tumor on prognosis has been widely studied.[26-29] These previous studies have shown that complete and intermediate pathologic responses were associated with improved long-term oncologic outcomes in patients with rectal cancer after PCRT independent of clinico-

pathologic parmeters.[27, 29] Tumor regression grade (TRG), used to evaluate the response level of primary tumor to PCRT, was determined by the amount of viable tumor versus fibrosis and classified into 3- or 4-tier grading system[29]. Several TRG systems has been already used as prognostic marker: Mandard, Dowrak/Rödel, Memorial Sloan Kettering Cancer Center (MSKCC), and American Joint Committee on Cancer (AJCC) Cancer Staging.[26]

In contrast, there are limited studies examining the effects of PCRT on the histopathology of LNs in rectal cancer and correlations with prognosis.[30, 31] M. Mirbagheri et al. suggested a nodal scoring system based on the percentage of fibrosis and the presence of residual tumor amount following PCRT and identified that the LN regression score was a significant predictor of tumor recurrence and survival.[31] Jun Li et al. evaluated response of LNs to PCRT by a 3-tier LN regression grade and indicated that LN regression grade may be an independent predictive factor of long-term oncologic outcomes.[32] The metastatic lymph node status is definitely important for recurrence or survival as well as primary tumor status. Therefore, the response level of metastatic lymph nodes has to be considered for prognostication along with primary tumor regression grade (TRG).

The correlation between the regression level of primary tumor and lymph node also has to be evaluated, because the clinical diagnosis of primary tumor regression level is used for surgical strategy decision after PCRT such as local excision or wait and watch strategies.[33, 34, 35] The presence of regional metastatic lymph node is one of the determinants avoiding organ-preserving strategies; however the accuracy is quite low for imaging diagnosis of metastatic lymph nodes than primary tumor regression.[36, 37] Some studies reported that residual LN metastasis risk remains high even with good PCRT response within the primary tumor, and they suggested that all acceptable-risk patients with a diagnosis of primary rectal cancer should undergo resection, regardless of their response to preoperative therapy.[38, 39] However, some authors suggested that LNs also responded well to PCRT in patients with complete response of primary tumor and metastatic LN with complete response (100% fibrosis) showed as good outcomes as normal LN.[31]

The aim of this study was to examine the regression level of metastatic LNs following PCRT using a pathological regression grading system, and to evaluate the prognostic impact of the lymph node regression grade (LRG) in rectal cancer patients treated with PCRT followed by radical resection.

Materials and Methods

Study population

We retrospectively analyzed 389 patients with locally advanced, mid and low rectal cancer (located within 10 cm from 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 tumor clinically diagnosed as T3/4 and/or N+ on magnetic resonance imaging without evidence of distant metastasis. Patients who underwent local excision and who could not be assessed for lymph node status were excluded in this study.

Preoperative chemoradiotherapy and surgery

The median radiation dose was 50.0 Gy (range, 43.2 to 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 a 1.8-2.0 Gy daily fractions. The primary tumor, perirectal adipose tissue, obturator, internal iliac, and presacral nodes were included to the clinical target volume. The superior border of clinical target volume was the lower margin of 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 preoperative chemoradiotherapy. Oral capecitabine (825 mg/m2) was administered twice daily during radiation therapy or 2 cycles of a bolus 5-fluorouracil (375 mg/m2/d for 3 days) with leucovorin during the first and fifth week of radiation therapy was used. was about 5.5-6 weeks followed with 6-8 weeks interval, 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.[40] No evidence of irradiational change (fibrosis, necrosis, vascular change) was defined as “no regression”; dominant tumor mass with obvious irradiational change as “minimal regression”, dominant irradiational change with

residual tumor (easy to find) as “moderate regression”, microscopic residual tumor (difficult to find) in fibrotic tissue as “near total regression”, No residual tumor cells, only fibrotic mass as “total regression”. The regression level of the metastatic LNs to PCRT was determined based on the proportion of tumor cells and fibrosis and classified into 6-tier grading system[27]; pathologic LN regression grade (pLRG). Lymph node with 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, complete replacement with cancer cells as pLRG5 (Fig 1). All retrieved lymph nodes were evaluated, and each lymph node was scored according to pLRG system. The perirectal and intermediate lymph nodes within radiation fields were evaluated by pLRG system. We also assessed the number of pathologic metastasized lymph nodes and lymph node ratio (LNR; metastatic lymph node/harvested lymph node) in patients who had metastatic lymph nodes.

Because variable responses of the LNs were identified in a patient, we determined used the sum of pLRG of each evaluated LNs as the final LRG score, LRG-sum, to evaluate LN regression grade of each patient. TRG and LRG of all specimens were assessed by 2 pathologists (SJ-K, SM-H) who specialized in colorectal cancer pathology.

Surveillance and oncologic outcomes

All patients were followed up every 3-6 months after operation, and the surveillance method consisted of a detailed history, physical examination, serum carcinoembryonic antigen measurement, abdominal, pelvic, and chest computed tomography (CT), and colonoscopy. Abdominal, pelvic, and chest CT were checked every 6 months. Colonoscopy was performed every 2 or 3 years. When multiple polyps or larger than 1cm in diameter polyp were identified, colonoscopy was evaluated every year. Local recurrence was defined as the presence of a suspicious lesion in the site of anastomosis or the bed of the primary resection on postoperative colonoscopy or pelvic imaging (CT, MRI, and/or PET scan). Distant metastasis was defined as the presence of recurrence beyond the operative fields including distant organs detected by CT or PET scan. 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, and overall survival (OS) was counted from the date of surgery to date of death or last follow-up.

Statistical analysis

Independent sample t-test and ANOVA (Analysis of Variance) were used to evaluate distribution of the LRG-sum and according to TRG and tumor stage. Cox proportional hazard regression analysis was used to determine the association between clinical variables and RFS. We used percentiles to determine cut-off points of LRG-sum to find the most suitable prognostic subgroup in survival data. Survival curves were constructed by the Kaplan-Meier method and compared using log-rank test. Data analysis was performed using SPSS software (version 21.0; IBM Statistics, Armonk, NY).

Results

Clinicopathological characteristics of patients

Among 389 enrolled patients, male patients (65.3%) were more common than female. The median number of harvested lymph nodes 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 (59.4%) and ypN0 (30.1%) were the most common in TNM pathologic staging. 69.9% of total patients had metastatic lymph nodes in the tumor specimen, and the mean number of (± SD) of tumor-involved lymph nodes was 2.3 ± 2.9. Among the patients who had metastatic lymph nodes, the mean number of lymph node ratio (± SD) was 0.20 ± 0.18 (Table 1). The median follow-up period was 58 months.

Association of Metastatic lymph node regression grade with primary tumor regression

Among the enrolled patients, the number of patients who had lymph node metastasis was 272. Distribution of pLRG of each LN were variable in a patient (Fig 2) and the average of LRG-sum (± SD) was 6.9 ± 9.2 (Table 1). LRG-sum showed a linear correlation with ypN stage. The distribution of LRG-sum was significantly associated with TRG of the primary tumor ($p<0.001$, Fig 3). Although the overall distribution showed significance, the difference of LRG-sum was prominent between total regression and other all regression, but it was not significant among total, near total, and moderate regression of primary tumor.

Determination of the risk groups of oncologic outcomes according to LRG-sum

The cut-off value of the LRG-sum was determined using percentile of LRG-sum distribution in order to discriminate the patient into risk groups of RFS. We analyzed RFS for each 5 and 10 percentiles besides LRG-sum 0 then determine cut-off values which discriminate the best risk subgroups based on survival curves. Cut-off points of 1 (35 percentile), 15 (85 percentile) of LRG-sum was selected and the patients were categorized into 3 groups: LRG1 ($0 \leq$ LRG-sum ≤ 1), LRG2 ($1 <$ LRG-sum < 15) and LRG3 (LRG-sum ≥ 15) for RFS. Comparing the distribution according to LRG groups and ypN stage, LRG1 and ypN0, LRG2 and ypN1 showed similar distribution. In 89 patients with ypN2 stage, however, 41 patients were included into LRG2 and 54 patients into LRG3 (Table2).

Recurrence free survival (RFS) demonstrated significant difference according to LRG

groups (Fig 3a). But, subgroups were not well discriminated using ypN stage although there is overall statistical significance (Fig 3b, Fig 3c). For overall survival (OS), it also significantly differed according to LRG groups, but there was no difference between LRG1 and LRG2 (Fig 4).

Association of LRG-sum with recurrence-free survival and overall survival

In overall patients, LRG-sum, ypN stage, and lymph node ratio were associated with RFS with univariate analysis along with ypT stage, TRG of primary tumor, circumferential resection margin (CRM) involvement, lymphovascular invasion, and perineural invasion. Multivariate analysis was done for variables related with metastatic lymph node status (LRG-sum, ypN stage, and lymph node ratio) to select lymph node related variable which involved in multivariate analysis together with other clinical factors, and LRG-sum was significantly associated with RFS among these variables. In multivariate analysis including LRG-sum and other clinical factors, LRG-sum and ypT stage were the associated factors with RFS (Table 3). The association between LRG-sum and RFS was also analyzed in patients with metastatic lymph nodes (Table 4). Among the patients with metastatic lymph nodes, LRG-sum was confirmed as associated factors with RFS along with ypT stage in multivariate analysis. For OS, LRG-sum was the factor associated with OS along with lymphovascular invasion and age in multivariate analysis (Table 5).

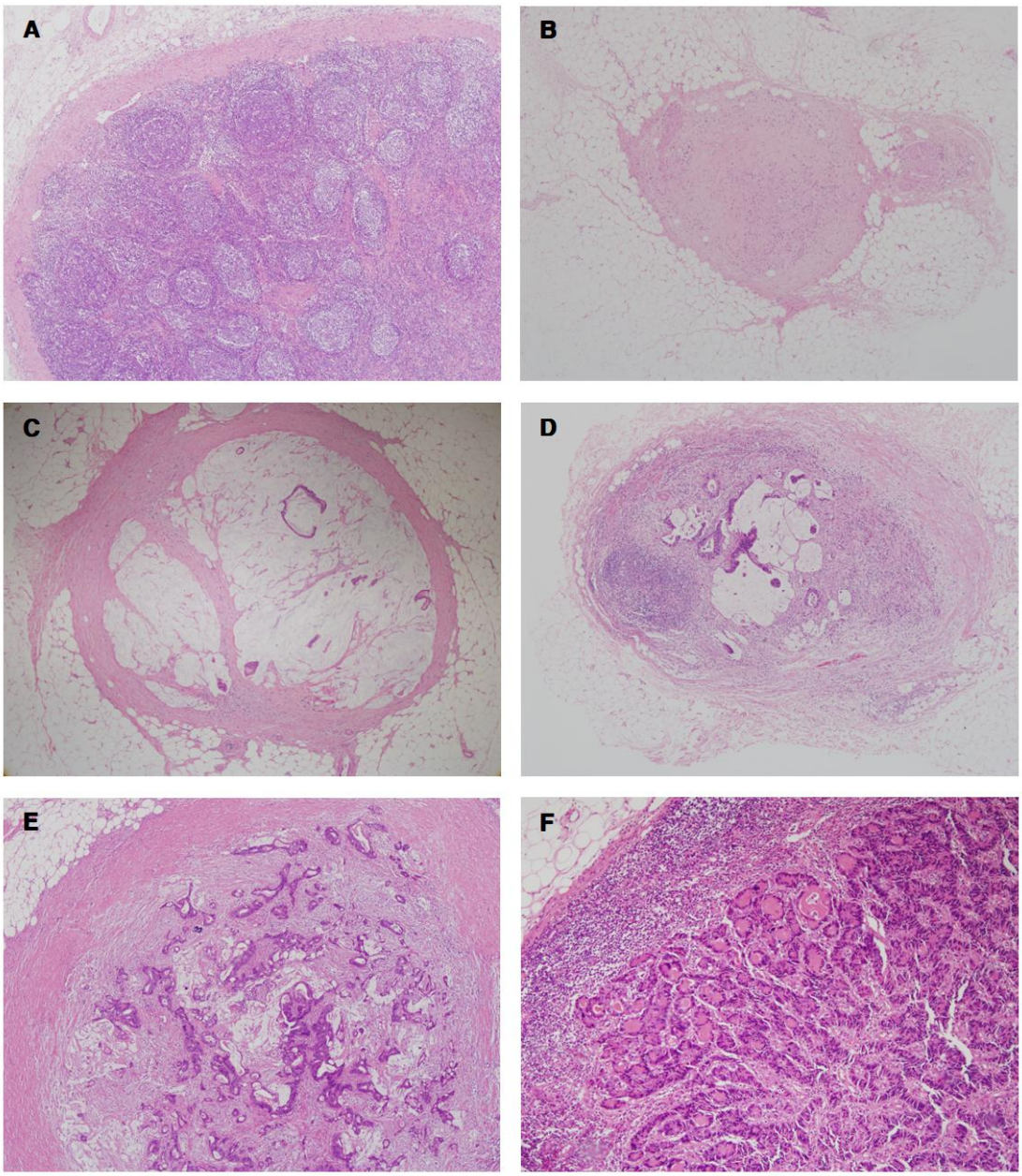
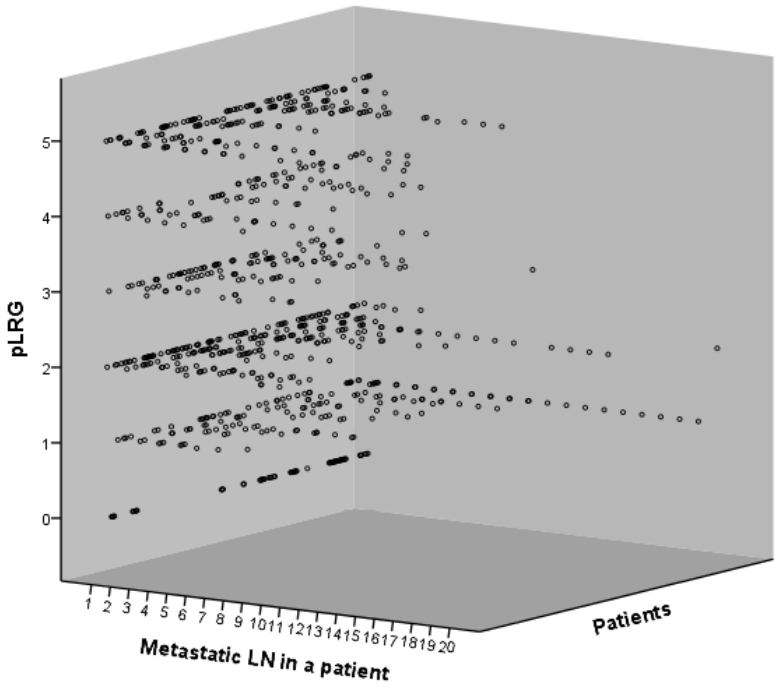


Fig 1. Lymph node regression grade. (A) pLRG0, LN with preserving normal nodal architecture without evidence of cancer cells or fibrosis (B) pLRG1; LN with 100% fibrosis (C) pLRG2, LN with <25% cancer cells (D) pLRG3, scattered glandular elements with fibrosis (E) pLRG4, LN with >50% cancer cells (F) pLRG5, complete replacement with cancer cells

(A)



(B)

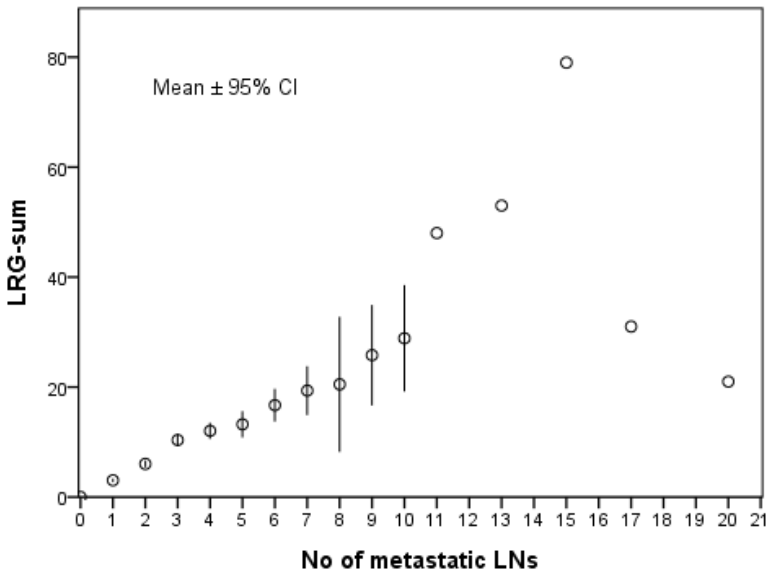
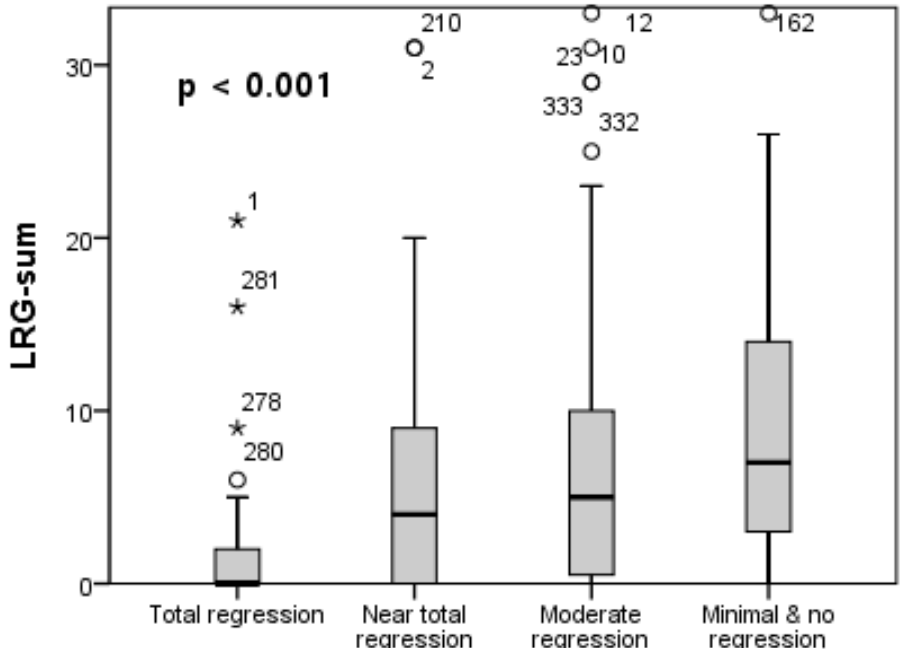


Fig 2. Distribution of lymph node regression grade (LRG). (A) Each metastatic lymph node showed various LRG in each patient. (B) LRG-sum also showed various distributions in the same number of metastatic LNs.

(A)



Total vs. other regression; p<0.01

Total vs. near total regression; p=0.088

Near total vs. moderate regression; p=0.643

Moderate vs. minimal/no regression: p=0.002

(B)

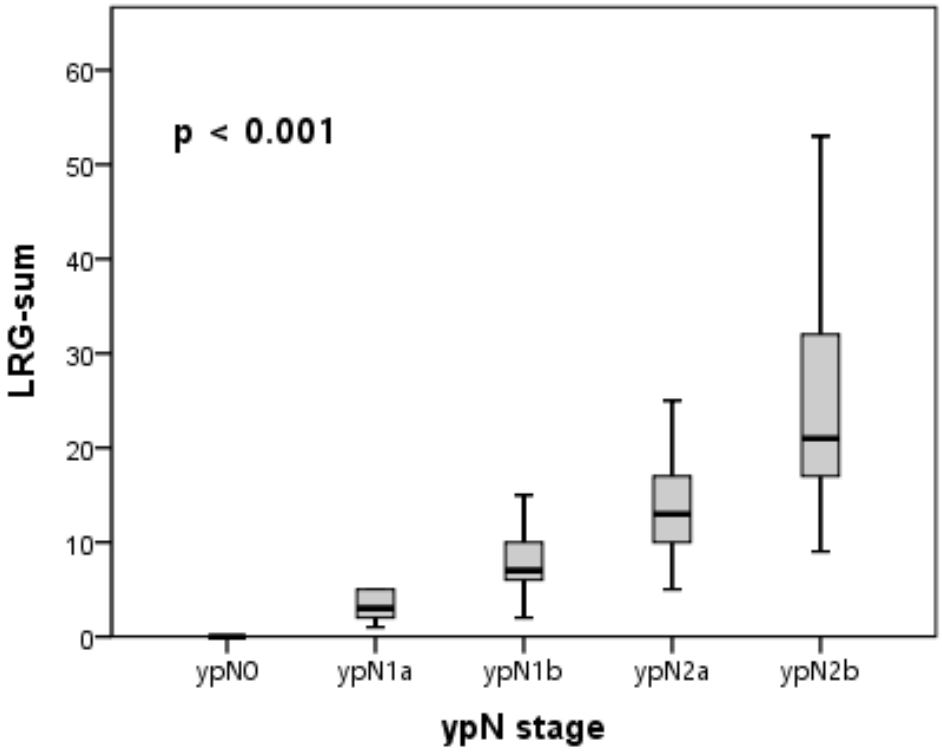
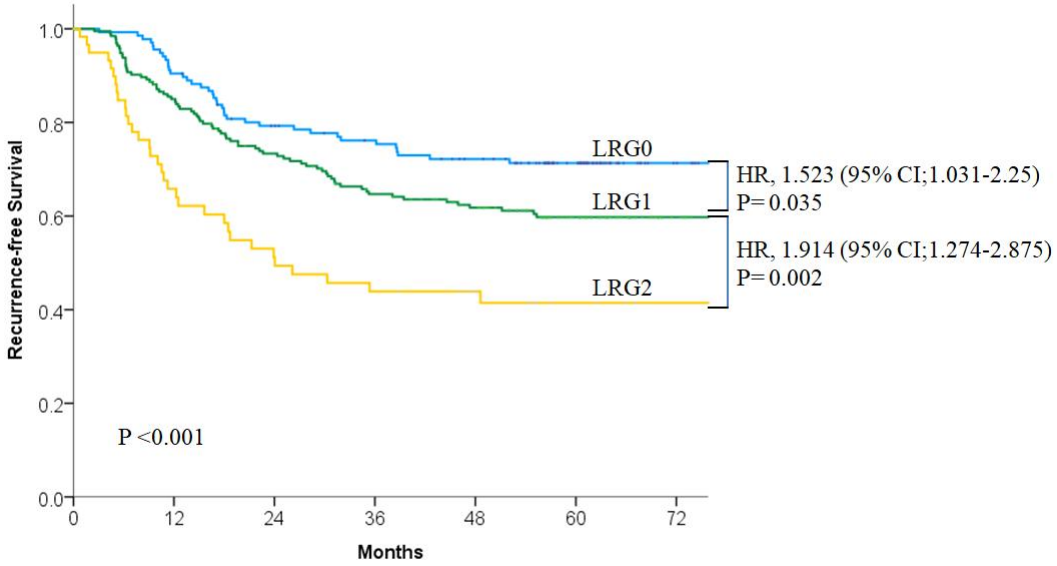
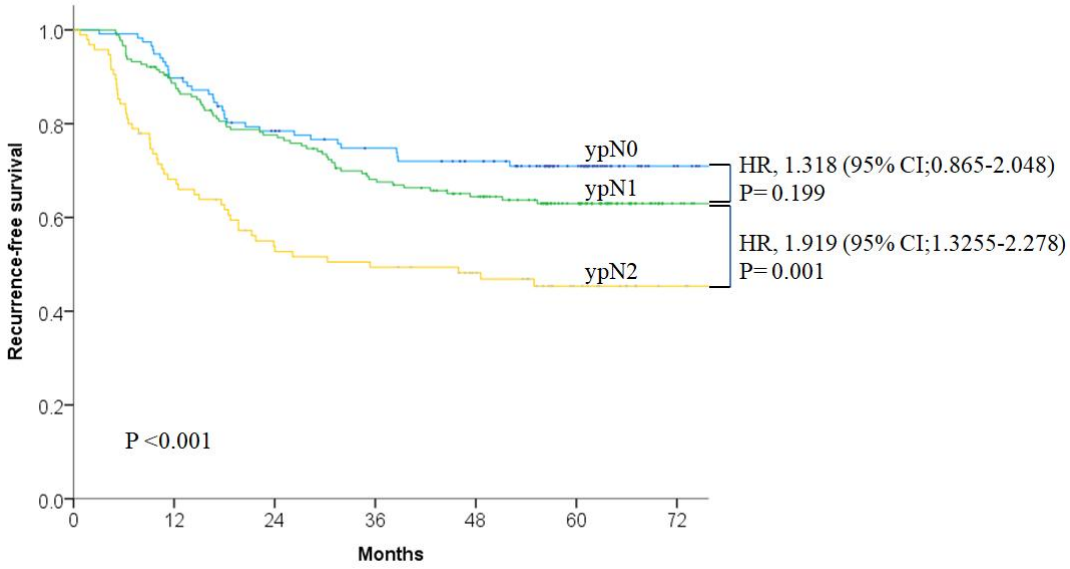


Fig 3. LRG-sum distribution according to (A) tumor regression grade (TRG), LRG-sum was correlated with TRG of primary tumor; LRG-sum of total regression was significantly different that of other regression group. (B) ypN stage. Linear correlation was observed between LRG-sum and ypN stage.

(A)


Recurrence-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Months
LRG0
LRG1
LRG2
HR, 1.523 (95% CI;1.031-2.25)
P= 0.035
HR, 1.914 (95% CI;1.274-2.875)
P= 0.002
P <0.001

(B)


Recurrence-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Months
ypN0
ypN1
ypN2
HR, 1.318 (95% CI;0.865-2.048)
P= 0.199
HR, 1.919 (95% CI;1.3255-2.278)
P= 0.001
P <0.001

(C)

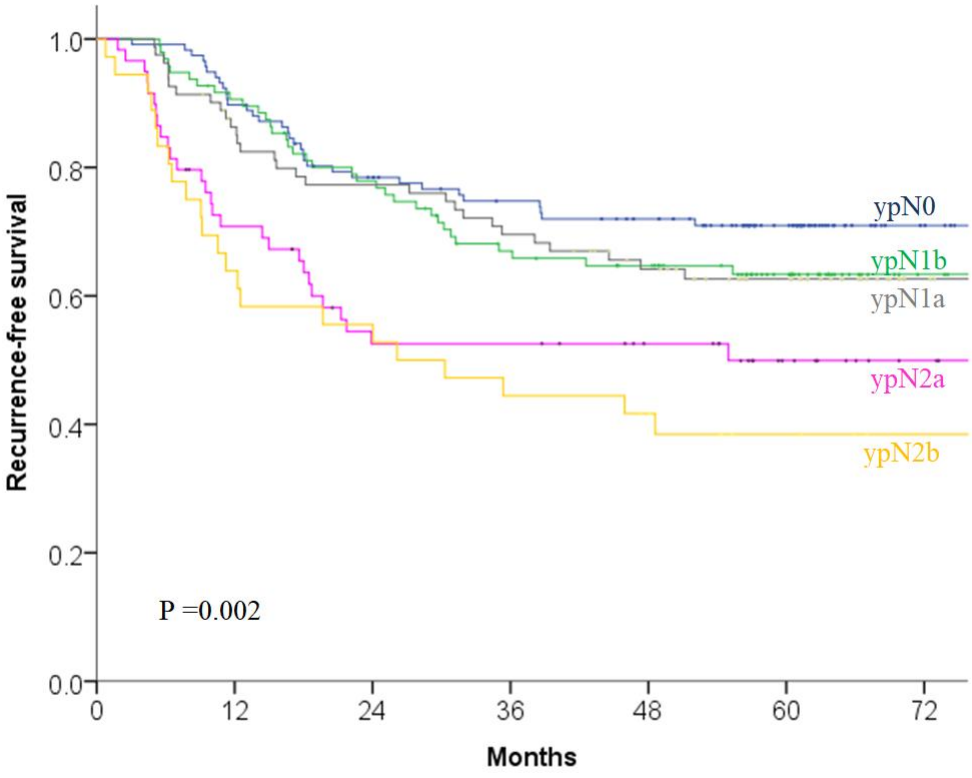
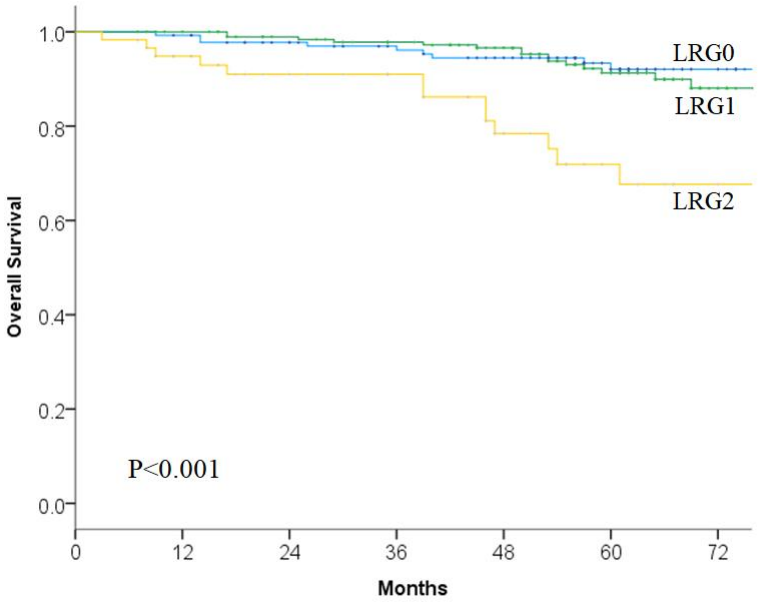


Fig 4. Recurrence-free Survival according to (A) LRG group and (B) ypN stage, and (C) ypN substage. LRG group reflects RFS most effectively. (A) The 5-year RFS for LRG0, LRG1, and LRG was 71%, 60%, and 41% each ($p<0.001$). (B) The 5-year RFS for ypN0, ypN1, and ypN2 was 71%, 63%, and 45% each ($p<0.001$). (C) The 5-year RFS for ypN0, ypN1a, ypN1b, ypN2a and ypN2b was 71%, 63%, 63%, 50%, and 39% each ($p=0.002$).

(A)



(B)

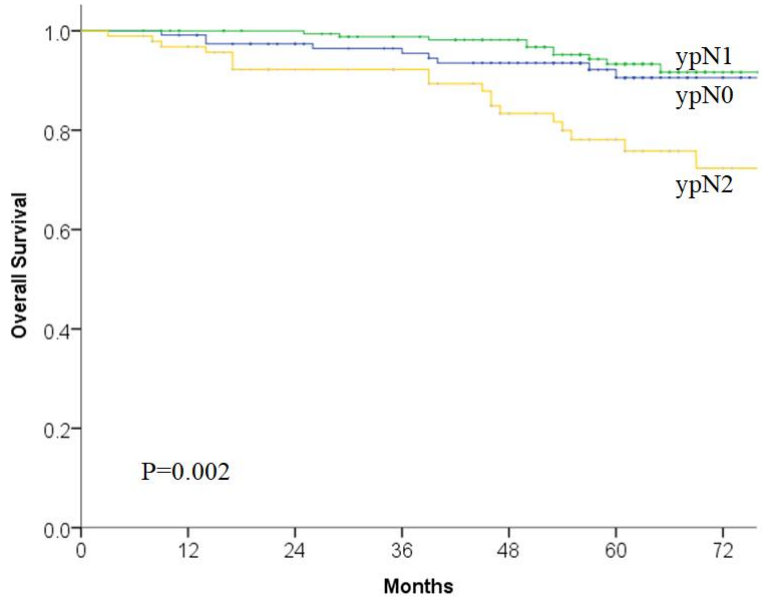


Fig 5. Overall Survival according to (A) LRG group and (B) ypN stage. Both of stage showed association with overall survival but, subgroup did not discriminate prognostic group in overall survival. (A) The 5-year OS for LRG0, LRG1, and LRG was 93%, 91%, and 72% months each ($p<0.001$). (B) The 5-year OS for ypN0, ypN1, and ypN2 was 92%, 93%, and 78% each ($p=0.002$).

Table 1. Clinicopathological characteristics of patients

Variable	Value
Age, years	57 (25-79)
Sex	
Male	254 (65.3%)
Female	135 (34.7%)
Median follow-up time, months	58 (3-108)
Tumor regression grade of primary tumor	
Total	50 (12.9%)
Near total	77 (19.8%)
Moderate	187 (48.1%)
Minimal & 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%)

LRG, lymph node regression grade; CRM, circumferential resection margin

Table 2. Comparison of the distribution according to LRG groups and ypN stage

		ypN stage			
		ypN0	**ypN1**	**ypN2**	**Total**
LRG group	**LRG1**	117	19	0	136
	LRG2	0	153	41	194
	LRG3	0	5	54	59
	Total	117	177	95	389

Table 3. Factors associated with recurrence-free survival in all patients

Variable	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
LRG-sum	1.04 (1.026-1.054)	<0.001	1.025 (1.008-1.042)	0.004
No of harvested LNs	0.999 (0.976-1.022)	0.912		
Lymph Node Ratio	8.265 (3.833-17.824)	<0.001		
ypN		0.001		
ypN0	1			
ypN1	1.305 (0.856-1.989)			
ypN2	2.516 (1.622-3.902)			
ypT		<0.001		0.035
ypT0-2	1		1	
ypT3-4	4.469 (2.19-9.118)		3.934 (1.101-14.052)	
TRG		0.001		0.891
Total regression	1		1	
Other regression	4.217 (1.862-9.550)		0.903 (0.21-3.881)	
CRM involvement	2.46 (1.415-4.274)	0.001	1.245 (0.659-2.352)	0.499
Lymphovascular invasion	2.263 (1.528-3.354)	<0.001	1.449 (0.923-2.277)	0.107
Perineural invasion	1.71 (1.188-2.463)	0.004	1.136 (0.768-1.680)	0.523

Gender			
Male	1		
Female	1.043 (0.744-1.463)	0.807	
Age	0.999 (0.983-1.015)	0.880	

CI, Confidence interval; TRG, tumor regression grade; CRM, circumferential resection margin

* multivariate analysis with metastatic lymph node related variable which are LRG-sum, lymph node ratio, ypN

Table 4. Factors associated with recurrence-free survival in patients with metastatic lymph nodes

Variable	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
LRG-sum	1.037 (1.021-1.052)	<0.001	1.027 (1.009-1.046)	0.003
Lymph Node Ratio	7.378 (3.023-18.006)	<0.001		
ypN		0.001		
ypN1	1			
ypN2	1.919 (1.325-2.778)			
ypT		0.014		0.190
ypT0-2	1		1	
ypT3-4	3.070 (1.252-7.53)		2.561 (1.195-10.462)	
TRG		0.031		0.896
Total regression	1		1	
Other regression	3.540 (1.124-11.151)		1.127 (0.195-6.858)	
CRM involvement	2.097 (1.15-3.822)	0.016	1.151(0.580-2.283)	0.688
Lymphovascular invasion	2.042 (1.343-3.105)	0.001	1.481 (0.92-2.386)	0.106
Perineural invasion	0.685 (0.458-1.024)	0.065		
Gender		0.692		
Male	1			

Female	1.080 (0.738-1.580)	
Age	0.997 (0.979-1.014)	0.691

CI, Confidence interval; TRG, tumor regression grade

* multivariate analysis with metastatic lymph node related variable which are LRG-sum, lymph node ratio, ypN

Table 5. Factors associated with overall survival in all patients

Variable	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
LRG_sum	1.059 (1.037-1.082)	<0.001	1.052 (1.022-1.082)	0.001
Lymph node ratio	23.066 (6.031-88.227)	<0.001		
ypN		<0.001		
ypN0	1			
ypN1	0.707 (0.287-1.739)	0.45		
ypN2	3.068 (1.385-6.799)	0.006		
ypT		0.046		0.152
ypT0-2	1		1	
ypT3-4	4.273 (1.028-17.756)		2.886 (0.677-12.304)	
TRG		0.075		
Total regression	1			
Other regression	6.066 (0.832-44.225)			
CRM involvement	3.685 (1.436-9.458)	0.007	1.703 (0.541-5.358)	0.362
Lymphovascular invasion	3.975 (2.029-7.788)	<0.001	2.562 (1.157-5.674)	0.020
Perineural invasion	2.676 (1.383-5.180)	0.003	1.376 (0.663-2.857)	0.373
Gender				

Male	1			
Female	1.132 (0.589-2.174)	0.71		
Age	1.035 (1-1.07)	0.047	1.068 (1.028-1.110)	0.001

CI, Confidence interval; TRG, tumor regression grade

* multivariate analysis with metastatic lymph node related variable which are LRG-sum, lymph node ratio, ypN

Discussion

In the present study, pathologic regression grade of metastatic LNs showed a correlation with TRG of primary tumor which is already used to assess the response to PCRT. Difference in LRG was the most significant between total regression and the other regression group of primary tumor. LRG was also confirmed as a significant associated factor with recurrence-free survival and overall survival.

Although the pathologic regression of primary tumor to PCRT and its clinical significance is under investigation, several studies have reported that TRG could be used to assess the response level following PCRT and predict the prognosis.[27, 38, 41, 42] However, only few studies analyzed the pathologic regression of lymph node following PCRT and its clinical significance as an important prognostic indicator.[30-32] In previous study, we only analyzed the patients who had diagnosed with ypN1 stage[30], and we extended the patient cohort to evaluate prognostic impact of LRG in overall patients.

In advanced rectal cancer patients treated with PCRT, it has been constantly questioned whether the primary tumor and metastatic LNs similarly respond to PCRT. Several studies have reported that metastatic LNs usually respond similar to the primary tumor.[38, 43] In contrast, other studies have indicated a difference in response between the primary lesion and the lymph nodes.[30, 39, 44-46] The present study showed that LRG had a correlation with TRG although it was not a stepwise correlation. Total regression and the other type of regression of primary tumor showed the most significant difference, however, total and near total regression, near total and moderate regression did not show significant difference in LRG. It may be one of the important key to decide treatment strategy following PCRT. The accuracy of the imaging modalities used to assess the metastatic LNs is limited as of now.[47, 48] Therefore we usually assess the primary tumor response after PCRT to decide surgical strategies. If we can expect the response of LNs to PCRT from TRG, it could support the local excision or “wait and watch” approach in treating clinically totally regressed tumor after PCRT.

Currently, the widely used staging system is solely based on the number of metastatic LNs. To complement this, the number of harvested LNs and lymph node ratio has been studied for identifying prognostic subgroups.[11, 12, 24] After PCRT, evaluation of nodal status using traditional staging system is more complicated, because radiation therapy has known to

influence on retrieved LNs. [20, 21] Although the current staging system recommends adequate number of harvested LNs of 12 or more[49, 50], the adequate number of harvested LNs for proper stating of rectal cancer after PCRT is not well established. Han J et al demonstrated that retrieval of LNs≥12 and LNs≥8 should be achieved to obtain accurate staging and optimal treatment for the non-pCRT and pCRT groups in rectal cancer, respectively[51]. Some authors even reported that retrieval of fewer than 12 lymph nodes in surgical specimen of rectal cancer who had received PCRT should be considered as a good indicator of tumor response with better local disease control, and a good prognostic factor, rather than as a pointer of poor diligence of the surgical and pathological assessment[52].

PCRT has also known to influence on the metastatic foci within each LN as well as the number of retrieved LNs. After PCRT, the metastatic foci within LN would be changed or even resolved. It has been constantly questioned whether we consider the resolved metastatic LNs as a metastatic lymph node. Likewise, we wonder that the lymph node with only 10% cancer cells following PCRT and the lymph node that fully comprises cancer cells have the same prognostic significance. Tumor regression in mesorectal LNs after PCRT for rectal cancer was first reported by Caricato et al[53]. They evaluated the LN regression grade using TRG system of Mandard, which is based on the ratio of residual tumor to fibrosis. Complete pathologic response was observed in 51% of the patients and no regression was observed in 11%. Their study, however, was limited by a small sample size (n=35) and didn't evaluate the prognostic value of LRG. The oncologic impact of the pathologic lymph node regression grade was first reported by N. Mirbagheri et al[31]. They also examined lymph node status after PCRT using a scoring system, and reported that LRG score was a significant predictor of tumor recurrence and 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 implication. In overall patients as well as patients with metastatic LNs, LRG was confirmed as good predictor of prognosis. It means that the responsiveness of LNs after PCRT needs to be considered for staging for prognostication.

The response level of each LN to PCRT can be variable even in a single resection specimen. We identified that pLRG score of each LN showed various distribution in the same patient. So the final LRG score should be assigned to represent the various responses of metastatic LNs in one patient. Some authors used the worst LRG score in each specimen and the sum of the LRG score from each LN.[31, 32] 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 lymph node and LRG-sum is the sum of LRG score of each lymph node. In this study, LRG-sum was chosen because it is the method that takes the number of metastatic LNs into account. LRG-sum was linearly correlated with ypN stage and confirmed as good prognostic indicator in our data. Therefore, LRG-sum would be used as an appropriate indicator to consider the regression level and the number of metastatic LNs together.

Whether the lymph node with totally resolved metastatic foci was considered as metastatic lymph node is not clearly defined. In the present study, 20 patients had 1 metastatic lymph node with pLRG1. These patients would be differed in their ypN stage under current TNM staging system, but, LRG group was not changed. Therefore, the LRG group was more stable categorization method of metastatic LNs.

Many authors reported the importance of lymph node ratio in patients with metastatic LNs even after PCRT.[25, 54, 55] In 2011, Klos et al was the first to study the prognostic value of LNR after PCRT, which demonstrated LNR could provide a better independent staging method than absolute positive LN counts when less than 12 LNs are harvested after PCRT.[55] Park IJ et al reported that LNR was a more important prognostic factor for RFS in patients with lymph node metastasis after PCRT than those who did not undergo PCRT.[25] In our present study, the Lymph node ratio was a significant associated factor with RFS in univariate analysis, but it was not confirmed as associated risk factor in multivariate analysis in both overall patients and patients with metastatic LNs. LRG is the most potent associated factors which are related with metastatic lymph nodes for RFS.

We found that LRG-sum grading system using percentile value was more effective prognostic indicator than currently used ypN stage for RFS. Even in patients with 1 metastatic lymph node, 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, cut-off values of LRG-sum discriminating prognostic subgroups effectively have to be determined with further studies in larger cohort.

This study has several limitations. Since it was retrospective study, it may cause selection bias. Also, the heterogeneity of the surgical techniques and pathologic preparation and evaluation of LNs may have affected the oncologic outcomes. However, a highly trained pathologist repeatedly reviewed the specimen in order to overcome this limitation in our

present study. It could be questionable how to score the lymph nodes out of the radiation fields (such as inferior mesenteric lymph node). In the present study, there were no metastatic LNs out of the radiation fields. In addition, the determination of prognostic subgroup using LRG has to be validated in extended cohort. .

Conclusion

LRG was an important prognostic factor of oncologic outcomes in patients with rectal cancer treated with PCRT followed by radical resection. We confirmed previous results through investigation of a larger patient cohort including all kinds of metastatic lymph node status. Before we apply LRG on clinical setting such as selection of poor prognostic patients for more intensive adjuvant treatment or tailored surveillance schedule according to risk group, we need to more extensively validate.

References

1. American Joint Committee on Cancer: “AJCC Cancer Staging Manual.“Springer International Publishing, 2017;
2. Sobin LH, Gospodarowicz MK, Wittekind C (eds) (2009) TNM classification of malignant tumours 7th edn. Wiley-Blackwell, Oxford]
3. Shi Q1, Andre T, Grothey A, et al. Comparison of outcomes after fluorouracil-based adjuvant therapy for stages II and III colon cancer between 1978 to 1995 and 1996 to 2007: evidence of stage migration from the ACCENT database. J Clin Oncol 2013; 31(29):3656-63.;
4. Chen L, Kalady MF, Goldblum J et al. Does reevaluation of colorectal cancers with inadequate nodal yield lead to stage migration or the identification of metastatic lymph nodes? Dis Colon Rectum 2014;57(4):432-7.;
5. Huh JW, Kim YJ, Kim HR. Distribution of lymph node metastases is an independent predictor of survival for sigmoid colon and rectal cancer. Ann Surg2012;255(1):70-78
6. Sarli L, Bader G, Iusco D et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005;41:272–279
7. Betge J, Harbaum L, Pollheimer MJ et al. Lymph node retrieval in colorectal cancer: determining factors and prognostic significance. Int J Colorectal Dis 2017;32(7):991-998
8. Peeples C, Shellnut J,Wasvary H et al. Predictive factors affecting survival in stage II colorectal cancer: is lymph node harvesting relevant? Dis Colon Rectum 2010;53(11): 1517-23
9. Le Voyer TE, Sigurdson ER, Hanlon AL et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21(15):2912-9.
10. Swanson RS, Compton CC, Stewart AK et al. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10(1):65-71.
11. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, Grebner A, Ulm K, Höfler H, Nekarda H, Siewert JR. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. Ann Surg 2008; 248: 968-978
12. Peschaud F, Benoist S, Julié C, Beauchet A, Penna C, Rougier P, Nordlinger B. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in

rectal cancer. Ann Surg 2008; 248: 1067-1073

13. R Sauer, H Becker, W Hohenberger , etal : Preoperative versus postoperative chemo-radiotherapy for rectal cancer N Engl J Med 2004;351:1731–1740
14. Rodel, R Hofheinz, T Liersch : Rectal cancer: State of the art in 2012 Curr Opin Oncol 2012;24:441– 447,2012
15. Chang GJ, Rodriguez-Bigas MA, Eng C et al. Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. Cancer 2009;115 (23):5432
16. Klos CL, Shellito PC, Rattner DW et al. The effect of neoadjuvant chemoradiation therapy on the prognostic value of lymph nodes after rectal cancer surgery. Am J Surg 2010;200(4):440
17. IJ Park, YN You, A Agarwal , et al : Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 2012;30:1770-1776
18. Yeo SG, Kim DY, Kim TH et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg 2010;252(6):998
19. Gollins S, Sun Myint A, Haylock B et al. Preoperative chemoradiotherapy using concurent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes. J Clin Oncol 2011;29:1042-1049
20. Le M, Nelson R, Lee W, et al. Evaluation of lymphadenectomy in patients receiving neoadjuvant radiotherapy for rectal adenocarcinoma. Ann Surg Oncol. 2012;19:3713–8
21. Ha YH, Jeong SY, Lim SB, Choi HS, Hong YS, Chang HJ, et al. Influence of preoperative chemoradiotherapy on the number of lymph nodes retrieved in rectal cancer. Ann Surg 2010;252(2): 336e40
22. Koo T, Song C, Kim JS et al. Impact of Lymph Node Ratio on Oncologic Outcomes in ypStage III Rectal Cancer Patients Treated with Neoadjuvant Chemoradiotherapy followed by Total Mesorectal Excision, and Postoperative Adjuvant Chemotherapy. PLoS One 2015;10(9)
23. Lee SD, Kim TH, Kim DY et al. Lymph node ratio is an independent prognostic factor in patients with rectal cancer treated with preoperative chemoradiotherapy and curative

resection. Eur J Surg Oncol 2012;38(6):478-83

24. Kim YS, Kim JH, Yoon SM, Choi EK, Ahn SD, Lee SW, Kim JC, Yu CS, Kim HC, Kim TW, Chang HM. lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009; 74: 796-802
25. Park IJ, Yu CS, Lim SB, et al. Ratio of metastatic lymph nodes is more important for rectal cancer patients treated with preoperative chemoradiotherapy. World J Gastroenterol. 2015;21:3274–3281;
26. Trakarnsanga A, Gönen M, Shia J, et al. Comparison of tumor regression grade systems for locally advanced rectal cancer after multimodality treatment. J Natl Cancer Inst 2014 Sep 22;106(10).
27. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 2014 May 20;32(15):1554-62;
28. Kim JY, Park IJ, Hong SM, et al. Is Pathologic Near-Total Regression an Appropriate Indicator of a Good Response to Preoperative Chemoradiotherapy Based on Oncologic Outcome of Disease? Medicine (Baltimore). 2015 Dec;94(50):e2257
29. Rödel C, Martus P, Papadoupolos T et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23(34):8688-96
30. Choi JP, Kim SJ, Park IJ, et al. Is the pathological regression level of metastatic lymph nodes associated with oncologic outcomes following preoperative chemoradiotherapy in rectal cancer? Oncotarget 2017; Feb 7;8(6):10375-10384
31. Mirbagheri N, Kumar B, Deb S, et al. Lymph node status as a prognostic indicator after preoperative neoadjuvant chemoradiotherapy of rectal cancer. Colorectal Dis 2014;16:0339-0336
32. Li J, Yuan J, Liu H, Yin J, Liu S, Du F, Hu J, Li C, Niu X, Lv B, Xing S. Lymph nodes regression grade is a predictive marker for rectal cancer after neoadjuvant therapy and radical surgery. Oncotarget. 2016;7:16975–84
33. Habr-Gama A, Perez RO, Nadalin W et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240(4):711

34. Borschitz T, Wachtlin D, Möhler M et al. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol 2008;15(3):712
35. Kim CJ, Yeatman TJ, Coppola D et al. Local excision of T2 and T3 rectal cancers after downstaging chemoradiation. Ann Surg 2001;234(3):352
36. Radovanovic Z, Breberina M, Petrovic T et al. Accuracy of endorectal ultrasonography in staging locally advanced rectal cancer after preoperative chemoradiation. Surg Endosc. 2008; 22:2412-2415
37. Bipat S, Glas AS, Slors FJ et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology. 2004; 232:773-783
38. Park IJ, You YN, Skibber JM et al. Comparative analysis of lymph node metastases in patients with ypT0-2 rectal cancers after neoadjuvant chemoradiotherapy. Dis Colon Rectum. 2013; 56:135-141.
39. Hiotis SP, Weber SM, Cohen AM et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg. 2002;194:131-135; discussion 135-136.
40. Chang HJ, Park CK, Kim WH, et al. A standardized pathology report for colorectal cancer. Korean J Pathol 2006; 40:193–203
41. Rodel C, Martus P, Papadoupolos T et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688–8696,
42. LJ Kuo, MC Liu, JJ Jian et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? Ann Surg Oncol 2007; 14:2766– 2772
43. Gollins S, Sun Myint A, Haylock B et al. Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes. J Clin Oncol. 2011; 29:1042-1049.
44. Tytherleigh MG, Ng VV, Pittathankal AA et al. Preoperative staging of rectal cancer by magnetic resonance imaging remains an imprecise tool. ANZ J Surg 2008; 78:194-198
45. Mignanelli ED, de Campos-Lobato LF, Stocchi L et al. Downstaging after chemo-radiotherapy for locally advanced rectal cancer: is there more (tumor) than meets the eye? Dis Colon Rectum. 2010; 53:251-256.

46. Berho M, Oviedo M, Stone E et al. The correlation between tumour regression grade and lymph node status after chemoradiation in rectal cancer. Colorectal Dis. 2009; 11:254-258.
47. Radovanovic Z, Breberina M, Petrovic T et al. Accuracy of endorectal ultrasonography in staging locally advanced rectal cancer after preoperative chemoradiation. Surg Endosc. 2008; 22:2412-2415.
48. Bipat S, Glas AS, Slors FJ et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology. 2004; 232:773-783.
49. Compton CC, Fielding LP, Burgart LJ et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979–994.
50. Sobin LH, Greene FL. TNM classification: clarification of number of regional lymph nodes for pNo. Cancer 2001;92:452.
51. Han J, Noh GT, Yeo SA et al. The number of retrieved lymph nodes needed for accurate staging differs based on the presence of preoperative chemoradiation for rectal cancer. Medicine (Baltimore) 2016;95(38):e4891
52. Gurawalia J, Dev K, Nayak SP et al. Less than 12 lymph nodes in the surgical specimen after neoadjuvant chemo-radiotherapy: an indicator of tumor regression in locally advanced rectal cancer? J Gastrointest Oncol 2016;7(6):946-957
53. Caricato M, De Dominicis E, Vincenzi B et al. Tumor regression in mesorectal lymphnodes after neoadjuvant chemoradiation for rectal cancer. Eur J Surg Oncol 2007; 33: 724–8.
54. Zuo ZG, Zhang XF, Wang H, et al. Prognostic Value of Lymph Node Ratio in Locally Advanced Rectal Cancer Patients After Preoperative Chemoradiotherapy Followed by Total Mesorectal Excision. Medicine 2016;95:9;
55. Klos CL, Bordeianou LG, Sylla P, et al. The prognostic value of lymph node ratio after neoadjuvant chemoradiation and rectal cancer surgery. Dis Colon Rectum. 2011;54:171–175

수술 전 항암방사선 치료 후 절제를 시행 받은 직장암 환자에서 병리학적 림프절 반응 정도가 예후에 미치는 영향

연구목적: 수술 전 항암 방사선 치료를 받은 직장암 환자에서 병리학적 림프절 반응 정도는 현재 병기 결정 시스템에서 고려되고 있지 않다. 본 연구는 수술 전 항암방사선 치료 후 근치적 절제를 시행했던 직장암 환자에서 림프절의 반응 정도가 예후에 미치는 영향을 평가하고자 하였다.

연구방법: 2008 년부터 2011 년까지 수술 전 항암방사선 치료 후 근치적 절제를 시행했던 직장암 환자 389 명을 대상으로 하였다. 병리학적 림프절 반응 정도를 평가한 점수(pLRG)는 종양세포와 섬유조직의 비율에 따라 결정되었다. (pLRG0: 종양세포나 섬유조직 없이 정상 구조를 갖추고 있는 림프절, pLRG1: 섬유조직이 100%, pLRG2: 종양세포가 25%미만, pLRG3: 종양세포가 25-50%, pLRG4: 종양세포가 50%이상, pLRG5: 림프절 전체가 종양 세포로 대체) 각 림프절에서 평가된 pLRG 값의 합을 최종적인 LRG 값으로 정하고 이를 LRG-sum 이라고 하였다.

연구결과: LRG-sum 은 원발종양의 반응 정도와도 유의한 상관관계가 있었다 ($p<0.001$). 백분위를 이용하여 LRG-sum 의 절사값을 구하고 이를 이용하여 환자군을 3 개의 군으로 분류하였다 (LRG1: $0 \leq$ LRG-sum ≤ 1, LRG2: $1<$LRG-sum<15, LRG3: LRG-sum ≥ 15). 재발까지의 무병생존율 및 전체생존율은 LRG 예후군에 따라 유의한 차이를 보였다. 다변량 분석에서 LRG-sum 은 ypT 병기와 함께 재발까지의 무병생존율에 유의한 영향을 주는 인자로 나타났다. LRG-sum 은 전체생존율에서도 영향을 주는 유일한 인자로 나타났다. **결론**: LRG 는 수술 전 항암방사선 치료 후 근치적 절제를 시행했던 직장암 환자에서 종양학적 결과에 중요한 영향을 미치는 예후 인자로 나타났다.

중심단어: 직장암, 수술 전 항암방사선 치료, 병리학적 림프절 반응 정도, 예후 인자