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Prognostic value of metastatic lymph node regression grade after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer

Tetsuro Tominaga, MD, PhD[a], Takashi Akiyoshi, MD, PhD[a,*], Noriko Yamamoto, MD, PhD[b], Koji Oba, MD[c], Toshiya Nagasaki, MD, PhD[a], Tomohiro Yamaguchi, MD, PhD[a], Tsuyoshi Konishi, MD, PhD[a], Yosuke Fukunaga, MD, PhD[a], Masashi Ueno, MD, PhD[a]

[a] Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[b] Division of Pathology, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan
[c] Department of Biostatistics, Graduate School of Medicine, The University of Tokyo, Japan

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ABSTRACT

Background: The prognostic value of classifying the degree of metastatic lymph node regression grade after neoadjuvant chemoradiotherapy remains unclear. The aim was to assess the prognostic value of lymph node regression grade in patients with rectal cancer treated with chemoradiotherapy.
Methods: We reviewed a total of 421 patients with rectal cancer who underwent neoadjuvant long-course chemoradiotherapy. All lymph nodes were examined retrospectively for evidence of response to chemoradiotherapy, and lymph node regression grade was scored as lymph node regression grade 0 (normal lymph node), lymph node regression grade 1 (100% fibrosis), lymph node regression grade 2 (< 25% cancer cells), lymph node regression grade 3 (25%–50% cancer cells), lymph node regression grade 4 (50%–75% cancer cells), and lymph node regression grade 5 (> 75% cancer cells). The prognostic importance of lymph node regression grade was evaluated.
Results: Among 301 ypN0 patients, 27 patients were scored as lymph node regression grade 1. The 5-year recurrence-free survival and local recurrence rates in lymph node regression grade 1 patients were similar to those in lymph node regression grade 0 patients (96.3% versus 88.1% in recurrence-free survival and 0% versus 2.7% in local recurrence); however, among 120 ypN+ (lymph node regression grade 2-5) patients, the 5-year recurrence-free survival and local recurrence rates were poor regardless of the lymph node regression grade score (38.1%–61.1% in recurrence-free survival and 8.4%–14.0% in local recurrence). In the multivariate analysis, an intensified regimen using systemic chemotherapy was independently associated with more lymph node regression grade 1 ($P < .001$; odds ratio, 6.06; 95% confidence interval, 2.33–16.20) among patients with lymph node regressions grade 1 through 5. Furthermore, in the multivariate analysis, ypT3-4 (hazard ratio, 7.82; 95% confidence interval, 2.80–27.32; $P < .001$), lymph node regression grade 1 (hazard ratio, 0.048; 95% confidence interval, 0.002–0.27; $P < .001$), the number of retrieved lymph nodes < 12 (hazard ratio, 5.48; 95% confidence interval, 1.48–16.38; $P = .014$), and no perioperative chemotherapy (hazard ratio, 3.01; 95% confidence interval, 1.53–5.68; $P = .002$) were independent predictors of recurrence-free survival.
Conclusion: Complete lymph node regression after chemoradiotherapy is a strong prognostic factor in rectal cancer.

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Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has become a standard treatment for locally advanced rectal cancer.[1] CRT decreases the size of both the main tumor and the surrounding metastatic lymph nodes, which results in preoperative downstaging, an improved rate of positive

* Reprint requests: Takashi Akiyoshi, MD, PhD, Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan.
E-mail address: takashi.akiyoshi@jfcr.or.jp (T. Akiyoshi).

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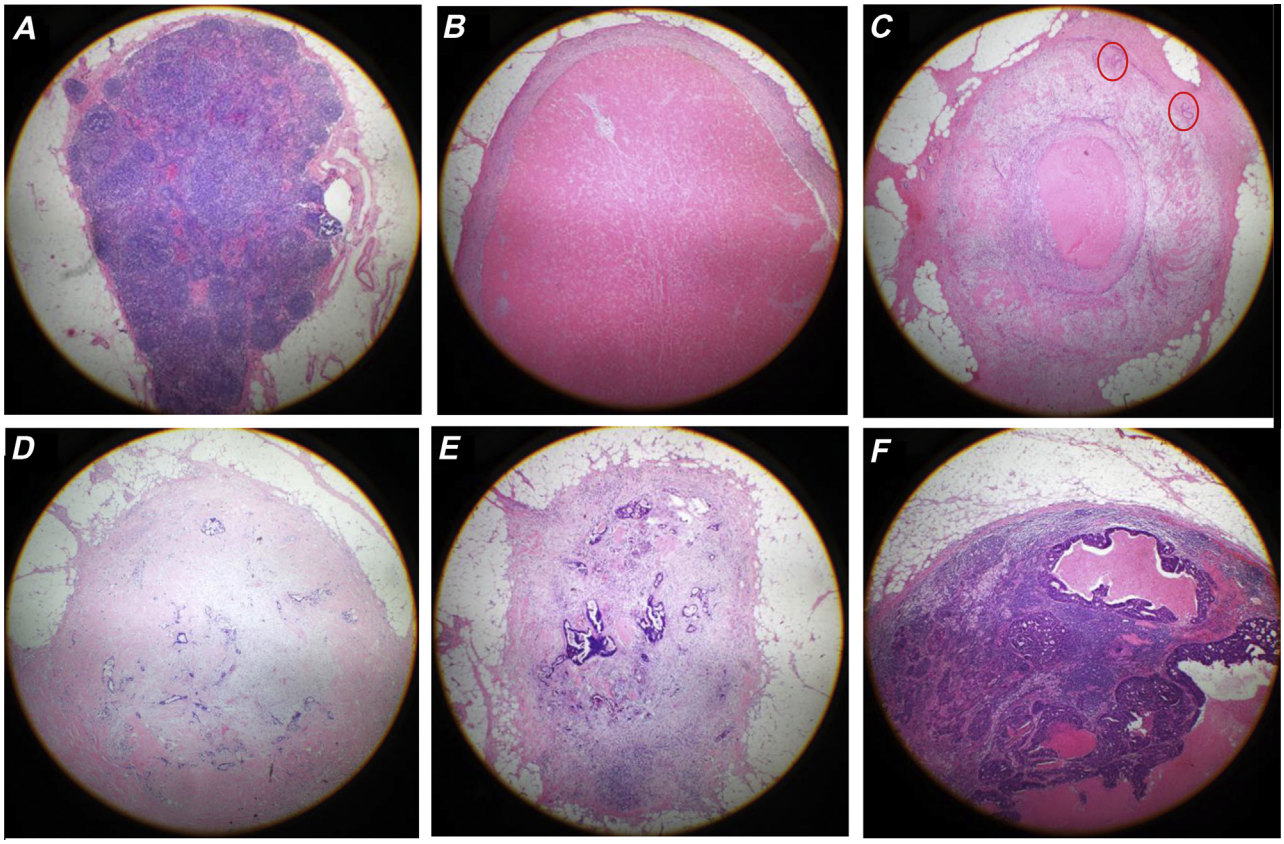

Fig 1. Histologic images of hematoxylin and eosin–stained lymph nodes representing lymph node regression (LRG) scores. (*A*) LRG0, normal lymph node. (*B*) LRG1, no residual cancer cells with fibrosis. (*C*) LRG2, viable tumor cells composed of <25% of the total tumor bed area. Viable cancer cells (*red circles*). (*D*) LRG3, viable tumor cells composed of 25% to 50% of the total tumor bed area. (*E*) LRG4, viable tumor cells composed of 50% to 75% of the total tumor bed area. (*F*) LRG5, viable tumor cells composed of >75% of the total tumor bed area.

circumferential resection margin, and a decrease in the rate of local recurrence.[2,3] Although adjuvant chemotherapy after preoperative CRT and TME is frequently recommended, the concept of total neoadjuvant therapy in which chemotherapy and CRT are administered before surgery is gaining traction. Total neoadjuvant therapy has been associated with an improved delivery of systemic chemotherapy and increased response to treatment[4,5]; however, it is not yet determined whether total neoadjuvant therapy improves the long-term outcomes compared with CRT with adjuvant chemotherapy.

Tumor regression grade (TRG) after CRT, determined based on the degree of fibrosis in proportion to the number of residual cancer cells, reflects therapeutic response and is associated with long-term outcomes in patients with rectal cancer.[6–9] The degree of regional lymph node regression after CRT, however, is not incorporated into

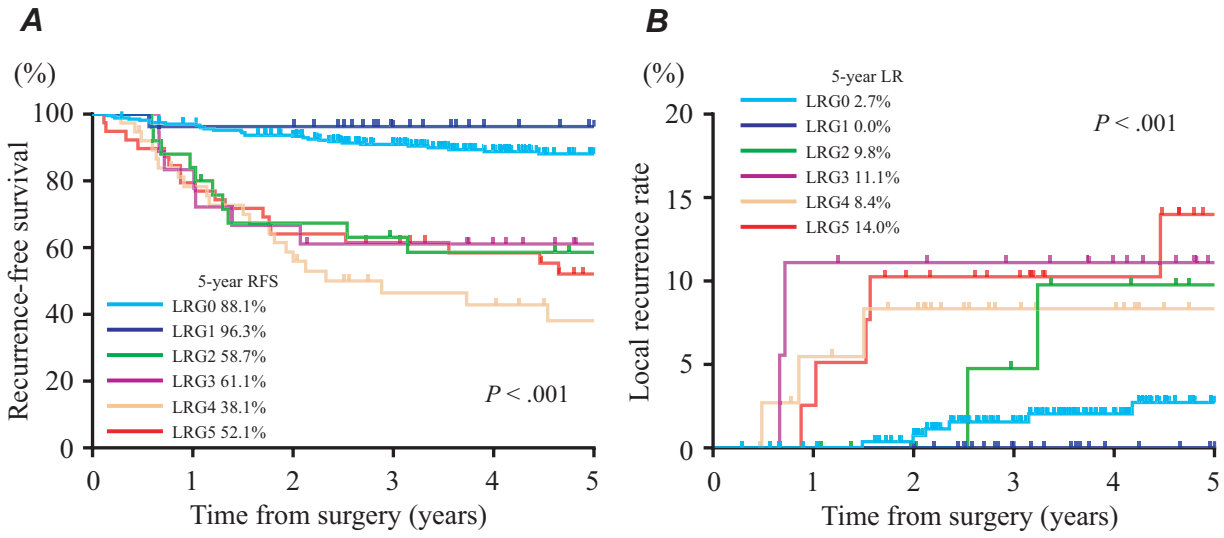

Fig 2. Kaplan-Meier analysis of (*A*) recurrence-free survival and (*B*) local recurrence rate according to the lymph node regression grade (LRG).

Table I
Patient characteristics according to the status of LRG

	LRG0 ($n = 274$)	LRG1 ($n = 27$)	LRG2–5 ($n = 120$)	LRG0 versus LRG1 *P*	LRG1 versus LRG2–5 *P*
Sex				.274	.826
Male	193 (70.4%)	16 (59%)	76 (63.3%)		
Female	81 (29.6%)	11 (41%)	44 (36.7%)		
Age (y) (range)	60 (28–78)	55 (30–68)	61 (27–81)	.007	.007
Distance of tumor from the AV (mm) (range)	40 (0–100)	40 (12–70)	40 (1.5–80)	.784	.874
Pretreatment CEA > 5.0 (ng/mL)	99 (36.1%)	8 (30%)	49 (40.8%)	.674	.382
Operative procedure				.826	.499
Sphincter preserving	191 (69.7%)	20 (74%)	78 (65.0%)		
Sphincter non-preserving	83 (31.8%)	7 (26%)	42 (35.0%)		
Clinical T				.770	.327
T2	4 (1.5%)	0	0 (0%)		
T3	227 (82.9%)	22 (82%)	107 (89.2%)		
T4	43 (15.7%)	5 (19%)	13 (10.8%)		
Clinical stage				.139	.263
I	2 (0.7%)	0	0 (0%)		
II	123 (44.9%)	7 (26%)	19 (15.8%)		
III	149 (54.4%)	20 (74.%)	101 (84.2%)		
Neoadjuvant chemotherapy	52 (19.0%)	14 (52%)	16 (13.3%)	< .001	< .001
ypT				.692	< .001
ypT0	72 (26.3%)	7 (26%)	5 (4.2%)		
ypT1	14 (5.1%)	3 (11%)	7 (5.8%)		
ypT2	92 (33.6%)	9 (33%)	19 (15.8%)		
ypT3	90 (32.8%)	8 (30%)	83 (69.2%)		
ypT4	6 (2.2%)	0	6 (5.0%)		
TRG				.695	< .001
TRG1	80 (29.2%)	5 (19%)	70 (58.3%)		
TRG2	96 (35.0%)	11 (41%)	40 (33.3%)		
TRG3	30 (11.0%)	3 (11%)	5 (4.2%)		
TRG4	68 (24.8%)	8 (30%)	5 (4.2%)		
Tumor differentiation				.669	1
Well/moderate	258 (94.2%)	25 (93%)	112 (93.3%)		
Mucinous/poor	16 (5.8%)	2 (7%)	8 (6.7%)		
Number of retrieved lymph nodes	17 (6–71)	17 (9–31)	18 (9–47)	.738	.300
Lymphovascular invasion				.090	< .001
Negative	177 (64.6%)	22 (82%)	26 (21.7%)		
Positive	97 (35.4%)	5 (19%)	94 (78.3%)		
Adjuvant chemotherapy	90 (32.9%)	17 (63%)	97 (80.8%)	.003	.071

Data are *n* (%) or medians (range).
AV, anal verge; *CEA*, carcinoembryonic antigen.

the current TRG grading system, and its clinical importance has been only evaluated superficially. Furthermore, there are no reports evaluating the impact of neoadjuvant chemotherapy on lymph node regression grade (LRG). The aim of this study was to examine the prognostic value of metastatic lymph node regression after CRT with or without neoadjuvant chemotherapy in patients with locally advanced rectal cancer.

Materials and Methods

Patients

We reviewed our experience with consecutive patients with clinical stage II/III, low rectal cancer who underwent curative resection after preoperative, long-course CRT between July 2004 and December 2015 at our hospital. A total of 39 patients who underwent short-course radiotherapy during the same period were excluded from this study. In our institution, the indication criteria for CRT were locally advanced low rectal cancer, T3/T4 stage or node-positive disease, and no evidence of distant metastasis. Low rectal cancer is diagnosed when the distal margin of the main tumor is below the peritoneal reflection. CRT consisted of oral 5-fluorouracil and radiotherapy with a total dose of 45 to 50.4 Gy. Beginning in 2013, selected patients with magnetic resonance imaging (MRI)–defined, high-risk features, including a circumferential resection margin (CRM) $\leq$ 1 mm, cT4, positive lateral nodes, mesorectal N2 disease, or requiring abdominoperineal resection, as decided during multidisciplinary team meetings, were treated with induction or consolidation systemic chemotherapy (primarily 6 courses of mFOLFOX6 with bevacizumab).[10] Only 2 patients underwent consolidation chemotherapy, and 80 patients underwent induction chemotherapy. TME was performed 6 to 10 weeks after the completion of long-course CRT. The following patient clinical data were collected: sex, age at operation, distance of the tumor from the anal verge, pretreatment serum carcinoembryonic antigen (CEA) levels, clinical T category, and clinical stage. Operative and pathologic data included the number of retrieved lymph nodes, operative procedure, pathologic T category, pathologic N status, TRG, tumor differentiation, lymphovascular invasion status, and treatment with or without adjuvant chemotherapy. Pathologic staging and classification were determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) criteria. This retrospective study was approved by the Clinical Research Review Board of the Cancer Institute Hospital (approval number 2017-1067).

Pathologic evaluation

Specimens, including the primary tumor and retrieved lymph nodes, were fixed in 10% buffered formalin for 24 h. The samples were embedded in paraffin and then cut and stained with

Table II
Multivariate analysis of pretreatment and treatment factors associated with LRG1 among patients with LRG1–5

	Odds ratio (CI)	*P*
Age	0.967 (0.929–1.006)	.098
Clinical stage II	2.085 (0.675–6.114)	.195
Neoadjuvant chemotherapy	6.061 (2.332–16.20)	< .001

hematoxylin and eosin (HE). Primary tumor regression after CRT was assessed according to Dworak's criteria[8]: TRG 1, dominant tumor mass with obvious fibrosis or vasculopathy; TRG 2, dominant fibrotic changes with few tumor cells or groups; TRG 3, very few tumor cells in the fibrotic tissue with or without mucus substance; and TRG 4, no viable tumor cells, only fibrotic cells. TRG3–4 were grouped as good responders.[11] For analysis of the lymph nodes, all slides of all lymph nodes were reviewed retrospectively by one senior pathologist without knowledge of the previous pathologic data. LRG was classified based on the percentages of tumor cells and fibrosis, as described elsewhere[12]: LRG0, normal lymph node; LRG1, 100% fibrosis (complete response); LRG2, <25% cancer cells; LRG3, 25% to 50% cancer cells; LRG4, 50% to 75% cancer cells; and LRG5, 75% to complete replacement with cancer cells (Fig 1). Because each specimen had a variable number of lymph nodes and each lymph node had a different regression grade, an overall score for each patient was given based on the worst grade of that specimen.

Statistical analysis

Differences in categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were analyzed with the Mann-Whitney *U* test. The Kaplan-Meier method with the log-rank test was used for survival analyses. Recurrence-free survival (RFS) was defined as the time from the date of operation to any recurrence. Local recurrence (LR) was defined as the time from operation to any anastomotic, pelvic, or perineal tumor recurrence as diagnosed either radiologically or histologically. Patient follow-up was performed every 3 months during the first 3 years and every 6 months thereafter. Blood tests, including measurements of carcinoembryonic antigen levels, were assessed at every visit. Chest and abdominal computed tomography (CT) were performed every 6 months. A multivariate logistic regression analysis was performed to evaluate predictors of LRG1. Univariate and multivariate analyses were performed using the Cox proportional hazard model to evaluate predictors of recurrence. Variables with *P* values <.2 in the univariate analysis were examined by multivariate analysis. Statistical analysis was performed using GraphPad Prism 7 software (GraphPad, San Diego, CA) or JMP software v10.0.2 (SAS Institute Inc, Cary, NC).

Results

This study included 421 patients, of whom 285 (67.7%) were male. The median age was 60 years, and the median distance of the tumor from the anal verge was 40 mm. A total of 269 patients (63.9%) had pretreatment stage III cancer, and neoadjuvant systemic chemotherapy was administered in 82 (19.5%) patients. Pathologically, 120 patients (28.5%) had residual lymph node metastases. According to TRG, 155 (36.8%) patients were classified as TRG1, 147 (34.9%) as TRG2, 38 (9.0%) as TRG3, and 81 (19.2%) as TRG4.

The median number of retrieved lymph nodes was 17, and 8,058 lymph nodes were re-evaluated for the presence of fibrosis or residual cancer cells. Among the 301 ypN0 patients, 27 (9.0%) patients were scored as LRG1. Among the 120 ypN+ patients, 25 (20.8%) patients were scored as LRG2, 18 (15.0%) as LRG3, 38 (31.7%) as LRG4, and 39 (32.5%) as LRG5. A total of 16 patients (13.3%) among the 120 ypN+ patients had lymph nodes considered as complete regression. RFS and LR according to LRG status are summarized in Figure 2. The 5-y RFS and LR in LRG1 patients were 96.3% and 0%, respectively. RFS among patients with LRG2–5 were 59%, 61%, 38%, and 52%, respectively. Therefore, patients classified as LRG1 were defined as "lymph node responders," and those as LRG2 though LRG5 were grouped as "lymph node nonresponders."

Table I presents the patient characteristics according to LRG status. The median age among LRG1 patients was younger than that for LRG0 and LRG2–5 patients. The rate of neoadjuvant chemotherapy in patients with LRG1 was significantly greater than that in LRG0 and LRG2–5. The percentage of good responders (TRG3–4) among patients with LRG1 was greater than that in LRG2–5 (41% vs 8%) but similar to that in LRG0 (41% vs 36%). The rate of adjuvant chemotherapy in patients with LRG1 was greater than that in LRG0 (63% vs 33%) but tended to be less than that in LRG2–5 (63% vs 81%). A similar rate of perioperative systemic chemotherapy

Table III
Univariate and multivariate analyses of factors associated with recurrence-free survival in patients with histologic evidence of LRG1 and LRG2–5

	Recurrence-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.000	0.978–1.024	.994			
Male sex	1.530	0.882–2.770	.132	1.550	0.876–2.869	.135
Distance from anal verge ≤ 40 mm	1.541	0.904–2.704	.113	1.192	0.680–2.145	.544
Pretreatment CEA > 5.0 ng/ml	1.603	0.947–2.698	.078	0.858	0.476–1.526	.603
Clinical T4 (versus T3)	1.185	0.519–2.363	.662			
Clinical stage III (versus II)	0.845	0.455–1.719	.623			
ypT3–4 (versus 0–2)	7.188	3.163–20.67	< .001	7.820	2.801–27.32	< .001
LRG1 (versus 2–5)	0.065	0.004–0.294	< .001	0.048	0.002–0.274	< .001
TRG3-4 (versus 1–2)	0.311	0.076–0.842	.018	1.722	0.338–7.040	.483
Tumor differentiation other than well/moderate	1.465	0.509–3.331	.439			
Number of retrieved lymph nodes < 12	2.623	1.324–4.805	.007	5.480	1.476–16.38	.014
Lymphovascular invasion	2.733	1.441–5.737	.002	0.771	0.353–1.861	.543
Neoadjuvant chemotherapy	0.818	0.389–1.555	.558			
No perioperative chemotherapy	1.867	1.001–3.295	.0495	3.011	1.531–5.679	.002

CEA, carcinoembryonic antigen.

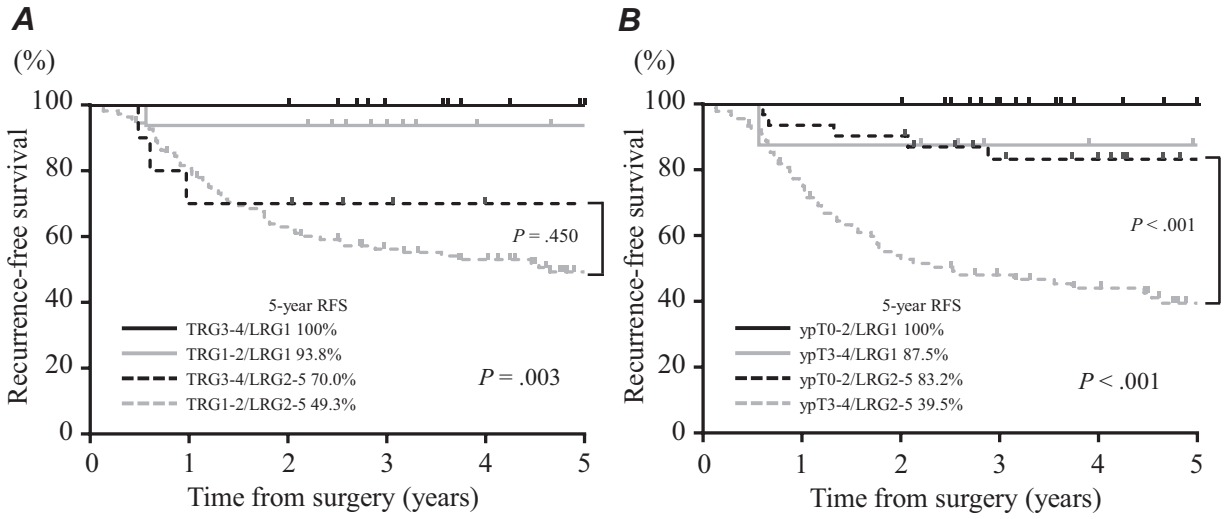

Fig 3. Kaplan-Meier analysis of recurrence-free survival according to the combined status of (*A*) the lymph node regression grade (LRG) and tumor regression grade (TRG) or (*B*) ypT among patients with LRG1–5.

(neoadjuvant or adjuvant chemotherapy), however, was found for patients with LRG1 and LRG2–5 (74% vs 82%).

Among patients with LRG1–5, the results of the multivariate analysis showed that neoadjuvant systemic chemotherapy was independently associated with LRG1 ($P < .001$; odds ratio, 6.061; 95% confidence interval [CI], 2.332–16.20) more so than the other LRG classifications (Table II); the percentage of LRG1 was 47% (14/30) among patients with neoadjuvant systemic chemotherapy and 11.1% (13/117) for those without neoadjuvant systemic chemotherapy ($P < .001$).

Table III shows the results of the univariate and multivariate analyses of factors associated with RFS in LRG1 though LRG5 patients. In the univariate analysis, ypT3-4 ($P < .001$), LRG2–5 ($P < .001$), TRG1–2 ($P = .018$), the number of retrieved lymph nodes < 12 ($P = .007$), and no perioperative chemotherapy ($P = .049$) were associated with worse RFS. In the multivariate analysis, ypT3-4 (HR, 7.82; 95% CI, 2.80–27.32; $P < .001$), LRG1 (HR, 0.048; 95% CI, 0.002–0.27; $P < .001$), the number of retrieved lymph nodes < 12 (HR, 5.48; 95% CI, 1.48–16.38; $P = .014$), and no perioperative chemotherapy (HR, 3.01; 95% CI: 1.53–5.68, $P = .002$) were independent predictors of RFS. Figure 3 shows RFS according to the combined status of LRG and TRG or ypT in patients with LRG1–5. Among lymph node nonresponders (LRG2–5), RFS was not different according to TRG ($P = .450$) but was markedly different according to ypT status ($P < .001$).

Table IV presents the results of the univariate and multivariate analyses of factors associated with RFS in LRG0 patients. In the univariate analysis, only TRG3–4 ($P = .031$) was associated with better RFS; however, this difference did not reach statistical significance in the multivariate analysis ($P = .09$). When "good responders" included only TRG4, we identified TRG4 as an independent predictor of better RFS in the multivariate analysis (HR, 0.29; 95% CI, 0.06–0.94; $P = .039$). The percentage of TRG3–4 was 60% (31 of 52) among patients with neoadjuvant systemic chemotherapy and 30.2% (67 of 222) for those without neoadjuvant systemic chemotherapy ($P < .001$).

Discussion

The present study showed that complete regression of regional lymph nodes after CRT is associated with improved survival in patients with rectal cancer, and the administration of neoadjuvant systemic chemotherapy is an independent predictor of complete regression of regional lymph nodes. To our knowledge, this is the

Table IV
Univariate and multivariate analyses of factors associated with recurrence-free survival in LRG0 patients

	Recurrence-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.001	0.978–1.044	.590			
Male sex	0.819	0.395–1.818	.609			
Distance from anal verge ≤ 40 mm	1.547	0.755–3.344	.237			
Pre-treatment CEA > 5.0 ng/ml	0.951	0.440–1.951	.894			
Clinical T4 (versus T2/3)	2.113	0.885–4.537	.088	1.855	0.754–4.126	.168
Clinical stage III (versus I/II)	1.013	0.500–2.087	.972			
ypT3-4 (versus 0–2)	1.839	0.900–3.738	.094	1.189	0.496–2.829	.695
TRG3-4 (versus 1–2)	0.405	0.150–0.923	.031	0.428	0.144–1.139	.090
Tumor differentiation other than well/moderate	2.432	0.719–6.226	.137	2.230	0.641–5.989	.186
Number of retrieved lymph nodes < 12	1.878	0.634–4.503	.231			
Lymphovascular invasion	1.727	0.845–3.512	.132	0.989	0.408–2.419	.981
Neoadjuvant chemotherapy	0.497	0.119–1.406	.207			
Perioperative chemotherapy	0.864	0.400–1.773	.696			

CEA, carcinoembryonic antigen.

largest study to have examined the correlation between the degree of lymph node regression and prognosis in patients with rectal cancer treated with neoadjuvant CRT.

In 2007, Caricato et al[13] first reported the histologic effect of preoperative CRT on mesorectal lymph nodes, with LRG1 observed in 18 (51%) of the 35 patients. Vychnevskaia et al[14] showed that 49 (24%) of 206 ypN0 patients had sterilized lymph nodes, as determined by the presence of fibrosis, acellular pools of mucin, necrosis associated with variable foamy histiocytic aggregates, or microcalcification. Fernandez-Acenero et al[15] similarly reported that 57% of ypN0 and 76% of ypN+ patients had histologic signs of regression using criteria comparable with those in the study by Vychnevskaia et al.[14] The presence of complete regression of lymph nodes among ypN0 and ypN+ patients in the present study was 9% (27 of 301) and 13.3% (16 of 120), respectively, which was less than that in these other studies. The lesser percentage of LRG1 in this study may be explained by the different definition of lymph node regression. Indeed, earlier work using the same LRG criteria that we used found a similar percentage of LRG1 (13.7%),[12] suggesting that our percentage of LRG1 is not exceptionally low.

In our study, we showed that patients with LRG1 had excellent survival. RFS was better for LRG1 patients than that for ypN0 patients who did not show signs of lymph node regression. This is consistent with the results from Vychnevskaia et al.[14] One possible explanation for the better RFS among patients with LRG1 as compared with those with LRG0 may be the greater percentage of perioperative systemic chemotherapy among patients with LRG1. Another explanation is that poor responders (TRG1–2) among the LRG0 patients might be driving some of the outcome differences between LRG0 and LRG1. The 5-y RFS was less in TRG1–2 patients than in TRG3–4 patients among LRG0 patients (86% vs 92%, $P = .040$) but not among LRG1 patients (100% vs 94%, $P = .407$). This difference might simply be attributable to the lesser number of LRG1 patients. Beppu et al[16] also reported that complete regression of lymph nodes was associated with an improved survival; however, the regimen used in their study was not common (short-course, hyperfractionated radiotherapy). Notably, the survival rate for ypN+ patients was poor, and this was irrespective of the number of residual cancer cells in the lymph nodes. This is in contrast to the findings of an earlier study of 256 esophageal adenocarcinoma patients who received neoadjuvant chemotherapy, which found improved survival for patients who presented with lymph node regression less than 50% remaining tumor (corresponds to LRG1–3 in this study).[17] The findings of our study suggest that only total regression of metastatic lymph nodes had a significant effect on prognosis among patients with rectal cancer.

This study was the first to show that the administration of neoadjuvant systemic chemotherapy combined with CRT was associated with a greater proportion of patients with LRG1. The percentage of patients with LRG1 among pretreatment, node-positive (LRG1–5) patients was 47% among those who received neoadjuvant systemic chemotherapy and 11.1% among those treated without neoadjuvant systemic chemotherapy. Of interest, the percentage of TRG4 (complete response) among LRG1–5 patients who received (20%; 6/30) or did not receive (6.0%; 7/117) neoadjuvant systemic chemotherapy was less than the percentage of patients with LRG1. This result suggests that metastatic cancer cells in the lymph nodes may respond better to neoadjuvant treatment than those with cancer cells at the primary site. Albeit, the presence of lymph node metastasis itself is suggestive of worse response to neoadjuvant treatment. Otherwise, a fewer number of cancer cells in the lymph nodes as compared with the primary site may be associated with a greater rate of total regression. An earlier study showed that total neoadjuvant therapy (induction chemotherapy followed by CRT) was associated with a greater rate of complete response (pathologic complete response and sustained clinical complete response at 12 months),[4] and our data suggest that this is also true for patients with lymph node metastasis. Possible explanations for the lack of improved rates of survival by neoadjuvant chemotherapy in this study are the relatively high percentage of adjuvant chemotherapy among the patients treated without neoadjuvant chemotherapy (88 of 117; 75.2%) as well as the lesser number of LRG1 patients among the LRG1–5 patient cohort. Prospective studies are necessary to evaluate whether a greater percentage of complete regression both in the primary tumor and in the lymph nodes through the addition of systemic chemotherapy is translated to improved survival compared with postoperative adjuvant chemotherapy in pretreatment, node-positive (LRG1–5) patients.

Earlier studies have shown TRG to have independent prognostic value in patients with rectal cancer treated with CRT.[9,18] Our data expand on these findings and show that TRG was not prognostic in terms of survival when adjusted for LRG and ypT among LRG1–5 patients. Consistent with our results, Rodel et al[7] also showed that TRG was not a significant, independent prognostic factor, but that ypT and ypN were independent prognostic factors for RFS. One possible explanation for these inconsistencies among the literature may be the use of different methods to assess TRG, such as the criteria followed by Dworak et al[8] or the AJCC criteria.[9,18] We showed that TRG tended to be associated with RFS in LRG0 patients, suggesting that the prognostic value of TRG might be different according to the presence or absence of lymph node metastasis. Karagkounis et al[19] showed AJCC TRG to be an independent prognostic factor for yp stage III rectal cancer but not yp stage II rectal cancer. Such a difference is likely attributable to the different definition of a "responder": Karagkounis et al[19] grouped AJCC TRG 3 (minimal or no tumor kill) as nonresponders and others as responders.

Our study has some limitations. First, this was a retrospective, single-center study. Second, the present study included a relatively small number of patients with LRG1 ($n = 27$), and, therefore, a larger study is necessary to confirm our results. Third, some patients with total lymph node regression may have been missed because of the absence of obvious fibrosis or a disappearance of lymph node structure by CRT. Finally, a significantly higher number of younger patients were treated with neoadjuvant chemotherapy, suggesting that patient factors influenced our decisions for more aggressive treatment, which could have led to a selection bias. Nonetheless, this study demonstrates the prognostic importance of the regression of metastatic lymph nodes after neoadjuvant CRT in patients with rectal cancer.

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Conflict of interest/Disclosure

The authors have no conflicts of interest to declare.

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