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Tumor regression grade as a clinically useful outcome predictor in patients with rectal cancer after preoperative chemoradiotherapy ☆

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ABSTRACT

Background: The prognostic role of tumor regression grade is not clear. This study evaluated the prognostic significance of tumor regression grade in patients with rectal cancer after preoperative chemoradiotherapy.

Methods: A total of 639 patients with confirmed rectal cancer who had undergone preoperative chemoradiotherapy and radical resection during the period October 2002 through December 2011 were included in this study. The tumor regression grade was graded: TRG0 (complete response), TRG1 (moderate), TRG2 (minimal), and TRG3 (poor). The prognostic significance of tumor regression grade was evaluated.

Results: With a median follow-up of 56.7 months, the rates of 5-year overall survival, disease-free survival, and local recurrence-free survival among the TRG groups differed significantly (all $P < .001$). For patients with TRG0, TRG1, and TRG2–3, disease-free survivals were different between the ypStage ($P < .001$, $P < .001$, and $P = .043$). Multivariate analysis revealed findings to substantiate that the tumor regression grade represents a valuable and independent prognostic factor for long-term, disease-free survival ($P = .041$). Independent predictors of TRG2–3 consisted of lymphovascular invasion, tumor budding, and the pretreatment serum level of carcinoembryonic antigen in multivariate regression analysis. Clinical risk grouping, using 3 predictors for TRG2–3 was different ($P < .001$).

Conclusion: The tumor regression grade may represent a useful prognostic variable to better individualize the prognosis and potentially further therapy for each rectal cancer patient who underwent chemoradiotherapy.

Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision for locally advanced rectal cancer generally serves to produce superior local control and disease-free long-term survival.[1,2] The pathologic tumor, node, metastasis (TNM) staging system of the American Joint Commission on Cancer (AJCC) is a standard prognostic indicator used for patients who undergo preoperative CRT. The TNM classification, however, was not designed to contain information about the degree of tumor response to the CRT. The treatment responses to preoperative CRT show a variability results, ranging from complete pathologic response to progression of cancer and complete or near-complete pathologic response, which predicts oncologic outcomes.[3–6]

The findings revealed by several recent studies suggest that there is a potential role for tumor regression grade (TRG) as a surrogate for oncologic outcomes, but the conclusion that TRG is a definite prognostic factor remains somewhat controversial.[3,4,7–9] The goal of this study was to evaluate the potential role of

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TRG as a prognostic indicator in patients with rectal cancer after preoperative CRT.

Methods

From October 2002 to December 2011, 953 consecutive patients who had undergone curative surgery after preoperative CRT for locally advanced rectal cancer at our institution (Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea) were reviewed in this study. Those patients with diagnoses of metastatic disease, recurrent disease, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, local resection, no TRG assessment, or no follow-up data were excluded from the study cohort. After exclusions, a total of 639 patients were included in the analysis. This study was reviewed and approved by the appropriate institutional review board.

Clinical staging before preoperative CRT was assessed radiologically, using endorectal ultrasonography, chest and abdominopelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), colonoscopy, and a positron emission tomography (PET) scanning, if available. To achieve standardization of clinical staging, a single radiologist reread the radiologic findings of the primary rectal lesion. All patients underwent concurrent CRT, consisting of preoperative 5-fluorouracil-based chemotherapy and pelvic radiation (4040–5040 cGy), followed by radical resection 6–8 weeks later.[10,11] The median time interval between preoperative CRT and the operation was 8 weeks (range, 2–52 weeks). Of the 461 patients who had documented postoperative treatment, 425 (92.2%) received postoperative adjuvant chemotherapy. All patients underwent total mesorectal excision. The rectal neoplasms were classified according to the 7th AJCC TNM classification. Histopathologic features, such as lymphovascular invasion, perineural invasion, and tumor budding, were evaluated using pathologic specimens by 2 experienced gastrointestinal pathologists who had no clinicopathologic information. The TRG was established implementing the AJCC criteria as follows: TRG0—complete response with no visible tumor cells remaining; TRG1—moderate response with a single or small group of tumor cells remaining; TRG2—minimal response with the residual cancer is outgrown by fibrosis; and TRG3—poor response with extensive residual cancer with minimal or no tumor kill.[4]

Postoperatively, the patients were seen in follow-up every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually thereafter. On a semiannual basis or whenever there was anything clinically suspicious for recurrence, the follow-up examination would include an interim clinical history obtained at that time, physical examination, serum level of carcinoembryonic antigen (CEA), chest X-ray, colonoscopy, and some type of cross-sectional imaging (chest and abdominopelvic CT, pelvic MRI, or PET scanning.

Statistical evaluation was carried out using the statistical package SPSS for Windows (v 18.0; SPSS Inc, Chicago, IL, USA). The differences between the two groups were tested using the Student t test and the χ^2 test or Fisher exact test, as appropriate. Survival curves were calculated using the Kaplan-Meier method, with differences between curves evaluated using the log-rank test. A Cox proportional hazards model (generated by a forward stepwise selection of variables) was used for multivariate analysis. Only factors for which a P value $\leq .05$, as determined in the univariate analysis, were entered into the multivariate analysis. Multivariate logistic regression analysis was used to identify variables independently associated with a minimal to poor TRG (TRG2–3). With the use of the three independent predictive variables for TRG2–3 derived from multivariate analysis, a clinical risk score model was performed according to the following criteria: no-risk group, zero factors; low-risk group, one factor; and, the high-risk group with two or three factors. The factors included were a pretreatment serum CEA level of ≥ 5 ng/mL, positive lymphovascular invasion, and positive tumor budding.

Results

This analysis included 437 (68.4%) male and 202 (31.6%) female patients, with a median chronologic age of 56 years (range, 24–80 years). The median distance from the anal verge was 4.0 cm (range 0–12 cm). Of the 639 patients, 557 (87.1%) underwent low anterior resection, 67 (10.5%) underwent abdominoperineal resection, and 15 (2.4%) underwent a Hartmann's procedure. The median number of harvested lymph nodes was 10 (range, 0–44). The median preoperative serum CEA level was 1.7 (range, 0.1–207.0 ng/mL). Using the 7th AJCC TNM classification system, 215 (33.6%) and 424 (66.4%) patients had pretreatment stage II and III cancers, respectively, and 144, 156, 151, and 188 patients had pathologic stage 0 (complete response), I, II, and III cancers, respectively. According to the TRG criteria, 147, 372, 114, and 6 patients had TRG0, TRG1, TRG2, and TRG3 cancers, respectively.

Clinicopathologic characteristics of patients, according to the TRG are presented in Table 1. The pretreatment TNM stage, distance of the tumor from the anal verge, size of the tumor measured at its maximum diameter, ypT category, ypN category, lymphovascular invasion, perineural invasion, tumor budding, circumferential resection margin, operative procedure, and preoperative serum CEA levels all differed significantly among the three TRG groups.

The univariate analysis indicated that the factors associated with overall survival consisted of pretreatment CEA level, operative procedure, tumor differentiation, tumor size, ypT category, ypN category, lymphovascular invasion, perineural invasion, tumor budding, postoperative chemotherapy, and TRG (Table 2). The factors associated with disease-free survival were found to be operative procedure, tumor size, ypT category, ypN category, circumferential resection margin, lymphovascular invasion, perineural invasion, and TRG (Table 2). On multivariate analysis, pretreatment CEA level, differentiation, ypN category, and postoperative chemotherapy were independent prognostic factors for overall survival; operative procedure, ypN category, lymphovascular invasion, and TRG were independent prognostic factors for disease-free survival (Table 3).

With a median follow-up period of 56.7 months (range, 0.1–147.9 months), the 5-year overall survival and disease-free survival rates of this cohort were 91% and 78%, respectively. The survival curves among the three TRG groups differed significantly (Fig 1, *A*, and Fig 1, *B*). The 5-year overall survival rates of patients with TRG0, TRG1, and TRG2–3 were 98%, 91%, and 79%, respectively ($P < .001$, Fig 1, *A*). In addition, the 5-year disease-free survival rates of patients with TRG0, TRG1, and TRG2–3 were 92%, 76%, and 67%, respectively ($P < .001$, Fig 1, *B*). When the TRG groups were separated into groups according to the pathologic TNM classification, differences were present in the 5-year disease-free survival between the groups (Fig 2). For the patients with TRG0, TRG1, and TRG2-3 cancers, the 5-year disease-free survival rates were different among the ypStage groups ($P < .001$, $P < .001$, and $P = .043$, respectively; Fig 2, *A*–2, *C*).

Given the potential important implications of minimal to poor TRG for survival, we performed a multivariate analysis to identify available clinical factors independently associated with TRG2–3 (Table 4). Positive lymphovascular invasion ($P < .001$), positive tumor budding ($P = .014$), and pretreatment serum CEA level of ≥ 5 ng/mL ($P = .031$) were independent predictors of minimal to poor TRG. Of 327 patients who had a documented history of 3 factors simultaneously, groups of 180 (55.0%), 102 (31.2%), and 45 patients (13.8%) were categorized as no-risk, low-risk, and high-risk groups, respectively. According to the clinical risk score model, incidence of

Table 1
Comparison of patients according to the TRG ($n = 639$).

	TRG0($n = 147$)	TRG1 ($n = 372$)	TRG2-3 ($n = 120$)	*P*
Age, years				.744
< 56	75 (51.0)	187 (50.3)	56 (46.7)	
≥ 56	72 (49.0)	185 (49.7)	64 (53.3)	
Sex				.649
Male	105 (71.4)	252 (67.7)	80 (66.7)	
Female	42 (28.6)	120 (32.3)	40 (33.3)	
Pretreatment TNM stage				< .001
II	72 (49.0)	114 (30.6)	29 (24.2)	
III	75 (51.0)	258 (69.4)	91 (75.8)	
Interval from completion of radiation to operation, weeks				.071
≤ 8	95 (64.6)	199 (53.5)	64 (53.3)	
>8	50 (34.0)	171 (46.0)	55 (46.8)	
Unknown	2 (1.4)	2 (0.5)	1 (0.8)	
Macroscopic ulceration				.188
No	11 (7.5)	26 (7.0)	4 (3.3)	
Yes	136 (92.5)	346 (93.0)	116 (96.7)	
Tumor location from anal verge, cm				.004
≤ 5	114 (77.6)	243 (65.3)	93 (77.5)	
> 5	33 (22.4)	129 (34.7)	27 (22.05	
Maximal diameter of tumor, cm				< .001
< 2.5	90 (61.2)	175 (47.0)	36 (30.0)	
≥ 2.5	57 (38.8)	197 (53.0)	84 (70.0)	
Differentiation				.927
Well+moderate	136 (92.5)	345 (92.7)	110 (91.7)	
Poor+mucinous	11 (7.5)	27 (7.3)	10 (9.3)	
Pathologic TNM stage				< .001
0	132 (89.8)	12 (3.2)	0	
I	3 (2.0)	134 (36.0)	19 (15.8)	
II	3 (2.0)	102 (27.4)	46 (38.3)	
III	9 (6.1)	124 (33.3)	55 (45.8)	
Pathologic T category (T)				< .001
T0	142 (96.6)	12 (3.2)	0	
T1	1 (0.7)	26 (7.0)	2 (1.7)	
T2	2 (1.4)	140 (37.6)	23 (19.2)	
T3	2 (1.4)	186 (50.0)	90 (75.0)	
T4	0	8 (2.2)	5 (4.2)	
Pathologic N category				< .001
N–	137(93.2)	248 (66.7)	65 (54.2)	
N+	10 (6.8)	124 (33.3)	55 (45.8)	
Lymphovascular invasion				< .001
Negative	2 (1.4)	297 (79.8)	78 (65.0)	
Positive	2 (1.4)	74 (19.9)	42 (35.0)	
Unknown	143 (97.3)	1 (0.3)	0	
Perineural invasion				< .001
Negative	4 (2.7)	343 (92.2)	105 (87.5)	
Positive	0	28 (7.5)	15 (12.5)	
Unknown	143 (97.3)	1 (0.3)	0	
Tumor budding				< .001
Negative	1 (0.7)	224 (60.2)	44 (36.7)	
Positive	0	68 (18.3)	37 (30.8)	
Unknown	146 (99.3)	80 (21.5)	39 (32.5)	
Number of lymph nodes harvested				.086
< 12	103 (70.1)	205 (55.1)	71 (59.2)	
≥ 12	42 (28.6)	165 (44.4)	49 (40.8)	
Unknown	2 (1.4)	2 (0.5)	0	
Circumferential resection margin, mm				< .001
< 1	1 (0.7)	12 (3.2)	15 (12.5)	
≥ 1	146 (99.3)	360 (96.8)	105 (87.5)	
Operative procedure				.130
Sphincter-saving operation	131 (89.1)	328 (88.2)	98 (81.7)	
Sphincter-sacrificing operation	16 (10.9)	44 (11.8)	22 (18.3)	
Preoperative CEA, ng/mL				.037
< 5	127 (86.4)	304 (81.7)	88 (73.3)	
≥ 5	6 (4.1)	16 (4.3)	12 (10.0)	
Not available	14 (9.5)	52 (14.0)	20 (16.7)	

CEA, carcinoembryonic antigen.

TRG2–3 for the no-risk, low-risk, and high-risk groups were 12.2%, 26.5%, and 40.0%, respectively ($P < .001$; Fig 3).

Discussion

This study shows the that, using AJCC criteria, TRG is an independent prognostic factor for disease-free survival on analysis of 639 patients with a documented history of rectal cancer treated with preoperative CRT. Our observations essentially confirm the findings of previous investigations by the German Rectal Cancer Study Group and AJCC, which reported the TRG as a relatively reliable prognostic factor and individual-level surrogate for the possibility of disease-free survival in rectal cancer patients treated with preoperative CRT.[3,4] We found that the various tumor and

Table 2
Univariate analyses of the factors for 5-year overall survival and disease-free survival.

		Overall survival		Disease-free survival	
	N	%	*P*	%	*P*
All patients	639	91		78	
Age, years			.682		.137
< 56	318	92		77	
≥ 56	321	91		82	
Sex			.640		.502
Male	437	92		80	
Female	202	91		78	
Tumor location from anal verge, cm			.117		.423
≤ 5	450	90		79	
> 5	189	94		81	
Pretreatment serum CEA, ng/mL			< .001		.089
< 5	519	94		81	
≥ 5	34	68		71	
Not available	86				
Interval from completion of radiation to operation, weeks			.864		.081
≤ 8	358	91		82	
> 8	276	92		76	
Unknown	5				
Operation method			< .001		.002
Sphincter-saving operation	557	93		81	
Sphincter-sacrificing operation	82	79		68	
Number of lymph nodes harvested			.999		.976
< 12	379	91		79	
≥ 12	256	91		80	
Unknown	4				
Differentiation			.001		.082
Well+moderate	591	92		80	
Poor+mucinous	48	79		71	
Maximal diameter of tumor, cm			.002		.008
< 2.5	301	95		84	
≥ 2.5	338	88		76	
Pathologic T category			< .001		< .001
T0–2	348	95		87	
T3–4	291	87		70	
Pathologic N category			< .001		< .001
N–	450	94		87	
N+	189	85		61	
Circumferential resection margin, mm			.064		< .001
< 1.0	28	82		57	
≥ 1.0	611	92		81	
Lymphovascular invasion			< .001		< .001
Negative	377	92		81	
Positive	118	81		58	
Unknown	144				
Perineural invasion			.043		< .001
Negative	452	90		78	
Positive	43	81		56	
Unknown	144				
Tumor budding			.009		.110
Negative	269	94		77	
Positive	105	86		69	
Unknown	265				
Postoperative chemotherapy			.007		.429
Yes	425	93		79	
No	36	81		75	
Unknown	178				
Tumor regression grade			< .001		< .001
TRG0 (complete)	147	98		93	
TRG1 (moderate)	372	92		78	
TRG2–3 (minimal to poor)	120	81		68	

CEA, carcinoembryonic antigen.

treatment factors that influenced long-term survival included pretreatment stage, tumor height, tumor size, ypT category, ypN category, lymphovascular invasion, perineural invasion, tumor budding, circumferential resection margin, operative procedure, and preoperative CEA levels were associated with the degree of tumor regression after preoperative CRT. We also observed that the TRG correlated well with the overall survival and disease-free survival rates. More important, we demonstrated that an unfavorable TRG (TRGs2, 3) may be predicted in the pretreatment setting by identifying several clinical factors, including lymphovascular invasion, tumor budding, and pretreatment serum CEA level. To the best of our knowledge, this is the first formal description of the potential factors predictive for an unfavorable TRG prognosis after preoperative CRT in documented cases of rectal cancer.

The potentially important prognostic value of TRG in rectal cancer treated with preoperative CRT has been suggested recently; however, the actual efficacy of TRG as an accurate and reliable prognostic factor is not well understood, has been widely debated,

Table 3
Multivariate analyses of the factors for 5-year overall survival and disease-free survival.

Factors	Hazards ratio (CI)	*P*
Overall survival		
Pretreatment serum CEA	4.054 (1.376–11.948)	.011
Operative procedure	2.214 (0.843–5.811)	.107
Differentiation	3.476 (1.390–8.693)	.008
Maximal diameter of tumor	1.177 (0.496–2.791)	.712
Pathologic T category	1.346 (0.468–3.873)	.582
Pathologic N category	3.103 (1.149–8.384)	.026
Lymphovascular invasion	1.098 (0.427–2.821)	.847
Perineural invasion	1.314 (0.408–4.226)	.647
Tumor budding	1.480 (0.535–4.094)	.450
Postoperative chemotherapy	4.570 (1.664–12.554)	.003
Tumor regression grade	2.599 (0.632–10.681)	.185
Disease-free survival		
Operation method	1.617 (1.020–2.564)	.041
Maximal diameter of tumor	1.164 (0.802–1.690)	.424
Pathologic T category	1.095 (0.699–1.714)	.693
Pathologic N category	2.343 (1.557–3.526)	<.001
Circumferential resection margin	1.410 (0.741–2.681)	.295
Lymphovascular invasion	1.526 (1.005–2.318)	.047
Perineural invasion	1.578 (0.940–2.648)	.084
Tumor regression grade	2.040 (1.029–4.044)	.041

CEA, carcinoembryonic antigen.

Table 4
Multivariate predictors of minimal to poor TRG after preoperative chemoradiotherapy.

	Odds ratio (CI)	*P*
Pretreatment clinical T category	1.604 (0.764–3.367)	.212
Tumor location from anal verge	1.480 (0.874–2.505)	.145
Differentiation	1.302 (0.558–3.034)	.542
Pretreatment serum CEA	2.411 (1.083–5.368)	.031
Lymphovascular invasion	2.630 (1.535–4.507)	< .001
Perineural invasion	1.874 (0.831–4.226)	.130
Tumor budding	2.036 (1.152–3.597)	.014

CEA, carcinoembryonic antigen.

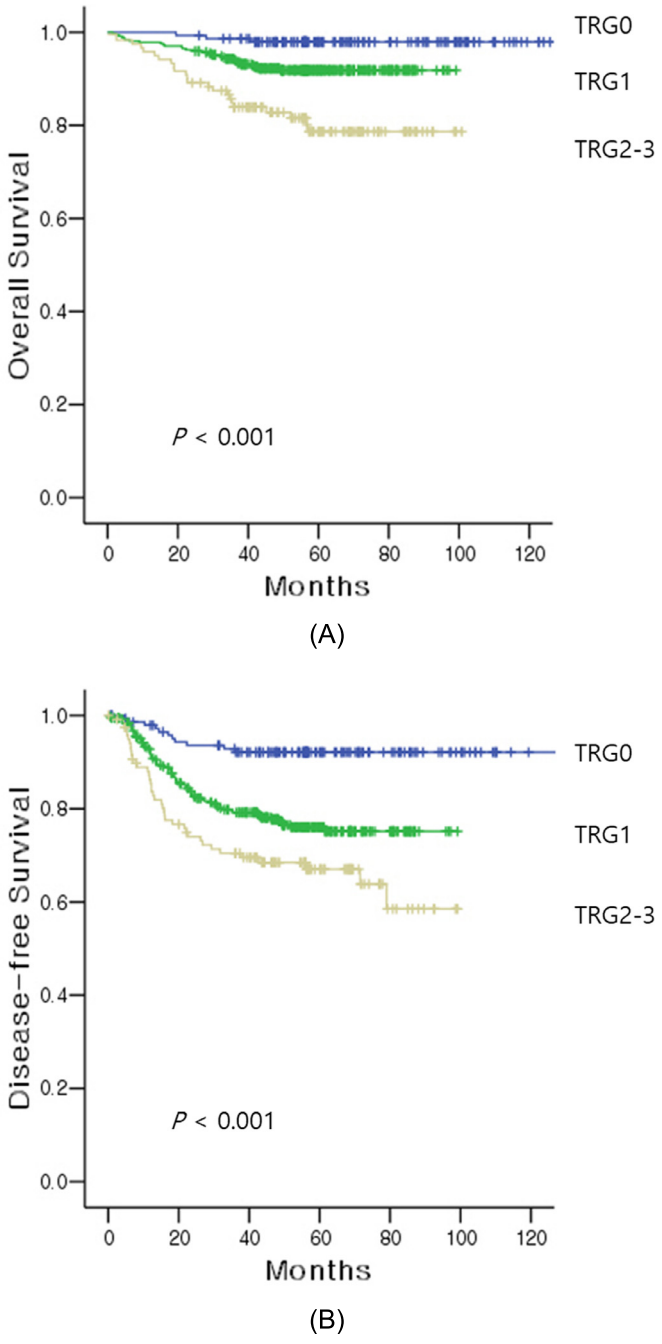

Fig. 1. Kaplan-Meier curves according to the tumor regression grade: (*A*) overall survival and (*B*) disease-free survival.

and still remains a matter of some controversy.[8,9] Kim et al[8] compared four tumor response-related, pathologic factors, including ypT, ypN, ypStage, and TRG in 420 rectal cancer patients treated with preoperative CRT. They found that ypN was the most dominant factor for predicting disease-free survival, and TRG was the least prognostic ability. Rodel et al[9] also reported that the TRG alone is not a statistically significant prognostic factor, and ypN remains the most important prognostic factor. We agree with the observation that ypN category is the most important factor in radiated rectal cancer because the ypN category was identified as the only independent prognostic factor for both overall survival and disease-free survival in our study as well. Nevertheless, our findings support the results from many previous studies that reported TRG as an important indicator of prognosis in patients with rectal cancer treated with preoperative CRT.[3–5,12,13] The German Rectal Cancer Study Group examined the prognostic value of TRG, using the Dworak classification in 1,179 patients treated as part of a randomized trial.[3] The authors found that the three-tier TRG system was an independent prognostic variable for disease-free survival. The AJCC/College of American Pathologists (CAP) four-tier TRG classification also confirmed the independent value of the TRG for predicting survival and recurrence.[4] We found that the TRG correlated well with the disease-free survival, especially when combined with ypStage in this study. These results indicate that the TRG classification combined with ypTNM may be beneficial to stratify the prognosis and tailor the optimal postoperative therapy accordingly.

Despite evidence supporting the prognostic significance of the TRG, the current TRG system still has constraints for clinical application because of poor reproducibility induced by the subjectivity of the grading criteria, interobserver variability, and different grading systems.[14–16] Current TRG classifications do not consider nodal status, although ypN is the most important prognostic factor in radiated rectal cancer. A recent publication by Kim et al[14] highlights the lack of consensus about which grading system is the most ideal classification by comparing the prognostic performance of four different TRG systems. The authors found that none was found to be a better predictor of prognosis than ypStage and that the pathologic staging has more objective and predictive value for prognosis and treatment response. We used the well-defined AJCC/CAP system for TRG evaluation in our analysis because the AJCC/CAP was believed to be superior to the previous regression

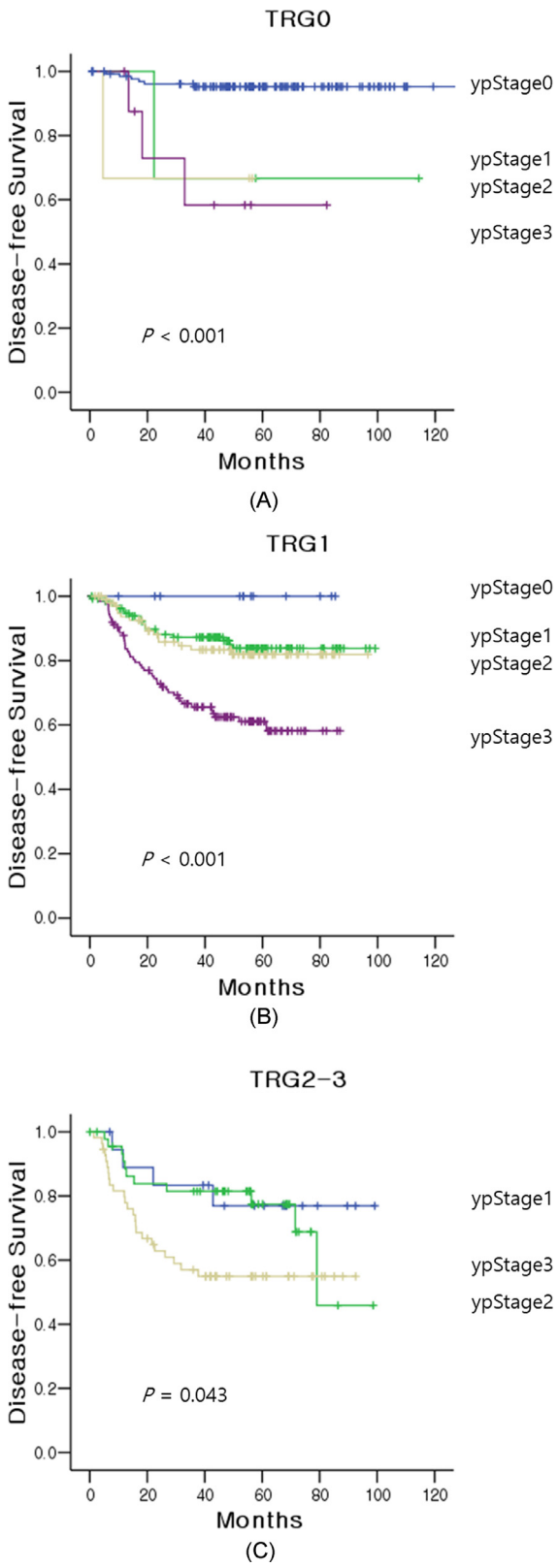

Fig. 2. Disease-free survival curves according to the ypTNM stage in patients with (*A*) TRG0, (*B*) TRG1, and (*C*) TRG2-3.

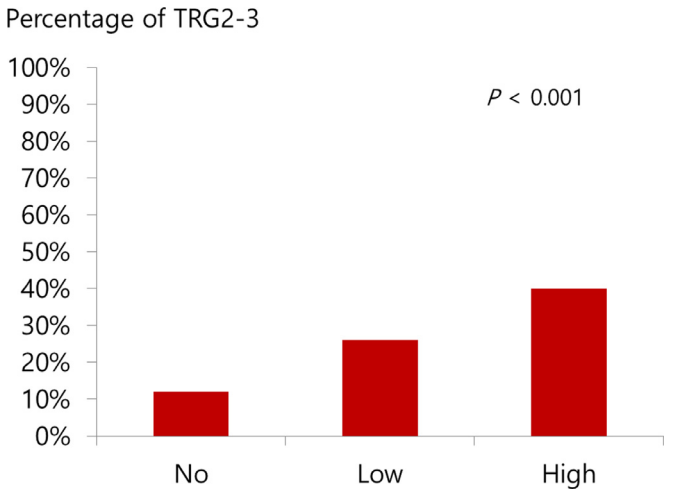

Fig. 3. Incidence of minimal to poor tumor regression grade (TRG 2-3) related to the clinical risk score. The factors included a pretreatment serum CEA level of ≥ 5 ng/mL, positive lymphovascular invasion, and positive tumor budding. The risk groupings were as follows: no-risk group, 0 factors; low-risk group, 1 factor; and high-risk group, > 2 factors.

grading scales in their report.[4] Further validation and consensus for a universally approved regression system would be warranted.

Our study has some limitations. First, this study was retrospective in nature, and thus it is subject to various biases. Second, analysis of inter- and intra-observer variability of the actual TRG classification was not conducted. Finally, during performance of the multivariate analysis for predicting TRG2–3, using potential clinical factors, the pathologic review was done using a specimen after CRT and radical surgery. We acknowledge that it may be better to conduct this procedure utilizing tissue biopsied pretreatment because CRT could alter the tumor biology. We wish this result to be understood and accepted as an encouragement to pose aggressive and appropriate questions regarding these issues and to gather the data with a universally accepted consensus. Further prospective studies using pretreatment tissue biopsies would be necessary to determine the predicting factors for unfavorable TRG in a pretreatment setting.

In conclusion, the TRG using AJCC criteria represents an independent and promising prognostic factor for long-term, disease-free survival in patients with rectal cancer treated with preoperative CRT. TRG may also represent a useful prognostic variable to individualize the prognosis and potentially direct the postoperative treatment of patients with resected rectal cancer who underwent preoperative CRT.

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