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Response Prediction after Neoadjuvant Chemotherapy for Colon Cancer Using CT Tumor Regression Grade: A Preliminary Study

대장암 환자의 수술 전 항암화학요법의 반응을 CT 종양퇴행등급을 이용한 반응 예측: 예비 연구

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Purpose To investigate whether CT-based tumor regression grade (ctTRG) can be used to predict the response to neoadjuvant chemotherapy (NAC) in colon cancer.

Materials and Methods A total of 53 patients were enrolled. Two radiologists independently assessed the ctTRG using the length, thickness, layer pattern, and luminal and extraluminal appearance of the tumor. Changes in tumor volume were also analyzed using the 3D Slicer software. We evaluated the association between pathologic TRG (pTRG) and ctTRG. Patients with Rödel's TRG of 2, 3, or 4 were classified as responders. In terms of predicting responder and pathologic complete remission (pCR), receiver operating characteristic was compared between ctTRG and tumor volume change.

Results There was a moderate correlation between ctTRG and pTRG (ρ = -0.540, p < 0.001), and the

interobserver agreement was substantial (weighted κ = 0.672). In the prediction of responder, there was no significant difference between ctTRG and volumetry (*Az* = 0.749, criterion: ctTRG ≤ 3 for ctTRG, *Az* = 0.794, criterion: ≤ -27.1% for volume, *p* = 0.53). Moreover, there was no significant difference between the two methods in predicting pCR (*p* = 0.447).

Conclusion ctTRG might predict the response to NAC in colon cancer. The diagnostic performance of ctTRG was comparable to that of CT volumetry.

Index terms Colonic Neoplasm; Multidetector Computed Tomography; Neoadjuvant Therapy

INTRODUCTION

Complete mesocolon excision with adjuvant chemotherapy is the standard treatment for patients with high-risk stage II and III colon cancer (1-3). Since the German Rectal Cancer Trial, patients with locally advanced rectal cancer (LARC) have been treated with neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (4). Landmark studies with strong evidence have demonstrated a reduction in the risk of disease recurrence over decades. However, despite the improved efficacy of adjuvant chemotherapy and NCRT, the risk of colorectal cancer recurrence cannot be avoided with current therapeutic strategies in 25%–30% of patients (5).

Recently, many researchers have focused on the use of neoadjuvant chemotherapy (NAC) for colon cancer treatment. The fluoropyrimidine oxaliplatin and targeted receptor preoperative therapy (FOxTROT) involving 1053 patients evaluated the effectiveness of NAC in colon cancer treatment and showed an improvement in the 2-year failure rate (hazard ratio = 0.77), 59% histological regression, and fewer positive resection margins (6). In addition, the UNICANCER-PRODIGE 23 trial for NAC with FOLFIRINOX and NCRT in patients with LARC demonstrated that the 3-year disease-free survival (DFS) improved by 7% in the NAC group compared to the standard treatment group (7). This neoadjuvant approach is based on the theory of earlier eradication of metastatic disease, fewer positive resection margins by downsizing the tumor, and reduction in tumor cell shedding during surgery by decreasing the tumor burden and improving patient compliance (8-11).

In terms of radiological imaging in NAC, accurate selection of the indicated patients and appropriate response assessment after NAC are essential to reduce the overtreatment of low-risk patients and prevent delayed surgery in poor responders (12). However, there has been no progress in response assessment after NAC beyond the Response Evaluation Criteria in Solid Tumors (RECIST) and TNM staging (13, 14). Not all patients with responsive tumors are allocated to the downstaging group. Although MRI-based tumor regression grade (TRG) is available for rectal cancer after NCRT, the histological regression after NAC can differ from that after NCRT (15). Radiologists cannot visualize the dark signal intensity of the fibrotic area representative of responsive tumors after NAC. Some studies have demonstrated that tumor volumetry is correlated with the response to chemotherapy and it has been proven to be a prognostic factor in several malignant tumor types (16-18). However, since this being time consuming, a novel image-based TRG system is required after NAC. We hypothesized that the

characteristics of length, thickness, layer pattern, and luminal and extraluminal appearance of tumors after NAC would allow us to distinguish responders from poor responders and devised a CT-based TRG (ctTRG) derived from these characteristics. Therefore, the purpose of our study was to investigate a preliminary result, namely, whether ctTRG is relevant for predicting the response in patients with colon cancer after NAC and whether it is better than tumor volumetry.

MATERIALS AND METHODS

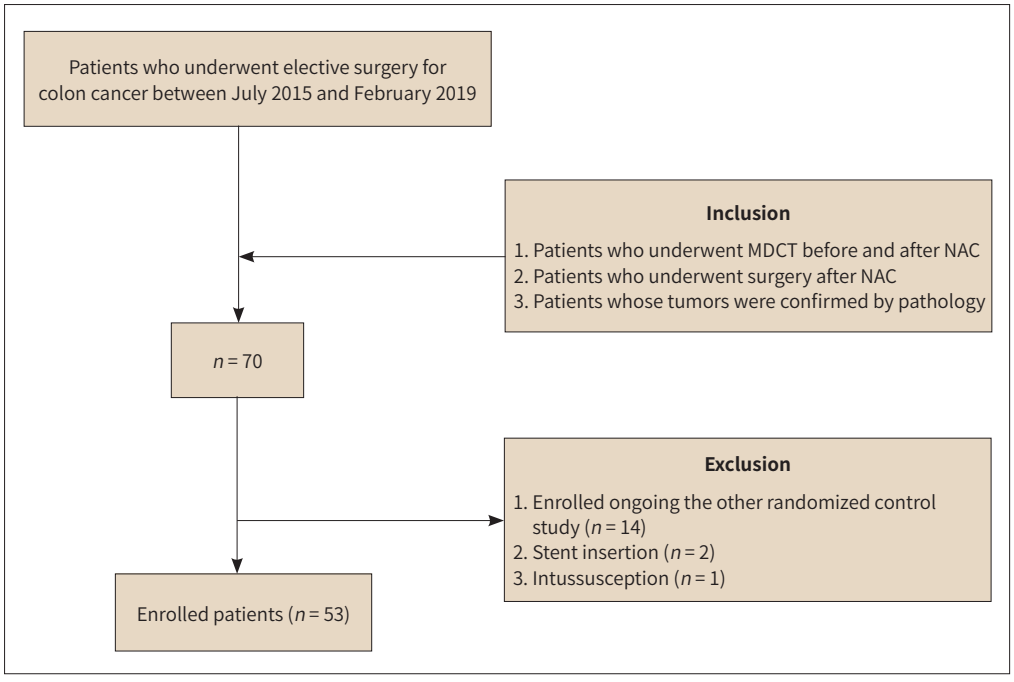
STUDY POPULATION

A total of 71 consecutive patients who underwent NAC for colon cancer at our institution between July 2015 and February 2019 were included. The study population was selected based on the following inclusion criteria: 1) patients who underwent CT before and after NAC, and 2) patients who underwent elective surgery at our institution after NAC. Of the 70 patients, 17 were excluded for the following reasons: 1) enrollment in ongoing randomized controlled trials (RCTs) (n = 14), 2) stents inserted into the colon (n = 2), and 3) intussusception (n = 1). Finally, 53 patients (male: female, 29:24; mean age ± standard deviation 60.0 ± 11.5 years) were enrolled (Fig. 1).

NEOADJUVANT CHEMOTHERAPY

NAC was administered through multidisciplinary team meetings during the study period. Based on the inclusion criteria suggested by our institution, patients who agreed to undergo treatment were administered NAC according to a previously defined protocol. The inclusion

Fig. 1. Flow chart of patient selection.



MDCT = multidetector computed tomography, NAC = neoadjuvant chemotherapy

criteria were as follows: radiologic T3/T4 and high risk features by CT scan (T3 with extramural depth of invasion > 5 mm, T3/T4 tumor equally or greater than 4 cm in longitudinal diameter), no metastasis on CT or PET, resectable tumor, or considered as potentially resectable after NAC Etc. The criteria for selecting patients were determined by colorectal surgeons, radiologists, hemato-oncologists, radiation oncologists, pathologists, and patients using a multidisciplinary team approach. The imaging criteria which were T3/T4 cancer with longitudinal diameter ≥ 4 cm, and T3cd (extramural depth of invasion > 5 mm) showed the highest reproducibility and the lowest overtreatment ratio each in a previous study (19, 20). The routine NAC protocol at our institution comprises four cycles of FOLFOX followed by surgery, and eight cycles of FOLFOX.

CT TECHNIQUE

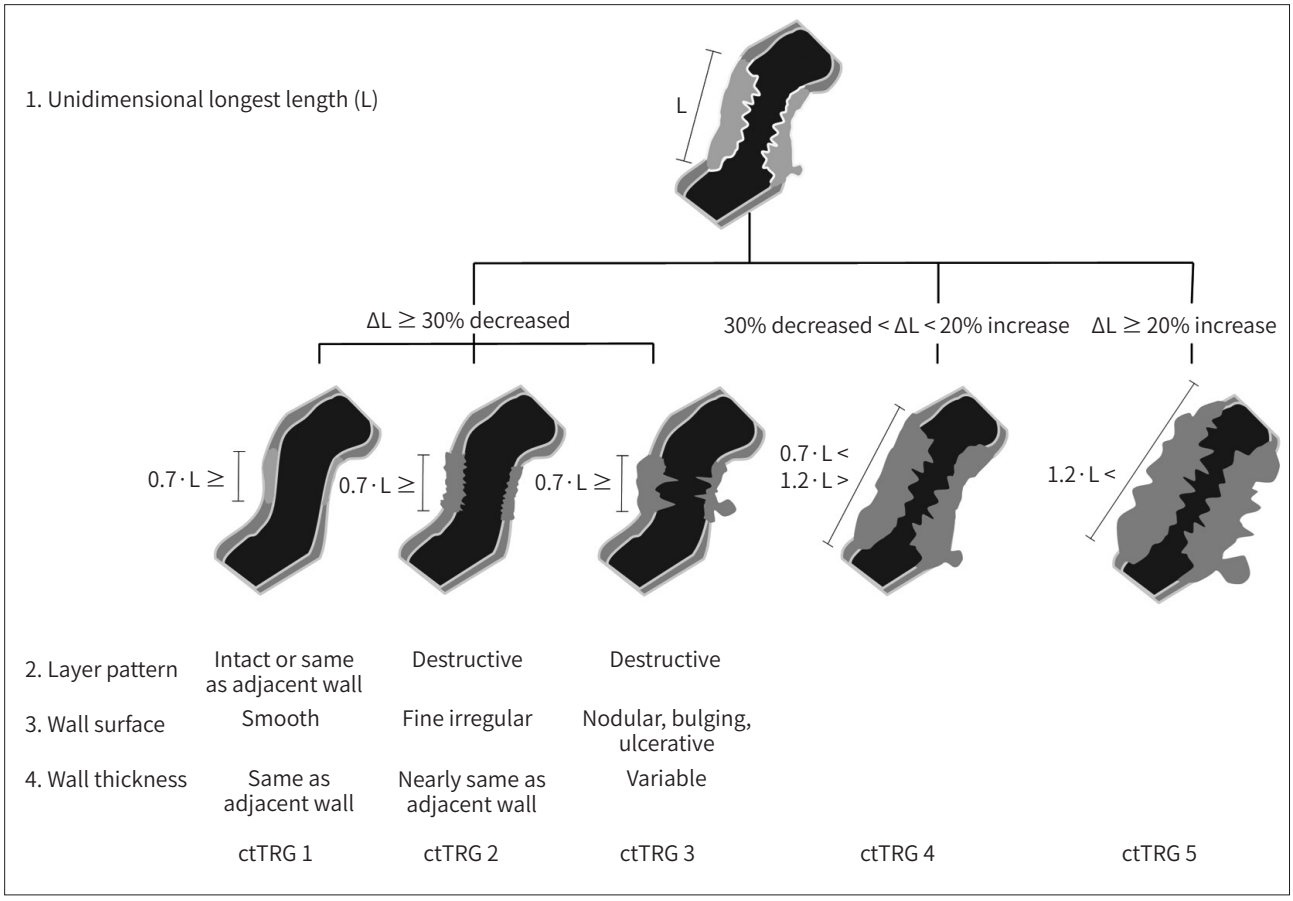
Most CT examinations before and after NAC were performed using multidetector CT scanners: Discovery 750 or LightSpeed VCT (GE Healthcare, Chicago, IL, USA) and Somatom Definition AS+ (Siemens Healthcare, Erlangen, Germany). All patients underwent single-portal venous-phase CT. The following scan parameters were used: detector collimation, 0.6–0.625 mm; pitch, 0.8–0.984; gantry rotation time, 0.5 seconds; 100 kVp, 130–300 effective mAs; and reconstruction slice thickness, 2–2.5 mm. Patients were administered 90–95 mL intravenous injection of nonionic contrast media (Iomeron® 300; Bracco Diagnostics) at a rate of 1.2–1.5 mL/s. CT images were reconstructed in the axial, coronal, and sagittal planes for all the patients.

IMAGE ANALYSIS AND DATA ACQUISITION

All CT images were independently reviewed by two board-certified radiologists (with 5 and 20 years of clinical experience in the interpretation of colon cancer staging) who were blinded to clinicopathological information. The two radiologists evaluated the following tumor parameters: unidimensional longest length (mm), wall layer pattern (intact or the same as the adjacent normal wall layer pattern vs. destructive), wall surface (smooth vs. fine irregular/spiculated vs. nodular/bulging/ulcerative), and wall thickness (the same as the adjacent normal wall thickness vs. nearly the same vs. variable). Both the luminal side and the mesocolic/peritoneal sidewall surfaces were considered during evaluation of the wall surface. The investigators assessed the regression grade of the tumors using these parameters.

The ctTRG was hypothesized as follows (Fig. 2): grade 1, decreases in the unidimensional longest length above 30%, intact or the same as the adjacent normal wall layer pattern, smooth wall surface, same as the adjacent normal wall thickness; grade 2, decrease in unidimensional longest length above 30%, destructive layer pattern, fine irregular/speculated wall surface, nearly same as adjacent normal wall thickness; grade 3, decrease in unidimensional longest length above 30%, destructive layer pattern, nodular/bulging or ulcerative wall surface, variable thickness; grade 4, increase in unidimensional longest length under 20% or decrease under 30%, destructive layer pattern, nodular/bulging or ulcerative wall surface, variable thickness; grade 5, increase in unidimensional longest length above 20%, destructive layer pattern; nodular/bulging or ulcerative wall surface; variable thickness (Fig. 3). Additionally, the investigators assessed the T category, including T3 subcategories (T3a, <1 mm; T3b, 1–5 mm; T3c, 5–15 mm; and T3d, > 15 mm), N category, and status of extramural venous in-

Fig. 2. Flow description and schematic representation of CT-based tumor regression grade.
For grade 1–3 tumors, the longest unidimensional length decreased by > 30%. Grade 1 tumors have the same adjacent wall layer pattern, smooth wall surface, and wall thickness as the adjacent walls. Grades 2 and 3 tumors exhibit destructive wall layer patterns. Grade 2 tumors have fine irregularities and nearly the same wall thickness as the adjacent walls. Grade 3 tumors have nodular, bulging, or ulcerative wall surfaces with variable wall thickness. The proportion of grade 4 tumors decreased by 30% or increased by 20%. The longest length of grade 5 tumors increased by > 20%.
ctTRG = CT-based tumor regression grade



vasion (EMVI) before and after NAC (20). Inter-reader discrepancies were resolved in the second session of a consensus review following the first session of an independent review.

For quantitative analysis, a radiology trainee (with 3 years of experience in abdominal CT) manually drew consecutive regions of interest along the border of the tumor throughout the entire tumor. The entire tumor volume (cm^3) and Hounsfield units (HU) before and after NAC were measured using segment statistics with 3D Slicer software (www.slicer.org) (Fig. 4). The accuracy of the estimation was improved using a function that automatically selects regions of equal tumor density. Errors in the automatically selected areas were manually corrected. In the absence of a tumor, the volume was measured as 0.

PATHOLOGIC TRG

All resected specimens were analyzed by an experienced pathologist with 12 years of clinical experience in interpreting colorectal cancer specimens, who was blinded to the patients' clinical information. Rödel's TRG was used as the reference standard, and the grading of re-

gression was recorded as follows: grade 0, no regression; grade 1, regression of < 25% of the tumor mass; grade 2, regression of 25%–50% of the tumor mass; grade 3, regression of > 50% of the tumor mass; and grade 4, complete remission (pCR). Five-year DFS rate was 86% (TRG 4), 75% (TRG 2 + 3), and 63% (TRG 0 + 1) (p = 0.006). pCR (grade 4) and intermediate pathologic response (grade 2 + 3) improved the 5-year DFS rate (21). Therefore, Rödel TRG 2, 3, and 4 were classified as responders.

Fig. 3. Examples of CT images and pathologic microscopic slides for each grade according to CT-based tumor regression grade.
Each figure on the left shows the tumors (white arrows) before chemotherapy, and those on the middle represent tumors (black arrows) after chemotherapy. Each figure in the right shows microscopic examination (haematoxylin and eosin stain, × 100).
A. Axial imaging shows circular wall thickening involving the sigmoid colon (left). After chemotherapy, the tumor almost disappeared, and the tumor wall layer is intact and smooth with the same thickness as the adjacent wall, thus reporting ctTRG 1 (middle). No viable tumor cells and only fibrosis is seen. Pathologist graded pTRG as 4 (right).
B. On coronal image, the tumor involves the cecum (left). After NAC, the tumor's length is decreased above 80%, wall layer is fine, regular, and slightly thick compared with adjacent wall, thus reporting ctTRG 2 (middle). A few tumor cells (white arrowhead) and inflammatory cells remain in submucosa and muscularis propria, thus confirming pTRG 3 (right).
C. Circumferential tumor with luminal narrowing in the sigmoid colon (left). The length of the tumor decreased above 30%, with a bulging contour and destroyed layer in the wall, thus reporting ctTRG 3 (middle). Dominant residual tumor cells (white arrowheads) observed with fibrosis in 26%–50% of the tumor mass, thus confirming pTRG 2 (right).
ctTRG = CT-based tumor regression grade, NAC = neoadjuvant chemotherapy, pTRG = pathologic tumor regression grade

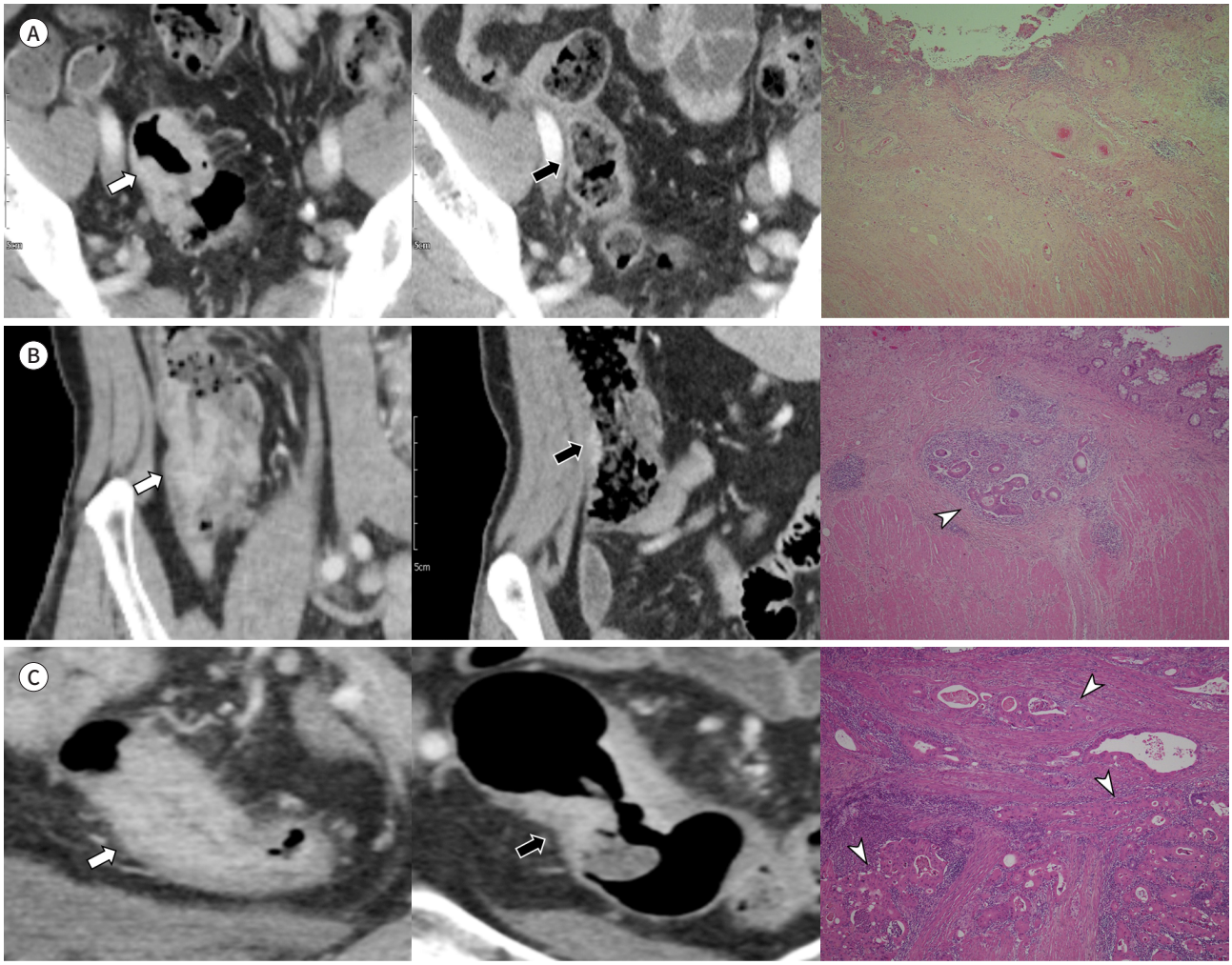


Fig. 3. Examples of CT images and pathologic microscopic slides for each grade according to CT-based tumor regression grade.
Each figure on the left shows the tumors (white arrows) before chemotherapy, and those on the middle represent tumors (black arrows) after chemotherapy. Each figure in the right shows microscopic examination (haematoxylin and eosin stain, × 100).
D. Despite NAC, tumor length is almost the same, thus reporting ctTRG 4 (left, middle). On the pathological slide, most of the tumor cells (white arrowheads) remain, thus confirming pTRG 1 (right).
E. Bulky mass in the sigmoid colon increased above 20% of the length, thus reporting ctTRG 5 and confirming pTRG 1.
ctTRG = CT-based tumor regression grade, NAC = neoadjuvant chemotherapy, pTRG = pathologic tumor regression grade

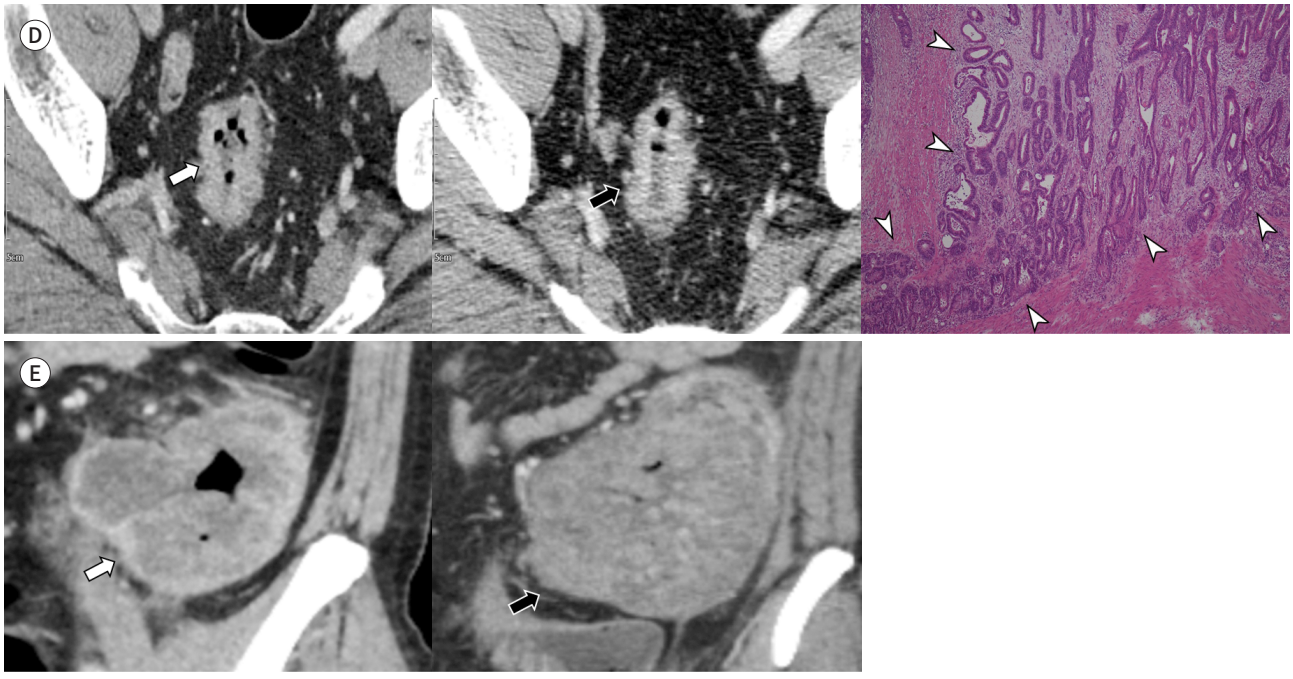
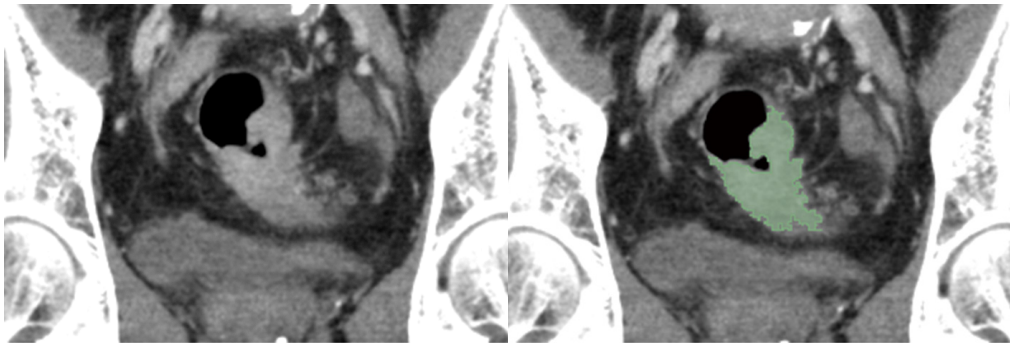


Fig. 4. Quantitative analysis for tumor volume and density. The tumors were automatically detected and segmented by 3D Slicer software. The radiologist inspected the result of the segmentation and adjusted it manually. However, the manual alteration was applied minimally. The software automatically calculated the volume and density of the volume.



STATISTICAL ANALYSIS

To evaluate the correlation between ctTRG and pathologic TRG (pTRG), we used Spearman's coefficient of rank correlation (strength of Spearman rank correlation coefficient: absolute rho value $\rho \geq 0.81$, very strong; $\rho = 0.80–0.61$, strong; $\rho = 0.60–0.41$, moderate; $\rho = 0.40–0.21$: weak; $\rho \leq 0.20$, negligible). To identify factors related to the pathological response, we performed univariate analysis with an independent *t*-test to evaluate continuous variables and

the chi-square test for categorical variables. Interobserver agreement was assessed using weighted κ statistics. The strength of weighted agreement was defined as follows: 1.00–0.81, almost perfect; 0.80–0.61, substantial; 0.60–0.41, moderate; 0.40–0.21, fair; and 0.20–0.00, slight. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis, and pairwise comparisons between ctTRG and tumor volume changes were performed. Statistical analyses were performed using MedCalc statistical software, version 20.006. Statistical significance was set at $p < 0.05$.

RESULTS

The characteristics of the 53 patients included in this study are presented in Table 1. With Rödel's TRG 2, 3, and 4 classified as responders, 30 (56.6%) patients were allocated to the re-

Table 1. Demographics of the Study Population

Characteristics	Number of Patients (*n* = 53)
Age, years (mean ± standard deviation)	60.0 ± 11.5
Sex	
Male	29 (54.7)
Female	24 (45.3)
Location	
Cecum	5 (9.4)
Ascending colon	12 (22.6)
Transverse colon	4 (7.5)
Descending colon	3 (5.7)
Sigmoid colon	29 (54.7)
ypT category	
pCR	4 (7.5)
T1	0 (0)
T2	5 (9.4)
T3	34 (64.2)
T4	10 (18.9)
ypN category	
N0	35 (66.1)
N1	13 (24.5)
N2	5 (9.4)
Pathologic TRG	
Grade 0	0 (0)
Grade 1	23 (43.4)
Grade 2	14 (26.4)
Grade 3	12 (22.6)
Grade 4	4 (7.5)

Values in parentheses are percentages. The pathological TRG was based on the grading system described by Rödel et al. (21).
pCR = pathological complete remission, TRG = tumor regression grade, yp = pathological staging when neoadjuvant therapy is given

sponder group and 23 (43.4%) to the poor responder group. Four (7.5%) and 49 (92.5%) patients were classified into the pCR and non-pCR groups, respectively.

RADIOLOGIC RESPONSE AND INTER-READER AGREEMENT

The mean value of the longest tumor length was 59.8 ± 17.4 cm before and 40.0 ± 21.2 cm after NAC. The mean whole tumor volume was 31.7 ± 26.7 cm^3 before and 27.8 ± 45.0 cm^3 after NAC. CT-based T staging before NAC was T2 in one (1.9%), T3 in 20 (37.7%), and T4 in 32 (60.4%) patients. After NAC, the CT-based T staging was T1 in 1 (1.9%), T2 in 4 (7.5%), T3 in 24 (45.3%), and T4 in 24 (45.3%) patients. The T stage was radiologically downstaged in 12 (22.7%) patients, pathologically downstaged in 32 (60.4%) patients, and upstaged in one (1.9%) patient.

In terms of the interobserver agreement of ctTRG, a substantial agreement was observed (weighted κ = 0.672, 95% confidence interval [CI] = 0.493, 0.852).

CORRELATION BETWEEN ctTRG AND pTRG

Of the 30 patients with responsive tumors based on CT (ctTRG 1–3), 24 (80%) showed pCR or intermediate pathologic tumor regression (pTRG 2–4), and the remaining 6 patients (20%) were classified as having poor regression (pTRG 0–1). Among the 23 patients with a predicted poor response (ctTRG 4–5), 17 (73.9%) patients were confirmed to have pTRG 1, whereas 5 (21.7%) and 1 (4.3%) patient showed a pTRG of 2 and 3, respectively (Table 2). Overall, there was a moderate correlation between ctTRG and pTRG (ρ = -0.540, $p < 0.001$).

IMAGING FEATURES OF RESPONDERS AND POOR RESPONDERS

The imaging features analyzed after NAC are summarized in Table 3. EMVI, ctTRG, and tumor volume changes were significantly different between the two groups. However, the predicted T stage after NAC (ycT category), predicted N stage after NAC (ycN category), and tumor HU changes were not statistically significant.

DIAGNOSTIC PERFORMANCE OF ctTRG

Diagnostic accuracies of ctTRG and tumor volume change (area under the ROC curve) for predicting response were 0.749 (sensitivity 80.0%, specificity 73.9%, optimal cut-off criterion:

Table 2. Comparison between Pathologic TRG and ctTRG

ctTRG	Pathologic TRG					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Grade 1	0	0	0	0	2	2 (3.8)
Grade 2	0	2	1	2	1	6 (11.3)
Grade 3	0	4	8	9	1	22 (41.5)
Grade 4	0	12	3	0	0	15 (28.3)
Grade 5	0	5	2	1	0	8 (15.1)
Total	0 (0)	23 (43.4)	14 (26.4)	12 (22.6)	4 (7.5)	53 (100)

Values in parentheses are percentages. The pathological TRG was based on the grading system described by Rödel et al. (21).
ctTRG = CT-based tumor regression grade, TRG = tumor regression grade

Table 3. Imaging Features of Responders and Poor Responders

Characteristics	Responder	Poor Responder	*p*-Value
Age, years	60.1 ± 13.0	60.6 ± 9.5	0.869
Sex			0.435
Male	15 (51.7)	14 (48.3)	
Female	15 (57.7)	9 (42.3)	
ycT category*			0.060
≤ T3b	17 (70.8)	7 (29.2)	
≥ T3c	13 (44.8)	16 (55.2)	
ycN category			0.080
N0	15 (71.4)	6 (28.6)	
≥ N1/N2	15 (46.9)	17 (53.1)	
EMVIpost			0.048
Absent	20 (69)	9 (31)	
Present	10 (41.7)	14 (58.3)	
ctTRG			< 0.001
≤ Grade 3	24 (80.0)	6 (20.0)	
≥ Grade 4	6 (26.1)	17 (73.9)	
Volume change	-45.2 ± 8.8	8.6 ± 17.5	0.010
HU change	-15.5 ± 4.2	-18.8 ± 3.6	0.436

Values in parentheses are percentages.
*Extramural depth of invasion >5 mm (≥ T3c) is a potential image-based criterion for a high-risk T category (20).
ctTRG = CT-based tumor regression grade, EMVIpost = extramural venous invasion after neoadjuvant chemotherapy, HU = Hounsfield units

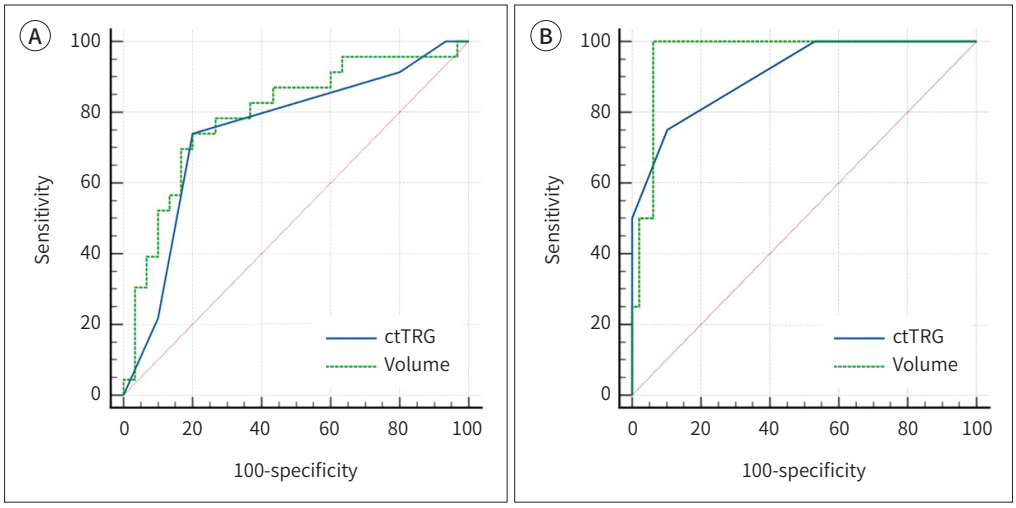
ctTRG ≤ 3, 95% CI: 0.661, 0.893) and 0.794 (sensitivity 80.0%, specificity 73.9%, optimal cut-off criterion: ≤ -27.1%, 95% CI: 0.610, 0.858), respectively (Fig. 5A). There was no significant difference in diagnostic accuracy between ctTRG and tumor volume change ($p = 0.530$).

In terms of predicting pCR, the diagnostic accuracies of ctTRG and tumor volume change were 0.908 (sensitivity, 75.0%, specificity 89.8%; optimal cut-off criterion: ctTRG ≤ 2, 95% CI: 0.797, 0.970) and 0.964 (sensitivity 100%, specificity 93.9%, optimal cut-off criterion: ≤ -80.1%, 95% CI: 0.890, 0.996), respectively (Fig. 5B). The difference in diagnostic accuracy between ctTRGs and changes in tumor volume was not significant ($p = 0.447$).

DISCUSSION

In the present study, we evaluated the relationship between the hypothesized ctTRGs and pTRG. Our results showed a significant correlation between ctTRG and pTRG, indicating that the better the response to ctTRG, the better the response to pathological tumor specimens. In addition, our study demonstrated that the interobserver agreement of ctTRG was acceptable, and a substantial agreement was reached therein. These results suggest the potential usefulness of the hypothesized ctTRGs as an additional imaging method for predicting the response of patients with colon cancer after NAC. For example, RECIST, a one-dimensional

Fig. 5. ROC curves of CT volumetry and tumor regression grade by CT to predict responder, pCR of colon cancer.
A. To predict responder, the area under the ROC curve (0.794) of CT volumetry is not significantly larger than that (0.749) of ctTRG (p = 0.53).
B. To predict pCR, the area under the curve value (0.964) of CT volumetry is greater than that (0.908) of ctTRG; however, the difference is not significant (p = 0.45).
ctTRG = CT-based tumor regression grade, pCR = pathological complete remission, ROC = receiver operating characteristic



measurement of the longest tumor length, may be sufficient for assessing changes in solid tumors (22, 23). In contrast, colon cancer is neither spherical nor symmetrical. Hence, regression grading using the longest tumor length alone may not be accurate for hollow viscus tumors (24, 25). Particularly, changes in wall thickness based on CT have been used previously to evaluate the response of gastric cancer to NAC (26). In addition, the three-tiered response regression schema for colonoscopy, which has been used in the response assessment of LARC to NCRT, is similar to the surface morphology adopted in the ctTRG (27, 28). Therefore, other parameters, such as wall thickness, layer pattern, and surface morphology, can be helpful in augmenting the predictability of the response.

Using a five-point grading system, we evaluated whether ctTRG could be used as a significant predictor of the pathological response to chemotherapy, including responders and complete remission. When ctTRG $\leq$ 3 was used as the cut-off criterion for discriminating responders from poor responder groups, the sensitivity and specificity were 80.0% and 73.9%, respectively. In addition, when ctTRG $\leq$ 2 was used as the cutoff criterion for differentiating pCR and non-pCR groups, the sensitivity and specificity were 75.0% and 89.8%, respectively. Based on these results, ctTRG after NAC can predict responders and complete remission in patients with colon cancer. This grading system might affect treatment plans (i.e., NAC duration and treatment methods, such as surgery or active surveillance) in the future. A watch-and-wait strategy or postponed surgery can be implemented as an option for patients with a pCR who receive NAC for rectal cancer (29). Similarly, in the complete remission group, we may offer a watch-and-wait strategy for patients with colon cancer as a treatment option, or early surgery may be an option for responders who have a high complication risk. The ctTRG system showed that indirect prognostic information may represent a radiological marker for

guiding patients after neoadjuvant treatment. Despite these promising results, it is important to note that our study was a preliminary study performed at a single institution, and further validation is required accordingly.

This study also demonstrated that the diagnostic accuracy of ctTRG in predicting responders and complete remission was comparable to that of CT volumetry. Several studies have demonstrated that tumor volumetry is correlated with response to chemotherapy, and it has been proven to be a prognostic factor in several malignant tumor types (16). Arredondo et al. (17) reported a significant relationship between tumor volume change measured using CT and pathological regression grade in locally advanced colon cancer after NAC. Martens et al. (18) reported that the most promising cut-off criterion for predicting pathological complete remission (ypT0) was a volume reduction from 80.0% to 86.6% in LARC after NCRT. This cut-off criterion is consistent with our results. However, our findings indicate that this grading system can be easily applied in daily practice. Volume measurement is time consuming since it requires manual tracing of lesion boundaries. Therefore, the ctTRG is a simple method for predicting responses.

This study had several limitations. First, the number of enrolled patients was small, since NAC is not the current standard treatment for colon cancer; therefore, only a small number of patients who agreed to receive NAC were included in this study. Owing to the limitations of the standard treatments for colon cancer, researchers have focused on NAC. Some trials, such as the UNICANCER-PRODIGE 23 trial, have demonstrated that NAC improves survival (7). Similarly, many patients have been enrolled in RCTs at our institution to evaluate the effectiveness of NAC (19). Large-scale studies may be possible after completion of RCTs. Second, the study design was retrospective, and the reference standard was pTRG. There may be an issue related to the pTRG in terms of the inherent limitations of sampling error. It would be worthwhile to study whether ctTRGs show prognostic stratification in RCTs. Third, ctTRG was assessed using routine abdominopelvic CT. Collapsed bowel or abundant feces may interfere with the evaluation by obscuring the tumor contour. To augment the accuracy of the ctTRGs, a combination of other tests would be helpful. For rectal cancer, a combination of MRI and endoscopy, which can reduce false diagnoses, is the most favorable approach for achieving pCR (30). In addition, CT colonoscopy with bowel preparation, instead of conventional abdominal CT, may be helpful for evaluating ctTRGs. Additional investigations regarding the combination of other methods are required to confirm the accuracy of bowel evaluation. Finally, the standard pathologic response to NAC is debatable. The standard was decided since Rödel's TRG 2+3 and 4 improved 5-year DFS (21). However, regression of less than 25% of the tumor (pTRG 2) may be a gray zone. When only Rödel's TRG 3, and 4 are classified as responders, the Spearman's coefficient of rank correlation (ρ) is -0.475 ($p \leq 0.001$, 95% CI; -0.061–0.235) and the strength of correlation is moderate. This finding is similar to previous results when TRG 2 was classified as a responder. The diagnostic accuracy is 0.784 (sensitivity 93.8%, specificity 59.5, criterion ≤ 3, 95% CI 0.649–0.885) when TRG 2 is a poor responder. These results indicate that the results are preserved when the standards are stricter.

Rodel's TRG was used as a reference standard to indirectly evaluate survival. Further investigations are needed to determine whether ctTRG can stratify the patient's risk, as mrTRG does in rectal cancer. This makes it possible for imaging markers to provide information about the extent of resection, the interval between follow-ups, and whether the drug must be

changed for the patient. Since a strict definition of ctTRGs is required, endoscopic findings, such as residual superficial ulceration, irregularity, or nodules in the bowel wall, were considered in this study (31). For better interobserver agreement, the longest diameter of the tumor was measured to determine the ctTRG instead of the length along the luminal center of the colon. However, further studies are required to determine which method reflects the response to NAC more accurately.

The prediction of pCR using CT may pose a potential risk. In cases of false-positive results when diagnosed with ctTRG1, patients may not receive adequate treatment. However, when determining the duration of NAC or extent of resection in patients with comorbidities, ctTRG may provide options. For example, for patients who require en bloc resection or extended colectomy for locally advanced cancer, standard resection or even segmental resection may be an option when evaluated with ctTRG 1 or 2. Since wide resection may be associated with high perioperative morbidity (32), it is necessary to consider the risks and benefits when radiologists diagnose ctTRG 1. Therefore, a multidisciplinary approach is important for the proper use of ctTRG.

In conclusion, our study demonstrated that ctTRG after NAC may predict the response and pCR in patients with colon cancer. The diagnostic performance of ctTRGs was comparable to that of CT volumetry. However, this preliminary study has several limitations, and further studies are required accordingly.

Author Contributions

Conceptualization, C.S.H., K.S.H., K.G.C., R.H.; data curation, C.S.H., O.H.S., C.G.; formal analysis, C.S.H., O.H.S., S.A.N., L.S.M.; funding acquisition, C.S.H.; investigation, C.S.H., L.S.M.; methodology, J.H.J., C.S.H., S.A.N., P.B.G., K.S.H., K.G.C., C.G.; project administration, C.S.H., L.S.M., K.S.H., K.G.C., R.H.; resources, S.A.N., P.B.G., C.G.; software, J.H.J., P.B.G.; supervision, S.A.N., P.B.G., L.S.M., K.S.H., K.G.C., R.H., C.G.; validation, J.H.J., S.A.N., K.S.H., R.H.; visualization, J.H.J.; writing—original draft, J.H.J.; and writing—review & editing, J.H.J.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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대장암 환자의 수술 전 항암화학요법의 반응을 CT 종양퇴행등급을 이용한 반응 예측: 예비 연구

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목적 대장암 환자에서 선행화학요법(neoadjuvant chemotherapy; 이하 NAC)의 반응을 CT를 이용한 종양퇴행등급(CT-based tumor regression grade; 이하 ctTRG)으로 예측할 수 있는지를 알아보고자 한 연구이다.

대상과 방법 총 53명을 대상으로 NAC 전후 종양의 길이, 두께, 장벽의 패턴과 모양으로 ctTRG를 정하고 부피도 측정했다. 병리 종양퇴행등급(pathologic TRG; 이하 pTRG)을 반응평가의 기준으로 ctTRG와 연관성을 평가했다. Rödel's TRG 2, 3 그리고 4를 반응군으로 분류하였다. ctTRG와 부피변화로 반응군 및 병리완전퇴행(pathologic complete remission; 이하 pCR)을 예측하는 성능을 비교하였다.

결과 ctTRG와 pTRG는 moderate의 연관성을 보였다(ρ = -0.540). 관찰자간 신뢰도는substantial으로 보였다(weighted κ = 0.672). 반응군을 예측하는데 ctTRG와 volume 변화의 성능은 유의미한 차이를 보이지 않았다(ctTRG의 *Az* = 0.749, 반응기준: ctTRG ≤ 3, volume 변화의 *Az* = 0.794, 반응기준: ≤ -27.1%, *p* = 0.53). pCR을 예측하는 두 방법 간의 성능도 차이가 없었다(*p* = 0.447).

결론 ctTRG는 대장암에 NAC 후 반응을 예측할 수 있었고, 그 성능은 종양부피변화 방법과 차이가 없었다.

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