The Evaluation of Transmural Healing by Low-dose Computed Tomography Enterography in Patients with Crohn’s Disease

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Abstract:
Objective Transmural healing (TH) has been attracting attention as a new therapeutic target for Crohn’s disease, but there are few clinical data on TH in Japan. We introduced low-dose computed tomography enterography (CTE) as a monitoring method for Crohn’s disease and retrospectively investigated the accuracy of evaluating TH by CTE.

Methods Among Crohn’s disease patients who underwent low-dose CTE at our hospital from January 2009 to March 2021, 122 patients who underwent colonoscopy or balloon endoscopy within 2 weeks were included. Results of radiological and endoscopic examinations were reviewed independently by radiologists and gastrointestinal endoscopists, respectively. The concordance rate of the diagnosis between CTE and endoscopy was evaluated.

Results Twenty-six patients (21.3%) achieved TH, and the kappa index was 0.743. On comparing the TH and non-TH groups, the Crohn’s disease activity index (p=0.02), endoscopic healing rate (p<0.001), serum albumin (p=0.043), and serum C-reactive protein level (p=0.018) showed significant differences. Among the 122 patients, 69 (56.5%) showed concordance between the diagnosis of CTE and endoscopy, and 22 (18.0%) achieved both TH and endoscopic healing.

Conclusion This study provides real-world data on Crohn’s disease evaluated with low-dose CTE in Japan. The TH criterion used in this study has a high kappa coefficient and can be used reproducibly in many institutions.

Key words: Crohn’s disease, CT enterography, transmural healing, endoscopic healing

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Introduction

Crohn’s disease (CD) is a chronic inflammatory bowel disease of unknown etiology that affects the entire gastrointestinal tract (1). The therapeutic goal in CD is to reduce irreversible intestinal damage caused by repeated relapses and to improve the long-term prognosis by avoiding surgery (2-4). Deep remission is a state in which clinical remission and endoscopic healing (EH) have been achieved and is reported to be associated with a good outcome (4).

In recent years, the concept of “treat to target” has been emphasized, wherein specific targets are set for treatment (5). The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) statement states that EH on ileocolonoscopy is the recommended target and that cross-
sectional imaging (CSI), which refers to computed tomography (CT), magnetic resonance imaging (MRI), and abdominal sonography, is an indicator of therapeutic efficacy in patients who cannot be adequately evaluated with ileocolonoscopy (6). STRIDE-II divides therapeutic targets into short-, medium-, and long-term targets, and EH was identified as a long-term target (7). However, because of the transmural nature of the inflammation in CD, the concept of transmural healing (TH) has recently received focused, and its association with the prognosis has been reported (8-10), but TH has not been defined as a formal target in STRIDE-II because of insufficient evidence.

CT enterography (CTE) is reportedly useful for evaluating TH, but clinical data on this method in Japan are scarce (11, 12). However, Japan has the most CT scanners in the world, and progress has been made in CT scanner technology to maintain a high image quality while reducing radiation exposure (13).

We herein report real-world data on the evaluation of TH for CD using low-dose CTE in Japan.

**Patients**

Between January 2009 and March 2021, 317 patients with CD who visited Yamaguchi University Hospital and underwent CTE were retrospectively selected from the medical records. Patients who did not receive polyethylene glycol solution (PEG; Niflec®, EA Pharma, Tokyo, Japan) as an oral contrast agent, who did not undergo low-dose CTE, who did not undergo gastrointestinal endoscopy at our hospital, and who underwent per oral double-balloon endoscopy were excluded from the study. We ultimately enrolled 122 patients (Fig. 1).

All patients underwent blood tests and ileocolonoscopy or balloon endoscopy within two weeks of CTE. The diagnosis of CD was based on the clinical symptoms and endoscopic and histopathological findings (14, 15). The date of birth, sex, date of the diagnosis of CD, location and behavior as defined by the Montreal classification (16), and current medications were recorded. Clinical activity was assessed with the Crohn’s disease activity index (CDAI). Clinical remission was defined as a CDAI score of <150. Serum levels of albumin and C-reactive protein (CRP) were also measured. Fecal calprotectin and the serum level of leucine-rich α2-glycoprotein (LRG) were also measured in some patients.

All researchers involved in this study conducted the study in accordance the World Medical Association’s Declaration of Helsinki (1964, and its later amendments). The study was reviewed and approved by the Ethics Committee on Human Research at Yamaguchi University Hospital.

**CTE evaluations**

With reference to the report by Huprich and Fletcher (17), CTE was performed with 1,000-1,800 mL of PEG that was divided into 4 doses and administered orally in 1 h. The patients were then immediately examined with a CT scanner [SOMATOM Sensation 64, SOMATOM Definition, SOMATOM Force (Siemens Healthcare, Erlangen, Germany); Optima CT660 (GE Healthcare, Milwaukee, USA); or Aquilion Precision (Canon Medical Systems, Otawara, Japan)]. We performed low-dose CTE, which is associated with a 50% reduction in radiation exposure compared to standard-dose CTE. In 2020, the Diagnostic Reference Levels in Japan (Ja-
pan DRLs 2020) were established as tools for optimizing medical radiation protection in the diagnostic field. The CT dose index volume (CTDI vol) and dose length product (DLP) are used as indicators of the radiation dose, and these values are 18 mGy and 880 mGy·cm for CT of the abdomen and pelvis in adults, respectively (18). The contrast medium was injected intravenously over 30 seconds, and 1 phase of imaging was performed 50 seconds after the start of injection (19). Plain CT was not performed. The slice thickness was 0.6-1.25 mm and the reconstruction interval was 1-2 mm.

The CTE images were interpreted using horizontal and coronal sections. Two experienced radiologists (M.T. and H.O., blinded to the clinical course of patients) individually judged TH or transmural inflammation. The level of agreement of the two radiologists was evaluated using the kappa index. If transmural inflammation was present, the location of the most severely affected area (index lesion) was also determined. Postoperative anastomoses were excluded from the assessment of inflammation. Another radiologist (M.H.) made the final judgment in case of disagreement between the two radiologists.

TH on CTE was defined as the absence of the following findings with reference to the report of Noh et al. (10): mural hyperenhancement, abnormal mural thickness (≥3 mm), increased mesenteric adipose tissue concentration, and fistula or abscess, which are findings of active inflammation in CTE (8, 20). The site of the index lesion was classified as the ileum and the terminal ileum, with the ileum within 10 cm of the ileocecal valve and lesions at the ileocecal valve included in the terminal ileum. The colon was classified into sections of the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

**Endoscopic evaluations**

Ileocolonoscopy was performed with a CF-H260AZI, CF-Q260DI, PCF-Q260AZI, PCF-PQ260I, or CF-HQ290AZI colonoscope (Olympus, Tokyo, Japan). For balloon endoscopy, an EN-450T, EN-480T, EN-580T, or EN-580XP enteroscope (Fujifilm, Tokyo, Japan) or SIF-Q260 (Olympus) enteroscope was used. Endoscopy was performed by experienced gastroenterologists, and all endoscopic images were stored in the image storage system of our center. All endoscopic images were individually evaluated by K.H. and A.G. (with more than 10 years of experience in gastrointestinal endoscopy and blinded to the clinical course of the patients) for the index lesion and findings. Postoperative anastomoses were excluded from the assessment of inflammation. In case of disagreement on endoscopic findings, agreement was reached after a thorough discussion. For endoscopic findings, the size of the ulcer (0: no ulcer, 1: aphtha-like ulcer 0.1-0.5 cm in size, 2: ulcer 0.5-2 cm in size, 3: large ulcer >2 cm) was determined among the evaluation items of the Simple Endoscopic Score for Crohn’s Disease, and the scores were listed as EH grades. EH was defined as 0 (no ulcer) or 1 (aphtha-like ulcer).

### Comparing the CTE and endoscopic findings

When endoscopy showed an EH grade ≥2, the site of the index lesion on endoscopy was estimated separately by authors S.H. and H.F. by referring to the medical record. If the judgment was different, a final judgment was made after thorough discussion. The concordance rate of the diagnosis between CTE and endoscopy was calculated, and the details of any differences between CTE and endoscopy were described.

### Statistical analyses

Continuous variables are summarized as the mean±standard deviation and categorical variables as numbers and percentages. For patient background factors in each diagnostic group, we used the unpaired t-test or Mann-Whitney U test for continuous variables and the χ² test or Fisher’s exact test for categorical variables. A receiver operating characteristic (ROC) analysis was applied to determine the optimal cut-off value for determining TH. A multiple regression analysis was also performed. Differences were considered statistically significant at a value of p<0.05. The kappa index was used for inter-rater agreement. The percentages of agreement were as follows: 0.01-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect or perfect agreement. All statistical analyses were performed with EZR, which is for R (under the GNU General Public License) (21). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

### Results

#### Patients

In total, 122 patients with an average age of 35.7 years old were included in the study. Only 40 of the 122 patients (32.8%) were women. The mean disease duration was 8.7 years. Thirty-five patients (28.7%) had structuring (B2) behaviors, and 4 patients (3.3%) had penetrating (B3) behaviors. Fifty-four patients (44.3%) had undergone major abdominal surgery, and 85 (69.7%) were using anti-tumor necrosis factor (TNF)-α agents (Table 1). The CTDI vol and DLP of the abdominal to pelvic region were 6.02±1.94 mGy and 332±145.3 mGy·cm, respectively.

#### Comparing the clinical background between the TH and non-TH groups

Twenty-six patients (21.3%) achieved TH, and the kappa index was 0.743, which corresponded to substantial agreement. The index lesion location in patients who did not achieve TH was the ileum in 7 patients (7.3%), terminal ileum in 41 patients (42.7%), cecum in 4 patients (4.2%), ascending colon in 3 patients (3.1%), transverse colon in 1 patient (1.0%), descending colon in 5 patients (5.2%), sigmoid...
Table 1. Clinical Background in the TH and Non-TH Groups.

| Factor                              | All patients | TH            | No TH           | p value |
|-------------------------------------|--------------|---------------|-----------------|---------|
| n (%)                               | 122 (100)    | 26 (21.3)     | 96 (78.7)       |         |
| Age (mean±SD, yrs)                  | 35.70±12.33  | 35.96±11.71   | 35.61±12.55     | 0.899   |
| Age at CD diagnosis (mean±SD, yrs) | 27.02±10.71  | 26.00±9.60    | 27.29±11.02     | 0.587   |
| Disease duration (mean±SD, yrs)     | 8.70±9.11    | 10.08±9.49    | 8.32±9.01       | 0.386   |
| Sex (%)                             | Male         | 82 (61.2)     | 18 (69.2)       | 1.00    |
|                                     | Female       | 40 (32.8)     | 8 (30.8)        | 0.122   |
| Montreal location (%)               | Ileal (L1)   | 25 (20.5)     | 8 (30.8)        | 1.00    |
|                                     | Colonic (L2) | 17 (13.9)     | 1 (3.8)         | 0.122   |
|                                     | Ileocolonic (L3) | 80 (65.6) | 17 (65.4)      | 1.00    |
| Montreal behavior (%)               | Non-penetrating (B1) | 83 (68.0) | 23 (88.5)       | 0.042   |
|                                     | Strictures (B2) | 35 (28.7) | 3 (11.5)       | 1.00    |
|                                     | Penetrating (B3) | 4 (3.3) | 0 (0.0)        | 1.00    |
| Previous major abdominal surgery (%)| No           | 68 (55.7)     | 9 (34.6)        | 0.025   |
|                                     | Yes          | 54 (44.3)     | 17 (65.4)       | 1.00    |
| Smoking status at diagnosis (%)     | No           | 102 (83.6)    | 21 (80.8)       | 0.765   |
|                                     | Yes          | 20 (16.4)     | 5 (19.2)        | 1.00    |
| Total colonoscopy (%)               | No           | 22 (18.0)     | 2 (7.7)         | 0.157   |
|                                     | Yes          | 100 (82.0)    | 24 (92.3)       | 1.00    |
| Current medication (%)              | No treatment | 12 (9.8)      | 1 (3.8)         | 0.227   |
|                                     | Immunomodulators | 25 (20.5) | 4 (15.4)       | 1.00    |
|                                     | Infliximab    | 19 (15.6)     | 6 (23.1)        | 1.00    |
|                                     | Adalimumab    | 57 (46.7)     | 11 (42.3)       | 1.00    |
|                                     | Ustekinumab   | 9 (7.4)       | 4 (15.4)        | 1.00    |
| CDAI (mean±SD)                      | 100.30±85.18 | 65.88±64.25   | 109.62±88.00    | 0.020   |
| Serum albumin (mean±SD, g/dL)       | 3.90±0.58    | 4.10±0.38     | 3.84±0.62       | 0.043   |
| Serum CRP (mean±SD, mg/dL)          | 0.65±0.14    | 0.23±0.58     | 0.77±1.10       | 0.018   |
| Fecal calprotectin (mean±SD, mg/kg) | 1,378.52±1,583.53 | 127.12±121.09 | 1,606.05±1,621.91 | 0.086 |
| LRG (mean±SD, μg/mL)                | 23.78±12.63  | 16.50±12.02   | 25.86±12.88     | 0.391   |

CD: Crohn’s disease, CDAI: Crohn’s disease activity index, LRG: leucine-rich α2-glycoprotein, CRP: C-reactive protein, TH: transmural healing

colon in 12 patients (12.5%), and the rectum in 23 patients (24.0%). On comparing the TH and non-TH groups, significant differences were noted in the CDAI (65.88±64.25 vs. 109.62±88.00; p=0.02), EH rate (84.6% vs. 40.6%; p<0.001), serum albumin (4.10±0.38 vs. 3.84±0.62 g/dL; p=0.043), and serum CRP level (0.23±0.58 vs. 0.77±1.10 mg/dL; p=0.018) (Table 1, 2). Fecal calprotectin was measured in 26 patients, and LRG was measured in 9 patients. No statistically significant differences were found in either biomarker (Table 1).

Results of an ROC curve analysis

The ROC curve of the CDAI for determining TH showed a cut-off value of 64.0 with a sensitivity of 65.4%, specificity of 64.6%, and area under the ROC curve (AUROC) of 0.665 [95% confidence interval (CI), 0.546-0.783]. In the ROC curve of serum albumin for determination of TH, the cut-off value was 3.7 g/dL with a sensitivity of 92.3%, specificity of 34.4%, and AUROC value of 0.619 (95% CI, 0.513-0.725). In the ROC curve of serum CRP for TH determination, the cut-off value was 0.14 mg/dL with a sensitivity of 73.1%, specificity of 61.5%, and AUROC of 0.700 (95% CI, 0.594-0.806) (Fig. 2).

Results of a multivariate analysis

The factors associated with TH were EH, serum albumin, serum CRP, and CDAI in the univariate analysis, but only EH was associated with TH in the multivariate analysis (Table 3).

Concordance rate of the diagnosis between CTE and endoscopy

Sixty-nine of the 122 patients (56.5%) showed concordance between the diagnosis of CTE and endoscopy, 22 (18.0%) achieved both TH and EH, and 47 (38.5%) had a concordant index lesion. Among the 122 patients, 53 (43.5%) had an inconsistent diagnosis, 39 (32.0%) had inflammation only on CTE, 10 (8.2%) had different index lesions on CTE and endoscopy, and 4 (3.3%) had inflammation only on endoscopy (Fig. 3, 4). In 8 of the 39 patients in whom inflammation was detected only by CTE, the endoscope was not able to reach the lesion detected by CTE. In 5 of the 10 patients whose index lesions differed between CTE and endoscopy, the endoscope was not able to reach the lesion detected by CTE. In two of the four patients in whom inflammation was detected only by endoscopy, ulcers...
Figure 2. Receiver operating characteristic curve analyses of CDAI, serum albumin, and serum CRP values for predicting transmural healing. CDAI: Crohn’s disease activity index, CRP: C-reactive protein, CI: confidence interval

Table 2. CTE and Endoscopic Findings in the TH and Non-TH Groups.

| Factor                                           | Groups          | All patients | TH | No TH | p value |
|--------------------------------------------------|-----------------|--------------|----|-------|---------|
| EH (%)                                           | No              | 61 (50.0)    | 4  | 15.4  | <0.001  |
|                                                 | Yes             | 61 (50.0)    | 22 | 84.6  | 39 (40.6)         |
| EH grade (%)                                     | 0               | 38 (31.1)    | 11 | 42.3  | 27 (28.1) <0.001 |
|                                                 | 1               | 23 (18.9)    | 11 | 42.3  | 12 (12.5)         |
|                                                 | 2               | 31 (25.4)    | 2  | 7.7   | 29 (30.2)         |
|                                                 | 3               | 30 (24.6)    | 2  | 7.7   | 28 (29.2)         |
| Mural hyperenhancement (%)                       | No              | 28 (23.0)    | 26 | 100   | 2 (2.1)  |
|                                                 | Yes             | 94 (77.0)    | 0  | 0.0   | 94 (97.9)         |
| Abnormal mural thickness (%)                    | No              | 118 (96.7)   | 26 | 100   | 92 (95.8)         |
|                                                 | Yes             | 4 (3.3)      | 0  | 0.0   | 4 (4.2)  |
| Increased mesenteric lipid concentration (%)    | No              | 96 (78.7)    | 26 | 100   | 70 (72.9)         |
|                                                 | Yes             | 24 (19.7)    | 0  | 0.0   | 24 (25.0)         |
| Fistula or abscess (%)                          | No              | 38 (31.1)    | 26 | 100   | 12 (12.5)         |
|                                                 | Yes             | 84 (68.9)    | 0  | 0.0   | 84 (87.5)         |

CTE: computed tomography enterography, EH: endoscopic healing, TH: transmural healing

Table 3. Multivariate Analysis for Factors Associated with Transmural Healing.

| Factor                                           | OR     | 95% CI      | p value |
|--------------------------------------------------|--------|-------------|---------|
| Endoscopic healing (%)                           | 6.14   | 1.52-24.70  | 0.01    |
| Previous major abdominal surgery (%)             | 2.18   | 0.769-6.20  | 0.14    |
| Clinical remission                               | 0.99   | 0.987-1.00  | 0.21    |
| Serum albumin (g/dL)                             | 0.62   | 0.17-2.23   | 0.46    |
| Serum CRP (mg/dL)                                | 0.61   | 0.235-1.60  | 0.32    |

CRP: C-reactive protein, CI: confidence interval, OR: odds ratio

Discussion

This study is one of the few reports to provide real-world data on the evaluation of TH using low-dose CTE for patients with CD in Japan, and three points were clarified. First, in the present study, 21.3% of the patients with CD achieved TH, and the kappa coefficient was 0.743, indicating substantial agreement between the two radiologists. Second, the factors associated with TH were EH, serum albumin, serum CRP, and the CDAI in the univariate analysis, but only EH was detected in the multivariate analysis. The ROC curve for serum albumin for the TH evaluation, the
Figure 3. The evaluation of transmural and endoscopic healing by CTE and endoscopy. CTE: computed tomography enterography.

Figure 4. The comparison of CTE and endoscopic findings. (a) An image from CTE shows wall thickness and contrast enhancement of the ascending colon (arrow). (b) An image from ileocolonoscopy shows a longitudinal ulcer (endoscopic healing grade 3) in the area corresponding to CTE. (c) An image from CTE shows wall thickness and contrast enhancement of the rectum (arrow). (d) An image from ileocolonoscopy shows no ulcer in the rectum in the area corresponding to CTE. CTE: computed tomography enterography.

cut-off value was 3.7 g/dL with a sensitivity of 92.3%, specificity of 34.4%, and AUROC of 0.619. Similarly, the ROC curve for serum CRP showed a cut-off value of 0.14 mg/dL with a sensitivity of 73.1%, specificity of 61.5%, and AUC of 0.700. Third, 69 (56.5%) of the 122 patients had concordance between the CTE and endoscopy diagnoses, 22 (18.0%) achieved both TH and EH, and 47 (38.5%) had a concordant index lesion.

Regarding the first point, 21.3% of the present patients with CD were found to have TH. According to previous studies, the rate of TH achievement ranged from 14-42.4%, but the timing and CSI used for the TH evaluation were dif-
ferent, which was consistent with our study (8, 10, 22-30). Although the definition of TH has not yet been confirmed, a systematic review by Geyl et al. recommended that the bowel wall thickness be <3 mm on CTE and that there should be no increased mesenteric lipid concentration or complications of penetration (31). This is almost consistent with the criteria in our study, and the kappa coefficient between the two radiologists was high, indicating the validity of the evaluation criteria.

Regarding the second point, it has been reported that TH is associated with serum albumin and CRP levels (10), and in the present study, the factors associated with TH were EH and the serum albumin and CRP levels in the univariate analysis but only EH in the multivariate analysis, suggesting that it is difficult to predict TH using only serum albumin or serum CRP levels (6, 7). Recently, fecal calprotectin and LRG, which are novel biomarkers for CD, have been reported to be associated with EH (32, 33). In the present study, no statistically significant difference was found in either biomarker, probably due to the small sample size. However, there are few reports on the prediction of TH, so further studies are needed.

Regarding the third point, the diagnosis by CTE and endoscopy was consistent in 56.5% of the patients. For patients with inconsistent diagnoses, inflammation was detected only by CTE in 32.0%, by both modalities in 8.2%, although the location of the index lesion was different; and only by endoscopy in 3.3%. The detection of inflammation by CTE alone in many of the patients suggests the importance of combining CTE with endoscopy. In STRIDE, it is stated that CSI is recommended in cases in which the endoscopic evaluation of inflammation is difficult (6). Previously, we reported that active ulcers were found in 93.6% of patients with contrast-enhanced wall thickening or an increase in the concentration of fat tissue surrounding the intestine detected on CTE (34); we therefore consider the ability to detect lesions that require therapeutic intervention to be high, and CTE provides useful information on the need for intensified treatment.

Achieving EH in CD has been associated with a prolonged relapse-free period and the avoidance of surgery (35-39). In STRIDE-II, EH is listed as a long-term target (7). However, considering that CD is a multilayered inflammation of the intestine, it is possible that inflammation can remain in the deeper layers of the intestine even if the mucosal surface is not active (40). Although TH is not considered to be a formal target due to insufficient evidence in STRIDE-II, it has recently been reported that achieving TH is associated with significantly higher rates of favorable long-term outcomes, including long-term remission, fewer treatment changes, and lower rates of hospitalization and surgery, suggesting that TH may be a new formal target (8).

Ultrasonography, CT, and MRI are used to evaluate TH (41, 42). All have been reported to have high diagnostic accuracy for the diagnosis of CD, assessment of disease activity, and gastrointestinal complications, and it is not clear which method has the best sensitivity or specificity (40). The advantage of CTE is the simplicity of the method and the high spatial resolution, but the disadvantage is the radiation exposure (43). Radiation exposure is particularly important in CD, as many patients experience an onset at a young age and may undergo multiple examinations on a periodic schedule (44). The consensus recommendations for CTE/ magnetic resonance imaging (MRE) reported in 2018 also recommended that CTE be performed in patients over 35 years old (20). In fact, many reports have used abdominal ultrasonography and MRE to evaluate TH (31). However, Japan has the highest rate of CT deployment in the world, and it has become an indispensable examination modality in gastrointestinal examinations (13). Therefore, as a preventive measure against radiation exposure at our hospital, we perform imaging with a 50% reduction in radiation exposure, which is considered equivalent to standard-dose CTE, and evaluate only a single contrast phase (45). With the improvement of CT performance and the development of image correction technology using artificial intelligence, radiation exposure is expected to be reduced even further, but the appropriate timing of examinations will also need to be examined in the future.

Several limitations associated with the present study warrant mention. First, this study is a single-center retrospective study, and because of the small number of cases, a prospective multicenter study should be conducted in the future. Second, the study period was long, and the performance of CT scanners and endoscopic instruments may have improved during that time. In this regard, it would be desirable to establish a database of multiple medical institutions to investigate a large number of cases in a short period of time. Third, the proportion of patients with moderately to severely active CD was relatively low in this study, and half of the patients were in clinical remission. To investigate the diagnostic potential of CTE in various CD conditions, data concerning patients with a high disease severity need to be accumulated. Fourth, in 8 of the 39 patients in whom inflammation was detected only by CTE, the endoscope was not able to reach the lesion detected by CTE. Therefore, the results of this study do not indicate that the diagnostic performance of CTE is superior to that of endoscopy but rather that CTE is a viable alternative modality when inflammation cannot be adequately assessed with endoscopy due to adhesions or stenosis, as shown in STRIDE (6). Finally, TH has been reported to be useful in predicting treatment effects (24). Currently, multiple drugs are available for the treatment of CD, and this number is expected to increase in the future. In this study, anti-TNF-α antibody agents were used in most of the patients, but the differences among the agents should be examined in order to select the most appropriate ones.

In conclusion, this is a valuable study that analyzed real-world data of patients with CD in Japan undergoing reduced-exposure CTE. The TH criterion used in this study has a high kappa coefficient and can be used reproducibly in
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References

1. Baumgart DC, Sandborn WJ. Crohn’s disease. Lancet 380: 1590-1605, 2012.
2. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn’s disease digestive damage score, the Lémann score. Inflamm Bowel Dis 17: 1415-1422, 2011.
3. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology 152: 351-361.e5, 2017.
4. Hommes-D, Colombel JF, Emery P, Greco M, Sandborn WJ. Changing Crohn’s disease management: need for new goals and indices to prevent disability and improve quality of life. J Crohn Colitis 6 (Suppl 2): S224-S234, 2012.
5. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: a proposed new paradigm for the management of Crohn’s disease. Clin Gastroenterol Hepatol 13: 1042-1050, 2015.
6. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 110: 1324-1338, 2015.
7. Turner D, Ricciuto A, Lewis A, et al.; the International Organization for the Study of IBD. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 160: 1570-1583, 2021.
8. Fernandes SR, Rodrigues RV, Bernardo S, et al. Transmural healing is associated with improved long-term outcomes of patients with Crohn’s disease. Inflamm Bowel Dis 23: 1403-1409, 2017.
9. Weinstein-Nakar I, Focht G, Church P, et al.; the ImageKids study group. Associations among mucosal and transmural healing and faecal level of calprotectin in children with Crohn’s disease. Clin Gastroenterol Hepatol 16: 1089-1097.e4, 2018.
10. Noh SM, Oh EH, Park SH, et al. Association of faecal calprotectin level and combined endoscopic and radiological healing in patients with Crohn’s disease receiving anti-tumour necrosis factor therapy. J Crohn Colitis 14: 1231-1240, 2020.
11. Arai T, Takeuchi K, Miyamura M, et al. Level of fecal calprotectin correlates with severity of small bowel Crohn’s disease, measured by balloon-assisted enteroscopy and computed tomography enterography. Clin Gastroenterol Hepatol 15: 56-62, 2017.
12. Shimoyama T, Yamamoto T, Umegae S, Matsumoto K. Faecal biomarkers for screening small bowel inflammation in patients with Crohn’s disease: a prospective study. Therap Adv Gastroenterol 10: 577-587, 2017.
13. Ohmiya N. Management of obscure gastrointestinal bleeding: comparison of guidelines between Japan and other countries. Dig Endosc 32: 204-218, 2020.
14. Yao T, Matsui T, Hiwatsuji N. Crohn’s disease in Japan: diagnostic criteria and epidemiology. Dis Colon Rectum 43 (Suppl 10): S85-S93, 2000.
15. Hisabe T, Hirai F, Matsui T, Watanabe M. Evaluation of diagnostic criteria for Crohn’s disease in Japan. J Gastroenterol 49: 93-99, 2014.
16. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 55: 749-753, 2006.
17. Huprich JE, Fletcher JG. CT enterography: principles, technique and utility in Crohn’s disease. Eur J Radiol 69: 393-397, 2009.
18. Matsunaga Y, Chida K, Kondo Y, et al. Diagnostic reference levels and achievable doses for common computed tomography examinations: results from the Japanese nationwide dose survey. Br J Radiol 92: 20180290, 2019.
19. Schindera ST, Nelson RC, DeLong DM, et al. Multi-detector row CT of the small bowel: peak enhancement temporal window - initial experience. Radiology 243: 438-444, 2007.
20. Brunning DH, Zimmermann EM, Loftus EV Jr, Sandborn WJ, Sauer CG, Strong SA; Society of Abdominal Radiology Crohn’s Disease-Focused Panel. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn’s disease. Gastroenterology 154: 1172-1194, 2018.
21. Kanda Y. Investigation of the freely available easy-to-use software EZR for medical statistics. Bone Marrow Transplant 48: 452-458, 2013.
22. Castiglione F, Testa A, Rea M, et al. Transmural healing evaluated by bowel sonography in patients with Crohn’s disease on maintenance treatment with biologics. Inflamm Bowel Dis 19: 1928-1934, 2013.
23. Ripollés T, Paredes JM, Martínez-Perez MJ, et al. Ultrasound changes at 12 weeks of anti-TNF drugs predict 1-year sonographic response and clinical outcome in Crohn’s disease: a multicenter study. Inflamm Bowel Dis 22: 2465-2473, 2016.
24. Deepak P, Fletcher JG, Fidler JL, et al. Radiological response is associated with better long-term outcomes and is a potential treatment target in patients with small bowel Crohn’s disease. Am J Gastroenterol 111: 997-1006, 2016.
25. Eder P, Łykowska-Szuber L, Katulska K, et al. Intestinal healing after anti-TNF induction therapy predicts long-term response to one-year treatment in patients with ileocolonic Crohn’s disease native to anti-TNF agents. Prz Gastroenterol 11: 187-193, 2016.
26. Sauer CG, Middleton JP, McCracken C, et al. Magnetic resonance enterography healing and magnetic resonance enterography remission predicts improved outcome in pediatric Crohn disease. J Pediatr Gastroenterol Nutr 62: 378-383, 2016.
27. Civitelli F, Nuti F, Oliva S, et al. Looking beyond mucosal healing: effect of biologic therapy on transmural healing in pediatric Crohn’s disease. Inflamm Bowel Dis 22: 2418-2424, 2016.
28. Laterza L, Piscaglia AC, Minordi LM, et al. Multimetric evaluation predicts different midterm outcomes in Crohn’s disease. Dig Dis 36: 184-193, 2018.
29. Orlando S, Fraquelli M, Coletta M, et al. Ultrasound elasticity imaging predicts therapeutic outcomes of patients with Crohn’s disease treated with anti-tumour necrosis factor antibodies. J Crohns Colitis 12: 63-70, 2018.
30. Paredes JM, Moreno N, Latorre P, et al. Clinical impact of sonographic transmural healing after anti-TNF antibody treatment in patients with Crohn’s disease. Dig Dis Sci 64: 2600-2006, 2019.
31. Geyl S, Guillo L, Laurent V, D’Amico F, Danese S, Peyrin-Biroulet L. Transmural healing as a therapeutic goal in Crohn’s disease: a systematic review. Lancet Gastroenterol Hepatol 6: 659-667, 2021.
32. Inokuchi T, Kato J, Hiraoka S, et al. Fecal immunochromatographic test versus fecal calprotectin for prediction of mucosal healing in Crohn’s disease. Inflamm Bowel Dis 22: 1078-1085, 2016.
33. Yasutomi E, Inokuchi T, Hiraoka S, et al. Leucine-rich alpha-2 glycoprotein as a marker of mucosal healing in inflammatory bowel disease. Sci Rep 11: 11086, 2021.
34. Hashimoto S, Shimizu K, Shibata H, et al. Utility of computed tomographic enteroclysis/enterography for the assessment of mucosal healing in Crohn’s disease. Clin Gastroenterol Hepatol 19: 1553-1561, 2021.
35. Hashimoto S, Shimizu K, Shibata H, et al. Utility of computed tomographic enteroclysis/enterography for the assessment of mucosal healing in Crohn’s disease. Clin Gastroenterol Hepatol 19: 1553-1561, 2021.
35. Rutgeerts P, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? Gut 56: 453-455, 2007.

36. Frøslie KF, Jahnsen J, Moun BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 133: 412-422, 2007.

37. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med 362: 1383-1395, 2010.

38. Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn’s disease. Aliment Pharmacol Ther 43: 317-333, 2016.

39. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn’s disease: real world experience from a multicentre cohort. Aliment Pharmacol Ther 45: 1232-1243, 2017.

40. Serban ED. Treat-to-target in Crohn’s disease: will transmural healing become a therapeutic endpoint? World J Clin Cases 6: 501-513, 2018.

41. Deepak P, Fletcher JG, Fidler IL, Bruining DH. Computed tomography and magnetic resonance enterography in Crohn’s disease: assessment of radiologic criteria and endpoints for clinical practice and trials. Inflamm Bowel Dis 22: 2280-2288, 2016.

42. Deepak P, Fowler KJ, Fletcher JG, Bruining DH. Novel imaging approaches in inflammatory bowel diseases. Inflamm Bowel Dis 25: 248-260, 2019.

43. Brenner DJ, Hall EJ. Computed tomography - an increasing source of radiation exposure. N Engl J Med 357: 2277-2284, 2007.

44. Sartor RB. Current concepts of the etiology and pathogenesis of ulcerative colitis and Crohn’s disease. Gastroenterol Clin North Am 24: 475-507, 1995.

45. Lee SJ, Park SH, Kim AY, et al. A prospective comparison of standard-dose CT enterography and 50% reduced-dose CT enterography with and without noise reduction for evaluating Crohn disease. AJR Am J Roentgenol 197: 50-57, 2011.