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## Endoscopic criteria to evaluate tumor response of rectal cancer to neoadjuvant chemoradiotherapy using magnifying chromoendoscopy

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## ABSTRACT

**Background and aims:** Precise endoscopic assessment of complete response to neoadjuvant chemoradiotherapy before surgery is important for optimizing surgical and non-surgical treatment. We prospectively evaluated the accuracy of the newly proposed endoscopic criteria to identify complete response, using magnifying chromoendoscopy.

**Methods:** New endoscopic criteria were created to define endoscopic complete response, near complete response and incomplete response, using magnifying chromoendoscopy. The criteria contained notable endoscopic findings, including shape of the scar, state of the ulcer, finding of white moss, presence of residual protruded nodules, regenerated pits of the scar, presence of neoplastic pit patterns, and extension of rectal wall. Seventy-nine patients with rectal cancer who received neoadjuvant chemoradiotherapy were prospectively evaluated 1–3 days before resection. Diagnostic accuracy to identify pathological complete response and interobserver agreement among a supervising colonoscopist and two trainees were investigated.

**Results:** Pathological complete response was obtained in 17 patients (21.5%). The diagnostic accuracy of endoscopic complete response was 85%, with a sensitivity of 47%, specificity of 97%, positive predictive value of 80% and negative predictive value of 77%. The kappa-value for interobserver agreement across 3 doctors was 0.57 (standard error, 0.74; 95% confidence interval, 0.39–0.76).

**Conclusion:** The newly proposed endoscopic criteria using magnifying chromoendoscopy achieved excellent diagnostic accuracy to determine good responders to neoadjuvant chemoradiotherapy in rectal cancer, with fair interobserver agreement. The criteria could be clinically useful to select patients for non-surgical management.

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## Introduction

The use of multimodal treatment for advanced rectal cancers has markedly increased in the past 10 years. Recently, reports have indicated a complete response (CR) rate of >35% with the combination of anticancer agents and radiotherapy with

enhanced systemic chemotherapy, in addition to preoperative chemoradiotherapy (CRT) [1–3]. Since the first report of long-term outcomes by Habr-Gama et al. in 2004, oncological safety of non-surgical “watch-and-wait” strategy for patients with clinical CR after chemoradiotherapy has been validated by multiple authors [4–8]. Precise assessment of clinical CR before surgery is important for optimizing such treatment. The Response Evaluation Criteria in Solid Tumors (RECIST) involves computed tomography (CT)-based measurements to determine the response to chemotherapy and radiotherapy on target lesions [9], but these criteria are not useful to detect the residual “too-small-to-measure” lesions in patients with good response.

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Instead, many studies have emphasized importance of endoscopic evaluation for assessing clinical CR [6–8,10]. In Japan, multiple studies have established usefulness of magnifying chromoendoscopy to detect tiny neoplastic lesions and healing epithelium [11,12]. Use of magnifying chromoendoscopy might further improve precise detection of small residual lesions after chemoradiotherapy. However, there have been few prospective studies that evaluated accuracy of endoscopic examination for assessing CR, and none used magnifying endoscopy. We previously reported a retrospective study that proposed endoscopic criteria for predicting pathological CR [13]. However, the study was retrospective, and further, the study used conventional endoscopy without magnification. In the present study, we prospectively evaluated endoscopic criteria using magnifying chromoendoscopy for assessing tumor response to neoadjuvant chemoradiotherapy.

## Patients and methods

### Patients

This was a prospective observational study performed in a single cancer center in Japan. The study was approved by the Institutional Review Board and Privacy Board of Cancer Institute Hospital (1015–1131). A total of 79 patients who underwent curative surgery for rectal cancer after neoadjuvant chemoradiotherapy, except those receiving short-course radiotherapy, between October 2013 and October 2015 were prospectively evaluated. Neoadjuvant CRT (oral fluorouracil+50.4 Gray radiation) was indicated for patients with cT3-4 and/or N positive rectal cancer below the peritoneal reflection. Induction chemotherapy with 12-week (6 courses) mFOLFOX plus bevacizumab (5 mg/kg every 2 weeks) followed by CRT was indicated for high-risk patients with a clinical stage of cT4, cN2, with a positive circumferential radial margin or positive lateral pelvic lymph nodes. All the patients had undergone preoperative and post-treatment endoscopic evaluation with informed consent.

### Evaluation protocol

1. The timing of evaluation was 1–3 days before surgical resection in order to prevent the effect of pathological changes during the interval between endoscopic evaluation and operation.
2. The same supervising colonoscopist (A.C.) recorded each image of endoscopic findings onto the hard disk prospectively.
3. The same magnifying colonoscope (PCF-260AZI, Olympus Co., Tokyo, Japan) was used for observation.
4. Staining with 0.05% crystal violet (Pyoktanin blue<sup>R</sup>, Wako Pure Chemical Industries, Tokyo, Japan) was performed, and the sites were examined under magnification.

5. All endoscopic evaluations were performed according to our criteria shown in Table 1.

### Evaluation criteria

In this study, we modified our previous criteria and incorporated magnifying endoscopy instead of tissue biopsy of the mucosal surface as summarized in Table 1. The criteria contained notable endoscopic findings as follows: (1) shape of the scar was classified as linear or flat, (2) state of the ulcer was classified as completely or incompletely closed, with or without white moss was classified as none or residual after careful rinsing that indicated residual ulcer, (3) Residual protruded nodules were present or not, (4) a neoplastic pit pattern was present or not under magnifying chromoendoscopy, moreover, regenerated pits of scar sites were uniform or not, and (5) extension of the rectal wall by insufflation was preserved or not. Meeting the magnified endoscopic complete response (ME-CR) was defined as satisfying all five findings. In contrast, not meeting the ME-CR (ME-non-CR) was defined as cases that satisfied at least 1 of the five findings. ME-near-CR was defined as ME-non-CR that demonstrated almost identical to ME-CR except the findings of covered but irregular surface rather than closed ulcers, or residual deformity without neoplastic pit pattern. Cases wherein the proximal side of the lesions were not evaluated due to stricture were classified as “not all evaluated” (NE).

Typical endoscopic findings in our criteria are presented in Fig. 1, including the features under white light conventional endoscopy (A-F) and those under magnifying chromoendoscopy (G-I) (Fig. 1).

A typical case that met the ME-CR criteria was presented in Fig. 2-a, wherein a linear scar with uniform regenerated pits was observed by magnifying chromoendoscopy. The pathological response was Grade 3 in this case (Fig. 2-a).

### Endpoints

The primary endpoint was the diagnostic accuracy of endoscopic evaluation to detect postoperative pathological response grade. The diagnostic accuracy was investigated in 3 models.

- (1) Pattern 1: diagnostic accuracy of ME-CR for predicting pathological Grade 3 (complete response).
- (2) Pattern 2: diagnostic accuracy of combined ME-CR and ME-near-CR for predicting pathological Grade 3 (complete response).
- (3) Pattern 3: diagnostic accuracy of combined ME-CR and ME-near-CR for predicting pathological Grade 3 and 2b (complete and near-complete response).

For assessing interobserver agreement which was the secondary endpoint, the endoscopic images were recorded onto a hard disk by the supervising colonoscopist, once the image background and the

**Table 1**  
Endoscopic evaluation criteria composed of five endoscopic findings.

	ME-CR (all of 5 items)	ME-near-CR	ME-non-CR (at least one of 5 items)
WL-C	(A) Linear scar (B) Flat scar Completely closed ulcer, No white moss	(C) Covered but irregular surface Closed ulcer	Not scar phase (D) Incompletely closed ulcer (E) Residual white moss
ME	No protruded nodule (G) Regenerated pits uniformly arranged (H) Hyper-cellular pits	No protruded nodule No neoplastic pit pattern	(F) Residual protruded nodules (I) Residual neoplastic pit pattern
Wall extension by insufflation	Normal extension	Decreased extension	Poor extension with submucosal tumor-like deformity

WL-C, White light conventional endoscopy; ME, Magnifying endoscopy under crystal violet staining; ME-CR, Endoscopic evaluation complete response with magnification.

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