Prediction of Histologic Regression on the Basis of Colonoscopic Findings in Patients with Locally Advanced Middle and Lower Rectal Cancer Who Receive Preoperative Chemoradiotherapy

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Objective: Preoperative chemoradiotherapy significantly reduces local recurrence in patients with locally advanced rectal cancer (LARC). Various biomarkers have been proposed as predictors of the response to chemoradiotherapy, but their reliability remains uncertain.
Methods: Surgery in combination with preoperative radiation and UFT- or S-1-based chemotherapy was used to treat 102 patients with LARC. Colonoscopy was performed before the start of chemoradiotherapy and immediately before surgery. Patients in whom the tumor mound flattened remarkably or disappeared were evaluated as responders. The endoscopic response was compared with histologic regression and the degree of tumor shrinkage.
Results: Histologic regression was marked in 59.8% of patients according to the Tumor Regression Grade criteria and 44.1% according to the Japanese Classification of Colorectal Carcinoma criteria. The degree of tumor shrinkage was 34.3% on average. Marked histologic regression was present in a significantly higher proportion of responders than non-responders ($p = 0.01$). The degree of tumor shrinkage was significantly greater in responders (38.8%) than in non-responders (30.9%; $p < 0.01$). T-downstaging was significantly more common among responders (64.3%) than non-responders (26.7%; $p = 0.04$).
Conclusions: Morphologic changes on colonoscopy were associated with the degree of tumor shrinkage, histologic regression, and T-downstaging, suggesting that such findings can be used to predict the response to preoperative chemoradiotherapy.

Key words: Rectal cancer, preoperative chemoradiotherapy, tumor shrinkage, tumor regression, colonoscope

INTRODUCTION

Multidisciplinary treatment including preoperative chemoradiotherapy significantly reduces the risk of local recurrence in patients with locally advanced rectal cancer (LARC) [1–4]. We administer multimodal therapy in which preoperative chemotherapy is combined with radiotherapy, given in a dose of 20 Gy in 10 fractions (extracorporeal X-ray irradiation), followed by intraoperative electron-beam irradiation of the entire dissected surface of the pelvis in a dose of 15 Gy. As compared with conventional chemoradiotherapy, in which the period from the start of therapy to surgery is 10 to 12 weeks, this treatment schedule allows the period until surgery to be shortened by 4 weeks and has a low local recurrence rate (3%) and good survival [5–7].

The histologic response to preoperative chemoradiotherapy has been reported to be closely related to oncologic outcomes. Disease-free survival (DFS) and overall survival (OS) are significantly better in patients with histologic complete regression or with downstaging than in patients without such findings [8–15]. Therefore, the ability to predict histologic regression after preoperative chemoradiotherapy but before surgery would be very valuable clinically.

We hypothesized that morphologic changes as assessed by endoscopy after chemoradiotherapy are closely related to histologic regression on the completion of treatment. In the present study, we performed colonoscopy before preoperative chemoradiotherapy and immediately before surgery (after preoperative chemoradiotherapy) to evaluate morphologic changes of rectal tumors. These changes were compared with histologic regression and the degree of tumor shrinkage at the time of surgery to determine whether morphologic changes on endoscopic examination could be used to predict the response to treatment.

PATIENTS AND METHODS

Between February 1999 and December 2007, we studied 102 consecutive patients with histologically confirmed adenocarcinoma of the middle or lower third of the rectum. The preoperative diagnosis was T2 N(+) or T3/4 Nx according to the TNM classification. Initial evaluations included digital examination of the rectum, chest radiography, colonoscopy, barium enema, computed tomography of the abdomen and

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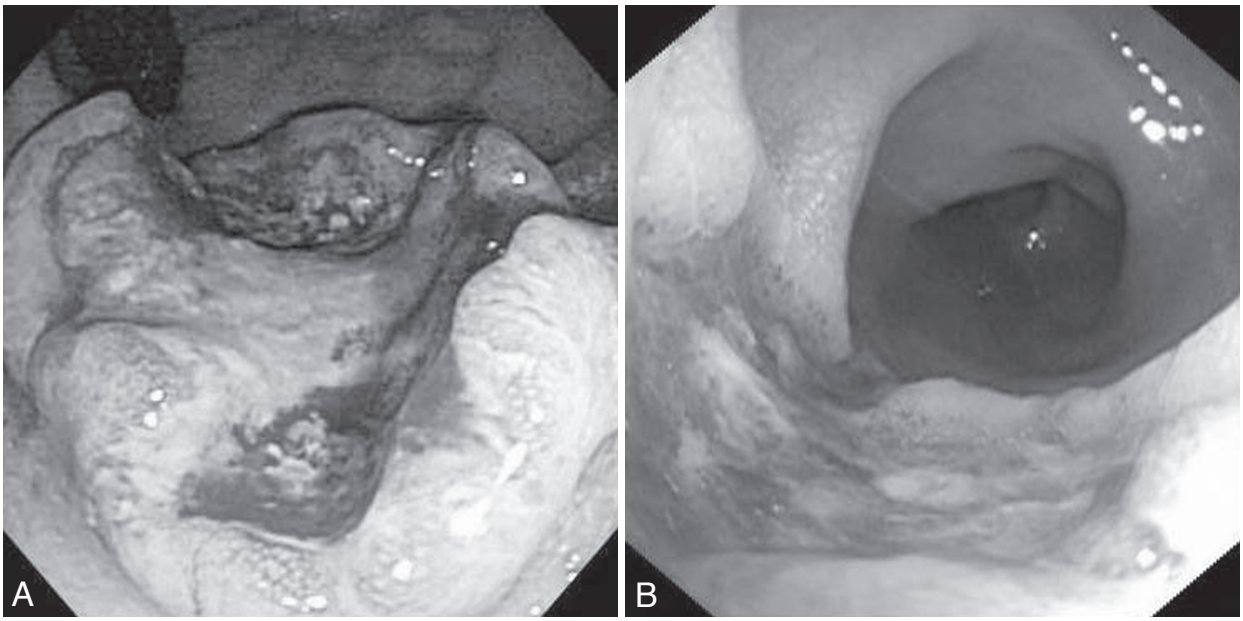

Fig. 1 A, B. Evaluation of a responder on colonoscopic examination.
A: Endoscopic findings before preoperative chemoradiotherapy.A type 2 rectal cancer was diagnosed.
B: Endoscopic findings after treatment. The tumor mound had flattened remarkably and disappeared.

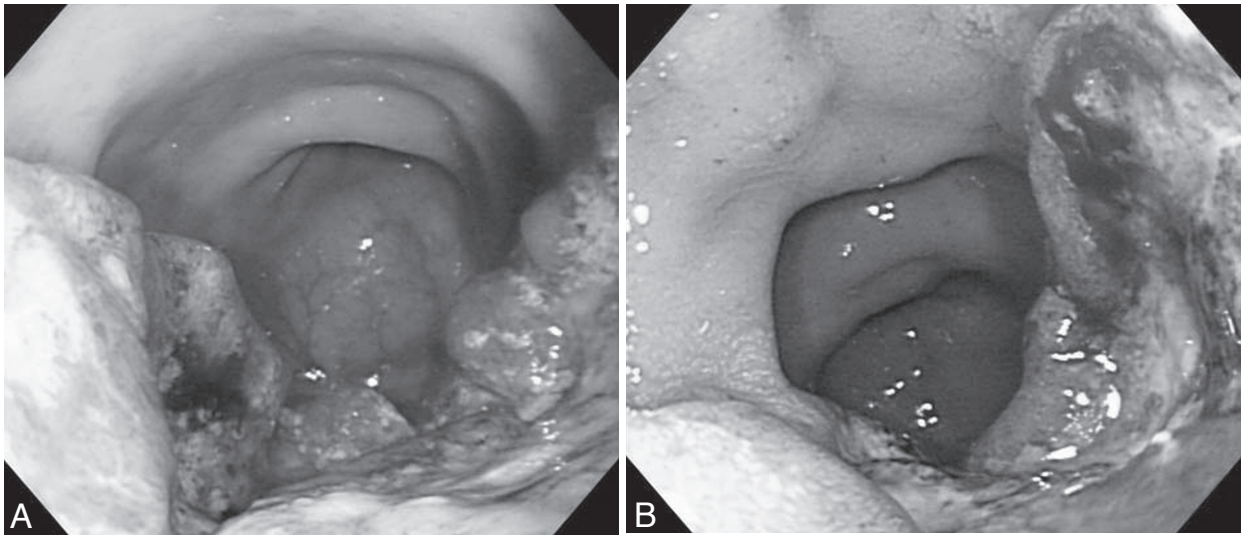

Fig. 2 A, B. Evaluation of a non-responder on colonoscopic examination.
A: Endoscopic findings before preoperative chemoradiotherapy.A type 2 rectal cancer was diagnosed.
B: Endoscopic findings after treatment. The tumor mound changed only slightly.

pelvis, and endorectal ultrasonography. Magnetic resonance imaging of the pelvis was also performed since 2003. Tumor location was defined according to the criteria of the Japanese Society for Cancer of the Colon and Rectum [16]. The upper third of the rectum is defined as the area between the promontory and the inferior margin of the second sacral vertebra on the lateral view of a barium enema image. The remaining rectum is divided into the middle and lower third of the rectum at the peritoneal reflection. The level of the peritoneal reflection corresponds to the level of the middle Houston valve on barium enema images.

CHEMORADIOTHERAPY

Preoperative radiotherapy was performed with an 18 MeV X-ray beam generated by a linear accelerator (Clinac 2100C, Varion Med System, Inc. Palo Alto, CA, USA), using the two-field technique (anterior-posterior and posterior-anterior fields). The radiation dose was 20 Gy (extracorporeal X-ray irradiation) preoperatively, followed by intraoperative electron-beam irradiation in a dose 15 Gy. For chemotherapy, 60 patients received oral uracil and tegafur (UFT, 400 mg/m^2 daily), and 42 received oral S-1 (80 mg/m^2 daily), beginning at the same time as radiotherapy. Chemotherapy was given for 5 days followed by a 2-day rest, on the

Table 1 Patient characteristics

Age (years)	
Mean ± SD	60 ± 10
Range	34–89
Sex	
Male	77 (75.5%)
Female	25 (24.5%)
Tumor location	
Middle rectum	48 (47.1%)
Lower rectum	54 (52.9%)
Circumferential extension	
≤ 1/2	42 (41.2%)
> 1/2	60 (58.8%)
Histological differentiation	
Well	53 (51.9%)
Moderate	41 (40.2%)
Poor	6 (5.9%)
Mucinous	2 (2.0%)

Middle rectum = middle third of the rectum; Lower rectum = lower third of the rectum; Well = well differentiated adenocarcinoma; Moderate = moderately differentiated adenocarcinoma; Poor = poorly differentiated adenocarcinoma; Mucinous = mucinous adenocarcinoma.

Table 2 Clinical outcomes

T stage (pathological)	
pCR	2 (2.0%)
0	0 (0%)
1	5 (4.9%)
2	29 (28.4%)
3	62 (60.8%)
4	4 (3.9%)
N	
(+)	39 (38.2%)
(-)	63 (61.8%)
TRG*	
≤ 3 (marked regression)	61 (59.8%)
≥ 4	41 (40.2%)
JSCC†	
≤ 1b	57 (55.9%)
≥ 2 (marked regression)	45 (44.1%)
Tumor shrinkage	
Mean ± SD	34.3 ± 10.5%
Range	9-63%

* Tumor Regression Grade [17]
† Japanese Classification of Colorectal Carcinoma [16]

same days as radiotherapy. This cycle was repeated. Chemotherapy was continued after the completion of radiotherapy and was given until the day before surgery. Surgery was done 2 weeks (range 9–28 days) after the completion of preoperative radiotherapy.

COLONOSCOPIC EVALUATION OF RESPONDERS

Colonoscopic findings before the start of chemoradiotherapy were compared with those immediately before surgery. Patients in whom the tumor mound flattened remarkably or disappeared were evaluated to be responders (Fig. 1A, 1B). All other patients were considered non-responders (Fig. 2A, 2B). Histologic regression as evaluated by examination of resected specimens and the degree of tumor shrinkage (%) was compared between the responders and non-responders.

EVALUATION OF ANTITUMOR EFFECTIVENESS

Antitumor effectiveness was evaluated on the basis of histologic regression on resected specimens and the degree of tumor shrinkage immediately before surgery.

Histologic regression was classified according to the tumor regression grade (TRG) [17] and the criteria of the Japanese Classification of Colorectal Carcinoma (JCCC) [16]. TRG was classified as Grade 1 (complete regression), Grade 2 (presence of rare residual cancer cells), Grade 3 (increased number of residual cancer cells), Grade 4 (residual cancer outgrowing fibrosis), or Grade 5 (absence of regressive changes). A grade of 1, 2, or 3 was defined as marked regression. Marked regression according to the JCCC criteria was defined as Grade 2 (necrosis or disappearance of the tumor involving more than two thirds of the entire lesion, but viable tumor cells remain) or Grade 3 (complete regression).

Double-contrast barium enema examination was performed before the start of chemoradiotherapy and immediately before surgery. The degree of tumor shrinkage was calculated by measuring the tumor along the major axis (length along the long axis of the bowel) on lateral views. Each measurement was corrected by the diameter of the first sacral vertebra [18]. The following formula was used to calculate tumor shrinkage:

Degree of tumor shrinkage (%) = $\{1 - B \times (C/D)/A\} \times 100$ (%)

(A = length of tumor immediately before chemoradiotherapy; B = length of tumor immediately before surgery; C = diameter of the first sacral vertebra before chemoradiotherapy; D = diameter of the first sacral vertebra immediately before surgery)

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Windows, version 18.0. P values of < 0.05 were considered to indicate statistically significant differences.

RESULTS

The study group comprised 77 men and 25 women with a mean age of 60 years. The tumor was located in the middle third of the rectum (Ra) in 48 patients and in the lower third of the rectum (Rb) in 54. Circumferential extension was one half or less in 42 patients (41.2%) and more than one half in 60 (58.8%). The histologic type was well-differentiated adenocarcinoma in 52 patients, moderately differentiated adenocarcinoma in 42, poorly differentiated adenocarcinoma in 5, and mucinous carcinoma in 3 (Table 1).

Two patients (2%) had a pathologic complete response (pCR). Histologically, marked regression was present in 61 patients (59.8%) according to the TRG criteria and 45 (44.1%) according to the JSCC criteria. The degree of tumor shrinkage was 34.3% on average (Table 2). Histologic marked regression and the degree of tumor shrinkage were not related to tumor site or histologic type (Table 3).

Table 3 Relations of tumor characteristics to histologic regression and the degree of tumor shrinkage

		Marked regression					
		TRG[§]		JSCC[‖]		Tumor	
	Pts	Grade 1,2,3 (%)	p-value	Grade 2,3 (%)	p-value	shrinkage (%)	p-value
Site							
Middle rectum	48	32(66.7)	0.26*	22(45.8)	0.90*	36.3 ± 10.6	0.07[†]
Lower rectum	54	29(53.7)		23(42.6)		32.5 ± 10.1	
Histologic differentiation							
Well	53	30(55.6)	0.63*	20(37.7)	0.29[‡]*	33.8 ± 11.0	0.30[‡]
Moderate	41	27(65.9)		20(48.8)		34.5 ± 9.9	
Poor	6	4(66.7)		4(66.7)		40.5 ± 9.4	

Middle rectum = middle third of the rectum; Lower rectum = lower third of the rectum; Well = well differentiated adenocarcinoma; Moderate = moderately differentiated adenocarcinoma; Poor = Poorly differentiated adenocarcinoma.
TRG: Well vs. Moderate p = 0.49*; Moderate vs. Poor p = 1.00*; Well vs. Poor p = 0.97*
JSCC: Well vs. Moderate p = 0.39*; Moderate vs. Poor p = 0.67*; Well vs. Poor p = 0.35*
Tumor shrinkage (%): Well vs. Moderate p = 0.76[†]; Moderate vs. Poor p = 0.17[†]; Well vs. Poor p = 0.16[†]
[*] Chi-square test for independence
[†] Student's t-test
[‡] Mann-Whitney U test
[§] Tumor Regression Grade 17
[‖] Japanese Classification of Colorectal Carcinoma 16

Table 4 Relations of the morphologic evaluation on colonoscopy (responder vs. non-responder) after chemo radiotherapy to histologic regression and the degree of tumor shrinkage

		Marked regression					
		TRG[‡]		JSCC[§]		Tumor	
	Pts	Grade 1,2,3 (%)	p-value*	Grade 2,3 (%)	p-value*	shrinkage (%)	p-value[†]
Responder	44	33 (75.0%)	0.01	28 (63.6%)	< 0.01	38.8 ± 10.7	< 0.01
Non-responder	58	28 (48.3%)		17 (29.3%)		30.9 ± 8.9	

[*] Chi-square test for independence
[†] Student's t-test
[‡] Tumor Regression Grade 17
[§] Japanese Classification of Colorectal Carcinoma 16

Table 5 Relations of morphologic evaluation on colonoscopy (responder vs. non-responder) after chemoradio therapy to T and N downstaging

	Pts	T downstage (+)	p-value*	N downstage (+)	p-value*
Responder	14	9 (64.3%)	0.04	2 (14.3%)	0.60
Non-responder	30	8 (26.7%)		8 (26.7%)	

[*] Chi-square test for independence

Histologic marked regression according to the TRG criteria was found in a significantly higher proportion of responders (33 patients, 75.0%) than non-responders (28 patients, 48.3%; p = 0.01) on colonoscopic examination. When the JSCC criteria were used, marked regression was similarly present in a higher proportion of responders (28 patients, 63.6%) than non-responders (17 patients, 29.3%; p < 0.01) (Table 4). The degree of tumor shrinkage was significantly higher in the responders (38.8%) than in the non-responders (30.9%; p < 0.01) (Table 4).

Among the 44 patients who underwent magnetic resonance imaging (MRI), T downstaging was found in 17 (38.6%) and N downstaging was found in 10 (22.7%). T downstaging was found in a significantly higher proportion of responders (9 of 14 patients, 64.3%) than non-responders (8 of 30 patients, 26.7%; p = 0.04). In contrast, the rate of N downstaging did not differ between the responders and non-responders (Table 5).

DISCUSSION

The response to preoperative chemoradiotherapy is closely related to outcomes in patients with rectal cancer. Many studies have therefore attempted to identify predictors of treatment response. Studies of tissue specimens obtained before and after treatment have assessed the cellular proliferation marker Ki-67, apoptosis, and apoptosis-related factors such as p53 and p21, but reliable predictors of response remain to be established [19–27].

A meta-analysis of 14 studies in patients with advanced rectal cancer who received preoperative chemoradiotherapy reported good outcomes in patients with a pCR [8] or nearly a pCR[9, 10]. Patients with tumor downstaging have also been show to have good outcomes [11–15].

Imaging techniques used to investigate the relation of the degree of tumor shrinkage after preoperative chemoradiotherapy to the histologic tumor response

include barium enema [18] or MRI [28–30], positron emission tomography-computed tomography [31, 32], and diffusion-weighted MRI [33, 34]. Kang *et al* [29]. showed that tumor shrinkage by 75% or higher as evaluated by MRI is significantly related to a pCR. Chapet *et al* [14]. reported that patients with tumor shrinkage of 80% or higher have good OS as well as DFS.

In the present study, we examined the relation between the change in endoscopic findings after chemoradiotherapy and the histologic response to such therapy. Our results demonstrated that morphologic changes on colonoscopy were significantly related to the degree of tumor shrinkage (Table 4). This finding suggests that the change in the tumor mound is intimately related to the degree of tumor shrinkage. Morphologic changes of tumors on endoscopy were also significantly related to histologic regression, as well as T downstaging (Tables 3 and 4). Taken together, our results suggest that morphologic changes of tumors on colonoscopy after preoperative chemoradiotherapy may be useful predictors of the response to such therapy in patients with rectal cancer. Future studies should investigate the optimal timing for evaluating morphologic changes of tumors after the start of chemoradiotherapy with respect to the prediction of response.

CONCLUSIONS

Morphologic changes on endoscopy after chemoradiotherapy were associated with the degree of tumor shrinkage and histologic regression in patients with advanced rectal cancer, suggesting that such findings could be used to predict the response to preoperative chemoradiotherapy.

CONFLICT OF INTEREST STATEMENT

Toshiyuki Suzuki and other co-authors have no conflict of interest.

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