学位論文

Effect of preoperative chemotherapy on distal spread of low rectal cancer located close to the anus

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Title: Effect of preoperative chemotherapy on distal spread of low rectal cancer located close to the anus

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ABSTRACT

Purpose This study aimed to clarify the frequency of distal spread and the optimal distal margin after preoperative chemotherapy for advanced low rectal cancer.

Methods The study included patients with advanced lower rectal cancer who received preoperative chemotherapy and underwent surgery during 2012-2015. We investigated the distal spread of tumor cells, defined as the distal distance from the intramucosal distal tumor edge to the farthest tumor cells located under the submucosal layer. Clinical characteristics were compared for distal spreads ≥10 and <10 mm, and risk factors for distal spread ≥10 mm were investigated.

Results Of the 71 patients, 42 (59%) showed distal spread. Distal spreads of 1-9, 10-19, and ≥20 mm were observed in 27 (38%), 11 (15%), and 4 (6%) patients, respectively. Multivariate analysis revealed 2 independent risk factors for distal spread ≥10 mm after preoperative chemotherapy. The first risk factor is the presence of different therapeutic effects between the mucosal and deeper layers (meaning that superficial tumor shrinkage was evident on colonoscopy, but little tumor shrinkage was evident on magnetic resonance imaging) (odds ratio, 11.6; 95% CI, 2.22-61.3). The second risk factor is poorly differentiated or mucinous adenocarcinoma (odds ratio, 8.86; 95% CI,

1.58-49.9).

Conclusion A distal margin of 20 mm is required (10 mm is insufficient) for advanced lower rectal cancer patients who receive preoperative chemotherapy followed by surgery. Independent risk factors for distal spread ≥10 mm include (1) the presence of different therapeutic effects between mucosal and deeper layers and (2) poorly differentiated or mucinous adenocarcinomas.

KEYWORDS

Distal spread, Chemotherapy, Rectal cancer, Distal margin

INTRODUCTION

In cases of rectal cancer, cancer cells sometimes spread to the distal side in submucosal or deeper layers beyond the intramucosal distal edge of the tumor. This is referred to as "distal spread." Several studies have reported that the frequency of distal spread ≥10 mm is between 4.5% and 13% in cases of rectal cancer without preoperative therapy [1-6]. Factors associated with distal spread ≥10 mm include tumor stage, lymph node metastases, and poorly differentiated or mucinous adenocarcinomas [1-4, 6-8]. Furthermore, Shirouzu et al. [2] reported that only 3.6% of 610 rectal cancer patients without preoperative therapies had distal spread ≥20 mm. Thus, 20 mm is considered to be an adequate distal margin in cases of rectal cancer without preoperative therapy.

Preoperative chemoradiotherapy (CRT) has been reported to improve local control and sphincter preservation rates in patients with locally advanced rectal cancers [9, 10]. Because the frequency of distal spread ≥10 mm has been reported to be between 0% and 9.3% after preoperative CRT, a distal margin of 10 mm is allowed after preoperative CRT [11-14]. However, preoperative CRT has been reported to have a negative effect on anal function after proctectomy,

especially after intersphincteric resection (ISR) for very low rectal cancer [15]. In recent years, preoperative chemotherapy has attracted attention as a potential means of achieving both favorable oncologic outcomes and good anal function after surgery for rectal cancer located close to the anus [16], even though there have only been limited reports about distal spread after preoperative chemotherapy. Because the distal resection line for rectal cancer has a huge impact not only on oncologic outcomes but also on anal function, it would be clinically valuable to understand the status of distal spread in patients who received preoperative chemotherapy for low rectal cancer.

This study aims to clarify the frequency of distal spread, the clinical factors that are related to distal spread, and the optimal distal margin of proctectomy in patients with low rectal cancer who received preoperative chemotherapy.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the National Cancer Center Hospital in Chiba, Japan (No. NCC2016-094). The study and manuscript adhere to the

STROBE guidelines for observational studies. The length of distal spread was measured for all included patients and the frequency of distal spread was evaluated. The patients were then classified into two groups: those with distal spread ≥10 mm and those with distal spread <10 mm. The clinical characteristics of the groups were compared and risk factors for distal spread ≥10 mm were investigated.

The study included consecutive patients who underwent surgery for advanced low rectal cancer after preoperative chemotherapy at the National Cancer Center Hospital East from January 2012 to July 2015. The number of patients included during the study period determined the study size. All patients had standardized preoperative evaluations to decide preoperative staging, such as digital rectal examination, colonoscopy, computed tomography (CT), and magnetic resonance imaging (MRI). All treatment strategies were determined through multidisciplinary team conferences. Patients in the following groups were treated with preoperative chemotherapy followed by surgery, if the circumferential resection margin (CRM) was significantly clear: patients with multiple lymph node metastases or concomitant resectable distant metastases, and patients who desired to retain anal function. Preoperative CRT was administered to patients who had a threatened CRM on preoperative MRI; however, these patients were excluded from the

current study.

We conducted a retrospective review of the patients' medical records. The following clinical factors were collected: demographics, tumor distance from the anal verge, clinical stage, RECIST assessment of colonoscopy and MRI findings, differences between the colonoscopy- and MRI-based therapeutic effect evaluations, type of chemotherapy, and type of surgery. The clinical stages of tumors were diagnosed according to the Union for International Cancer Control tumor-node-metastasis (TNM) classification, 7th edition. The clinical responses of the tumors to preoperative chemotherapy were evaluated with colonoscopy and MRI using the Response Evaluation Criteria in Solid Tumors (RECIST) classification, as follows: complete response (CR), disappearance of the primary tumor; partial response (PR), at least a 30% decrease in the sum of diameters of the primary tumor; progressive disease (PD), at least a 20% increase in the sum of diameters of the primary tumor; and stable disease (SD), neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD [17]. Therapeutic effects were determined to have differed between the mucosal and deeper layers if colonoscopy- and MRI-based valuations were different. Dominant tumor shrinkage in the mucosal layer was defined as follows: tumor shrinkage was found only in the mucosal layer in the colonoscopy evaluation (evaluated as CR

or PR by RECIST), but little shrinkage of the tumor was observed in the MRI evaluation (evaluated as SD by RECIST) (Fig 1a–d).

Pathological Analysis

Each specimen was opened immediately after removal and its anterior side was marked with a string. Then, the specimen was stretched and pinned to a corkboard. The specimen was fixed in 10% neutral buffered formalin within 48 hours. The fixed specimen was cut longitudinally at an interval of 5 mm. Paraffin-embedded tumor blocks were obtained from tissue slices. All sections were stained with hematoxylin and eosin. Distal spread was defined as the distal extent of tumor cells, below the submucosal layer and beyond the intramucosal distal tumor edge (Fig. 2). Distal spread was identified histopathologically, and the length of distal spread was prospectively measured using a micrometer scale by two of the authors (K.A. and K.M.) to minimize the measurement bias (Fig. 3). K.M. is a specialist in the pathology of colorectal cancer. In the current study, we focused on whether distal spread was ≥10 or <10 mm because several studies reported that the frequency of distal spread ≥10 mm was low in rectal cancer patients who received preoperative CRT followed by surgery [11-13].

The pathological tumor regression grade was semiquantitatively determined by the ratio of the area of viable cells to the entire tumor area containing fibrotic or necrotic changes. This tumor regression grade ranged from no evidence of any treatment effect (Grade 0) to complete response (Grade 3), as follows: Grade 0, no evidence of any treatment effect; Grade 1a, viable tumor mass with obvious treatment effect in one third or less of the entire tumor mass; Grade 1b, viable tumor mass with obvious treatment effect greater than one third but less than two thirds of the entire tumor mass; Grade 2, viable tumor mass with obvious treatment effect greater than two thirds of the entire tumor mass; and Grade 3, no viable tumor cells, only fibrotic or necrotic mass [18].

Data on pathological tumor grade, depth of tumor invasion, nodal status, tumor size, and pathological tumor regression grade of preoperative chemotherapy were retrospectively collected from medical charts.

Statistical Analysis

Tumor distance from the anal verge was summarized in terms of the median value. Univariate analyses of categorical variables were performed using the chi-square test. Multivariate logistic regression analysis was used to identify independent risk factors for distal

spread ≥10 mm. Variables were included in the multivariate analysis only if they had statistically significant associations with distal spread (≥10 vs. <10 mm) in the univariate analysis. Odds ratios (ORs) are reported with 95% confidence intervals (95% CIs). All of the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 22; IBM Statistics, Chicago, IL). *P* values less than 0.05 were considered statistically significant.

RESULTS

Seventy-one patients with low rectal cancer who underwent surgery after preoperative chemotherapy were included in this study. Distal spread of the primary tumor was observed in 42 (59.2%) of these 71 patients. Distal spreads of 1-9 mm, 10-19 mm, and ≥20 mm were observed in 27 (38.0%), 11 (15.5%), and 4 (5.6%) patients, respectively. The maximum length of distal spread was 35 mm. Of the 4 patients with distal spread ≥20 mm, none showed downstaging of T stage after preoperative chemotherapy and 2 (50.0%) had more than 7 involved regional lymph nodes after preoperative chemotherapy, as determined pathologically.

Table 1 summarizes the characteristics of the patients in this study. The median distance from the tumor to the anal verge was 4 cm (range, 0-6 cm). All patients had a clinical stage of T3 or T4

before preoperative chemotherapy, and clinical downstaging of T stage after preoperative chemotherapy was observed in 20 patients (28.2%). Clinical evaluations shown TNM downstaging in 16 patients (22.5%). More than half of the patients (53.5%) were diagnosed with clinical stage III disease, and nine patients (12.7%) were diagnosed with clinical stage IV disease, but the tumors that included metastatic lesions were considered to be resectable. All patients received oxaliplatin-based preoperative chemotherapy, such as FOLFOX6 or CapeOX. Almost all patients received 6 cycles of FOLFOX6 or 4-5 cycles of CapeOX, except for 1 patient who received only 2 cycles of FOLFOX6 because of tumor growth. This patient immediately underwent an operation after 2 cycles of chemotherapy. The median time from the last dose of chemotherapy to surgery was 30 days (range, 21-52 days). The therapeutic effect was evaluated by colonoscopy in 70 patients and by MRI in 69 patients. Three patients were not included in the univariate and multivariate analyses because insufficient information was available regarding colonoscopy or MRI findings before chemotherapy. Therapeutic effects were found to differ between the mucosal and deeper layers in 17 patients (24.6%) (Fig. 4). Of these 17 patients, 9 (52.9%) showed dominant tumor shrinkage in the mucosal layer. In the remaining 8 patients (47.1%), the tumor response was confirmed only by MRI (and little tumor response was seen on

colonoscopy).

Table 2 summarizes the surgical and pathological characteristics of the patients. Pathologically evaluated downstaging of T stage was found in 34 patients (47.9%), and TNM downstaging was found in 32 patients (45.1%). Pathological CR was observed in 5 patients (7.1%). Of all the patients, 8 (11.3%) had poorly differentiated or mucinous adenocarcinomas. The median length of the pathological distal margin was 15 mm (range, 0-35 mm). One patient had a pathological distal margin of 0 mm, and this patient received postoperative radiotherapy.

The univariate analyses are shown in Table 3. The following characteristics had significant associations with distal spread ≥10 mm after preoperative chemotherapy: absence of tumor shrinkage on MRI findings after preoperative chemotherapy (evaluation as SD by RECIST) (p = 0.008), presence of poorly differentiated or mucinous adenocarcinomas (p = 0.009), and dominant tumor shrinkage in the mucosal layer (p = 0.003). The multivariate analysis showed that poorly differentiated or mucinous adenocarcinomas (OR 8.86, 95% CI 1.58-49.9) and dominant tumor shrinkage in the mucosal layer (OR 11.6, 95% CI 2.22-61.3) were independent risk factors for distal spread ≥10 mm after preoperative chemotherapy.

DISCUSSION

In this study, distal spread ≥10 mm was observed in 21.1% of advanced low rectal cancer patients who received preoperative chemotherapy followed by surgery. Our study also identified two independent risk factors for distal spread ≥10 mm after preoperative chemotherapy: (1) poorly differentiated or mucinous adenocarcinoma, and (2) dominant shrinkage only in the mucosal layer (in other words, the presence of therapeutic effects that are confirmed by colonoscopy but are not evident on MRI).

Previous studies have reported that the frequency of distal spread ≥10 mm is 4.5%-13% for rectal cancer without preoperative therapy [1-6] and 0%-9.3% for rectal cancer with preoperative CRT [11-14]. Shimada et al. [7] evaluated microscopic distal tumor spread in patients who underwent surgery without preoperative therapy. They found intramural or mesorectal distal spread ≥10 mm beyond the distal mucosal tumor edge in 8 (5.8%) of 137 patients with low rectal cancer. Chmielik et al. [11] found microscopic distal spread in 92 (47.9%) of 192 patients treated with preoperative radiation or CRT followed by surgery, but only 4 (4.3%) of the patients had microscopic distal spread greater than 10 mm. It is notable that distal spread ≥10 mm occurred at

a higher rate in the present study of patients who received preoperative chemotherapy than in the previous studies of patients who received preoperative CRT or no preoperative treatment.

Regardless of preoperative therapy, obtaining a negative distal resection margin in rectal surgery is extremely important for reducing postoperative recurrence. Nash et al. [24] reported that the presence of a close distal resection margin identified patients with increased risks of mucosal and overall cancer recurrence. Furthermore, Ihn et al. [25] showed that bowel function was significantly worse in patients with lower rectal cancer that was located close to the anus. Excessive resection of the distal rectum should be avoided to retain bowel function.

Therefore, rectal surgeons should obtain an adequate distal resection margin and assess the distal spread of invisible cancer cells prior to the operation, using imagining evaluations. Shirouzu et al. [2] evaluated the frequency of distal spread in rectal cancer without preoperative therapy, and found that only 3.6% of 610 patients with rectal cancer had distal spread ≥20 mm. In several studies of rectal cancer, the frequency of distal spread ≥20 mm has been only 0.7%-4.4% [2, 4-7]. Accordingly, distal spread ≥20 mm is thought to be rare in cases of low rectal cancer without preoperative therapy [2, 4, 6, 7], and Japanese guidelines therefore note that a distal resection margin of 20 mm from the gross distal tumor edge is suitable in anterior resection without

preoperative therapy for low rectal cancer [18]. National Comprehensive Cancer Network guidelines for rectal cancer also indicate that a negative distal bowel wall margin of 1-2 cm may be acceptable for distal rectal cancer [26]. In contrast, several studies have stated that distal spread ≥10 mm was rare after preoperative CRT followed by surgery [11-13], which suggest that a distal resection margin of 10 mm is suitable for patients who received preoperative CRT [19-23]. Similarly, Guillem et al. [12] concluded that distal resection margins of only 10 mm may be acceptable for rectal cancer patients treated with preoperative CRT in a series of 109 patients. In a study that evaluated local recurrence rates and recurrence-free survival in patients receiving preoperative CRT followed by low anterior resection, Moore et al. [20] observed no significant difference between patients with ≤10 and >10 mm distal margins. Thus, in rectal cancer patients treated with preoperative CRT, the length of the gross distal resection margin could be less than that applied in patients who do not receive preoperative therapy.

Besides the abovementioned research, the frequency of distal spread and the adequate intraoperative distal margin have not been evaluated thoroughly for rectal cancer patients who received preoperative chemotherapy. In our study, distal spread ≥10 mm after preoperative chemotherapy was shown to have been present in 21.1% of patients. Additionally, poorly

differentiated or mucinous adenocarcinomas and dominant tumor shrinkage in the mucosal layer were identified as independent risk factors for distal spread ≥10 mm. Tumor differentiation was previously reported by Komori et al. [8] to be associated with distal spread in patients who did not receive any preoperative therapy. Komori et al. [8] examined distal spread, focusing on histopathological findings. For non-solid poorly differentiated adenocarcinomas, they reported that the average length of distal spread was 10 mm. However, dominant tumor shrinkage in the mucosal layer has not been discussed previously. In the course of our research, we observed that cancer cells are more likely to remain below the submucosal layer and scatter at more distal or lateral sites in cases with preoperative chemotherapy. This finding may indicate that tumor cells are likely to remain below the submucosal layer during the time that cancer cells in the mucosal layer are shrinking. Surgeons should be more cautious about the presence of distal spread after preoperative chemotherapy in cases that show tumor shrinkage in colonoscopy-based evaluation (evaluated as CR or PR by RECIST), yet do not show tumor shrinkage in MRI-based evaluation (evaluated as SD by RECIST). This pattern of tumor shrinkage in patients who received preoperative therapy has not been reported previously, even for patients who received preoperative CRT. Our results may suggest that the optimal distal resection margin may differ

between patients who received preoperative chemotherapy and those who received preoperative CRT.

Therefore, while a distal resection margin of only 10 mm from the gross tumor edge could be adequate for rectal cancer patients with preoperative CRT, a distal resection margin of 10 mm seems to be insufficient for those with preoperative chemotherapy, especially if they have poorly differentiated or mucinous adenocarcinomas and dominant tumor shrinkage in the mucosal layer in the post-chemotherapy evaluation of tumor status. Our findings indicate that the optimal distal resection margin is 20 mm (and not 10 mm) to obtain a negative distal resection margin in patients who received preoperative chemotherapy. In our study, distal spread ≥20 mm was observed only in 4 patients (5.6%). Of the 4 patients, none had downstaging of T stage after chemotherapy, and 2 (50%) had more than 7 involved regional lymph nodes after preoperative chemotherapy, as determined pathologically. In such patients, a distal resection margin of >20 mm may be required.

There are several limitations to this study. First, the study had a retrospective, single-center design and only included a moderate number of patients. Second, this study did not include long-term outcomes, so a follow-up study is warranted. Moreover, we were unable to clarify the differences between the distal spread frequencies and lengths associated with preoperative CRT

vs. preoperative chemotherapy. Therefore, this comparison needs to be made directly in future research. In this study, detailed information on tumor location (i.e., the distance from the anal verge or anal ring) could not be collected before or after chemotherapy. A prospective study should be performed to determine adequate distal margins in cases with preoperative chemotherapy or CRT. The study should include estimation of the excised tumor location before and after preoperative therapy, and should investigate tumor scatter for rectal cancer. Despite the limitations to the current study, our findings could help to improve surgical outcomes for advanced low rectal cancer treatment. Furthermore, concerning the applicability of this study, it could serve as a model for advanced low rectal cancer after preoperative chemotherapy because consecutive patients were included during a fixed period at a single institution. However, given to the retrospective design, the types of administered chemotherapies have varied, and tumor status could not be evaluated after preoperative chemotherapy in some patients (by colonoscopy or MRI). These limitations could affect both the estimation of distal spread frequency and the analyses of related risk factors.

CONCLUSIONS

In this study of patients who received preoperative chemotherapy for advanced low rectal cancer, the overall frequency of distal spread was 59.2% and the frequencies of distal spread ≥10 mm and ≥20 mm were 21.1% and 5.6%, respectively. Poorly differentiated or mucinous adenocarcinomas and dominant tumor shrinkage in the mucosal layer are associated with elevated risks of distal spread ≥10 mm. This study also suggests that, after preoperative chemotherapy for rectal cancer, there are likely to be tumor cells scattered distally below the submucosal layer. Based on the available evidence, we conclude that the optimal distal margin is 20 mm (not 10 mm) for advanced low rectal cancer after preoperative chemotherapy. Additionally, we recommend that surgeons select abdominoperineal resection or additional preoperative CRT if a >10 mm margin cannot be guaranteed based on preoperative studies.

COMPLIANCE WITH ETHICAL STANDARDS

Funding This study was not funded.

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in

accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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Figure Legends

Fig. 1 A case with dominant tumor shrinkage evaluated by colonoscopy and magnetic resonance imaging (MRI). Colonoscopy results before and after preoperative chemotherapy are shown in (a) and (b). Tumor shrinkage was significant based on colonoscopic evaluation. MRI findings before and after preoperative chemotherapy are shown in (c) and (d). Red arrowheads indicate the tumor area. The MRI findings show less tumor shrinkage after preoperative chemotherapy. Surgical specimens are shown in (e) and (f). The macroscopic tumor edge is indicated by the black-dotted line in (e). The histopathological tumor area is shown in (f); the tumor areas in the mucosa are indicated by white lines, and tumor areas below the submucosal layer are indicated by red lines

Fig. 2 Schema of distal spread. The tumor cells located below the submucosal layer are indicated by asterisks. The distal mucosal edge of the tumor body is indicated by the green-dotted line, and the distal edge of the tumor cells located below the submucosal layer is indicated by the blue-dotted line. The length of distal spread is shown by the red two-headed arrow

Fig. 3 Histopathological findings. (a) The distal mucosal edge of the tumor body is indicated by the black arrowhead, and distal edge of the tumor cells that are below the submucosal layer is indicated by the black arrow. The length of the distal spread is indicated by black two-headed arrow, and the length of the distal margin is indicated by the red two-headed arrow. (b) Enlarged view of the blue rectangle in (a). Black arrows indicate tumor cells below the submucosal layer. (c) Enlarged view of the green rectangle in (a). Black arrowheads indicate the mucosal distal edge of the tumor cell

Fig. 4 Therapeutic effects evaluated by colonoscopy and magnetic resonance imaging (MRI). Different therapeutic effects between the mucosal and deeper layers were found in 17 patients (blue square). Dominant tumor shrinkage in the mucosal layer was found in 9 patients (red square). CS, colonoscopy; CR, complete response; PR, partial response; SD, stable disease

Table 1. Clinical characteristics of the patients

Variable	*N (%)*
Age, y[a]	59 (27-77)
Sex	
Male	23 (32.4)
Female	48 (67.6)
Tumor distance from AV, cm[a]	4.0 (0-6)
Clinical T stage	
T3	52 (73.2)
T4	19 (26.8)
Clinical N stage	
N0	24 (33.8)
N1	38 (53.5)
N2	9 (12.7)
Clinical tumor stage	
Stage II	24 (33.8)
Stage III	38 (53.5)
Stage IV	9 (12.7)
CS-based tumor regression grade[b]	
SD	23 (32.9)
PR or CR	47 (67.1)
MRI-based tumor regression grade[c]	
SD	21 (32.4)
PR	48 (67.6)
Different therapeutic effects between mucosal layer and deeper layer (different evaluations based on CS and MRI)	
CS = CR or PR; MRI = SD	9 (12.7)
CS = SD; MRI = PR	8 (11.3)
None	51 (71.8)
Preoperative chemotherapy	
FOLFOX6	69 (97.2)
CapeOX	2 (2.8)

AV = anal verge; CS = colonoscopy; SD = stable disease; PR = partial response; CR = complete response.

[a]Median (range) shown.

[b]Missing colonoscopy findings before preoperative chemotherapy in 1 (1.4%) patient.

[c]Missing MRI findings before preoperative chemotherapy in 2 (2.8%) patients.

Table 2. Surgical and pathological characteristics of the patients

Variables	*N (%)*
Type of operation	
LAR	4 (5.6)
ISR	49 (69)
APR	18 (25.4)
Tumor grade	
Well differentiated	29 (40.8)
Moderately differentiated	34 (47.9)
Poorly differentiated or mucinous	8 (11.3)
Tumor size (surgical specimens), cm[a]	3.9 (1.2-9.2)
Pathological T stage	
T0	5 (7.1)
T1	5 (7.1)
T2	16 (22.5)
T3	33 (46.4)
T4	12 (16.9)
Pathological N stage	
N0	41 (57.7)
N1	16 (22.5)
N2	14 (19.8)
Pathological tumor regression grade	
Grade 1a	41 (57.7)
Grade 1b	16 (22.5)
Grade 2	9 (12.7)
Grade 3	5 (7.1)

LAR = low anterior resection; ISR = intersphincteric resection; APR = abdominoperineal resection.

[a]Median (range)

Table 3. Analysis of variables associated with distal spread ≥10 mm

	Distal spread (mm)		*Univariate analysis*	*Multivariate analysis*	
Variables	*< 10*	*≥ 10*	*P value*	*Odds ratio (95% CI)*	*P value*
Tumor distance from AV					
< 4.0	36	10			
≥ 4.0	20	5	0.80		
Clinical T stage					
T3	43	9			
T4	13	6	0.10		
Clinical N stage					
N −	20	4			
N +	36	11	0.50		
Clinical M stage					
M0	49	13			
M1	7	2	0.60		
CS-based tumor regression grade[a]					
SD	16	7			
PR or CR	39	8	0.20		
MRI-based tumor regression grade MRI[b]					
SD	12	9			
PR	42	6	0.008		
Dominant tumor shrinkage in the mucosal layer[c]					
No	50	9			
Yes	3	6	0.003	11.6 (2.2-61.3)	0.004
Tumor grade					
Well or moderately differentiated	53	10			
Poorly differentiated or mucinous	3	5	0.009	8.9 (1.6-49.9)	0.01

AV = anal verge; CS = colonoscopy; SD = stable disease; PR = partial response; CR = complete response.

[a]Missing colonoscopy finding before preoperative chemotherapy in 1 (1.4%) patient.

[b]Missing MRI findings before preoperative chemotherapy in 2 (2.8%) patients.

[c]Dominant tumor shrinkage in the mucosal layer was defined as follows: tumor shrinkage was found only in the mucosal layer in the colonoscopy evaluation (evaluated as CR or PR by RECIST), but little shrinkage of the tumor was evident in the MRI evaluation (evaluated as SD by RECIST)

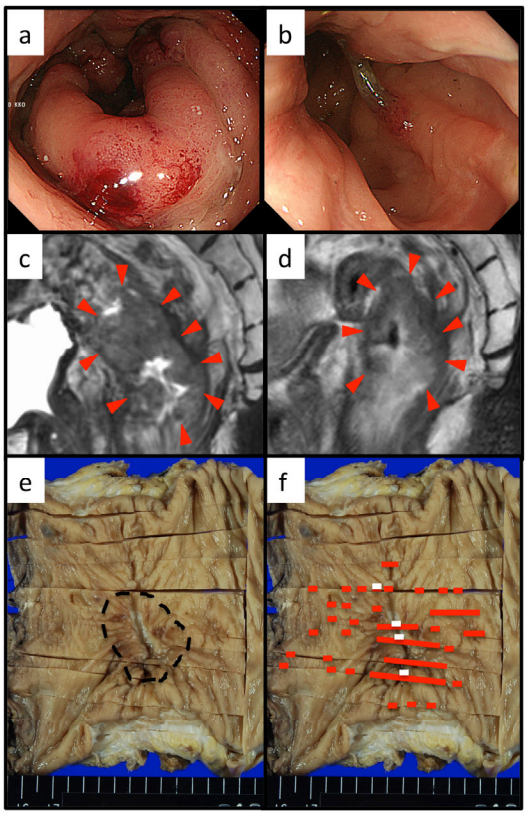


Figure 1

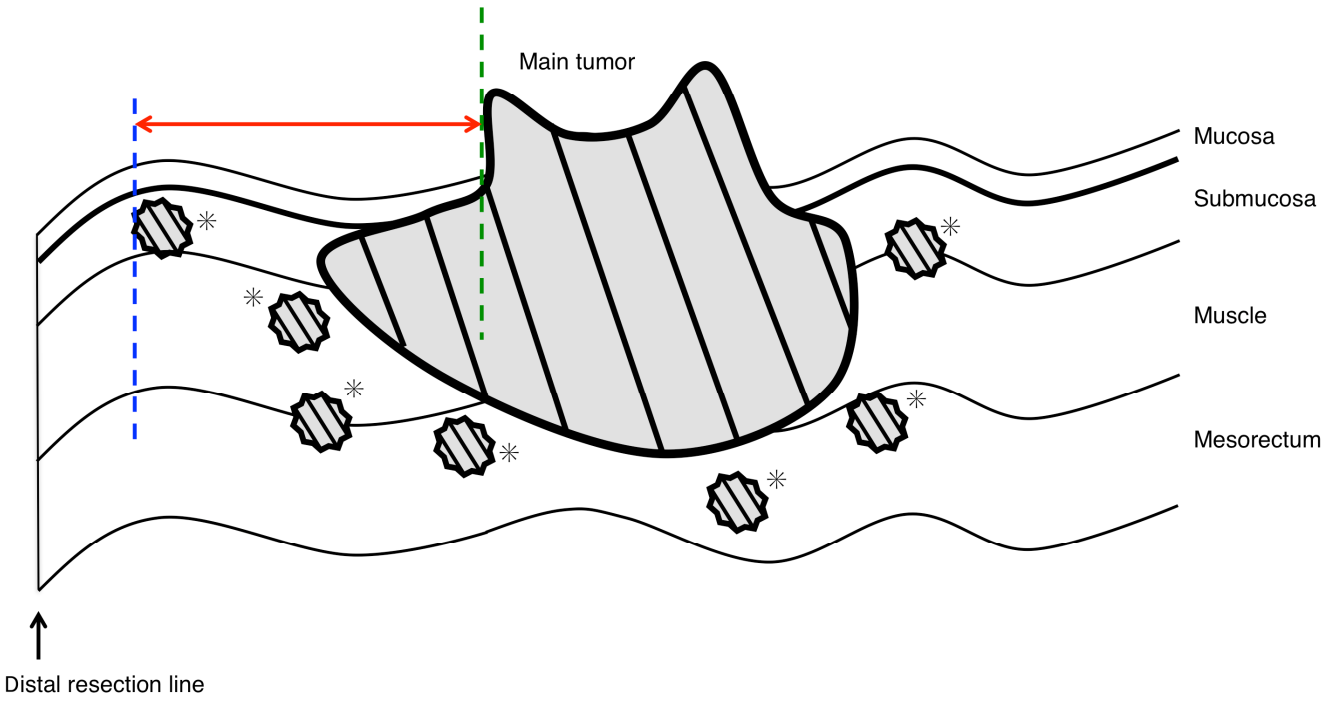

Main tumor
Mucosa
Submucosa
Muscle
Mesorectum
Distal resection line

Figure 2

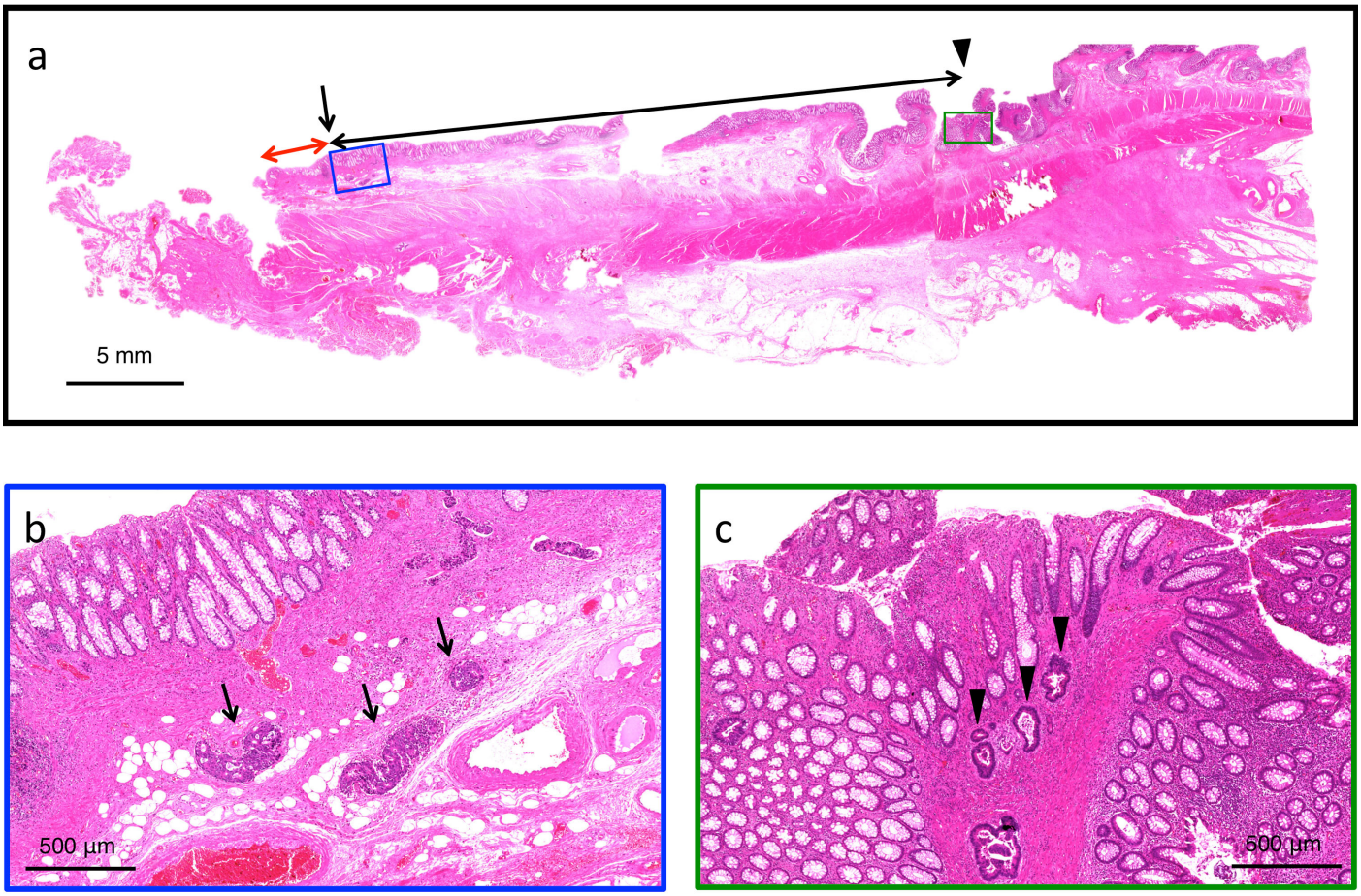
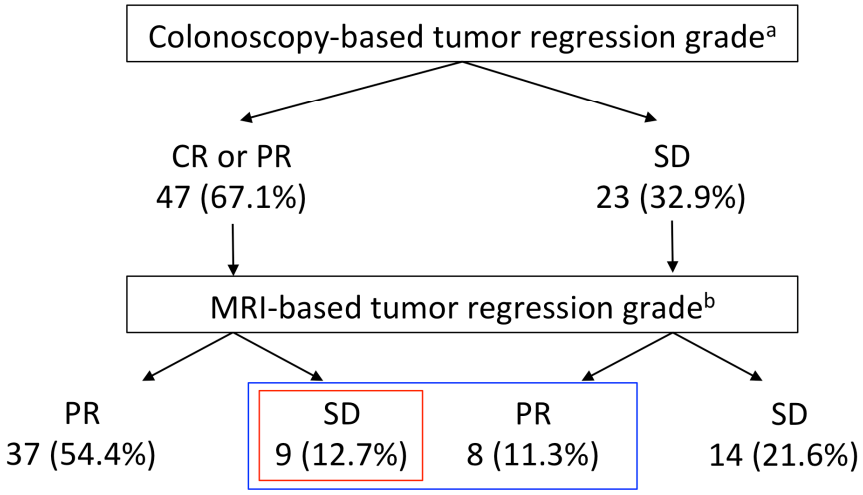


Figure 3



[a]Missing colonoscopy findings before preoperative chemotherapy in 1 (1.4%) patient.
[b]Missing MRI findings before preoperative chemotherapy in 2 (2.8%) patients.

Figure 4