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Influence of preoperative anti TNF alpha antibody therapy on postoperative recurrence of Crohn's disease

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Anti-TNFα antibodies are effective in controlling intestinal inflammation caused by Crohn's disease. However, many patients undergo surgery due to diminished efficacy of the antibodies during maintenance therapy. Currently, the decision between intensification of TNFα therapy and surgery is difficult to make. The purpose of this study was to determine the effect of preoperative treatment with anti-TNFα antibodies on postoperative recurrence of Crohn's disease. One hundred and fourteen consecutive patients with Crohn's disease who underwent bowel resection with anastomosis between 2009 and 2021 were retrospectively analyzed on the preoperative treatment history and perioperative information. Of the 74 patients who used anti-TNFα antibodies preoperatively, 43 underwent surgery after intensification of therapy following attenuation of anti-TNFα antibody efficacy. Time to postoperative endoscopic recurrence was significantly shorter in the group using anti-TNFα antibodies than in the group not using them ($p = 0.0055$). We found no difference in time to postoperative endoscopic recurrence between patients who underwent intensified therapy and those who underwent immediate surgery. Patients who received preoperative anti-TNFα antibody had a shorter time to postoperative endoscopic recurrence, but the presence or absence of intensified treatment after weakening of the anti-TNFα antibody effects did not affect the time to postoperative endoscopic recurrence.

Keywords Crohn's disease, Anti-TNF alpha, Preoperative treatment, Postoperative recurrence, Loss of response

Crohn's disease (CD) is a chronic inflammatory bowel disease common among young people in their late teens and early 20 s. In recent years, the number of CD patients in Asia, including Japan, has increased[1,2]. As of 2014, the number of CD patients in Japan was estimated to be 70,700[3]. Although the etiology of CD is currently unknown, it is considered to be a multifactorial disease caused by a combination of environmental and genetic factors. Many patients require intestinal surgery during the course of CD. The cumulative operative rate within 10 years of CD diagnosis is approximately 44–50%[4]. The recurrence rate of CD is high even after surgery, and controlling intestinal inflammation with medical therapy is important[5] to prevent repeat surgeries and improve patients' prognosis.

Antibody preparations against the inflammatory cytokine tumor necrosis factor alpha (TNFα), drugs such as Infliximab and Adalimumab, can be used in patients with CD[8,9]. In addition, Ustekinumab, an anti-IL-12/23p40 monoclonal antibody; Janus kinase (JAK) inhibitor; and Vedolizumab, monoclonal antibodies targeting α4β7 integrin heterodimers have been used to induce or maintain remission of CD[10,11].

In patients with CD who have undergone ileal resection and have no residual disease, 1 year of maintenance therapy with infliximab started within 4 weeks postoperatively significantly reduces endoscopic recurrence

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at 1 year[12]. In the POCER study, which examined the usefulness of endoscopy in evaluating postoperative recurrence and the efficacy of intensified treatment when early mucosal lesions are detected, adalimumab-treated patients had significantly fewer recurrences than patients treated with thiopurine[13]. Planned adalimumab maintenance therapy after surgery has also been shown to be beneficial in Japanese patients with CD[14]. Thus, postoperative administration of anti-TNFα antibodies may be effective in preventing postoperative recurrence of CD. However, the efficacy of intensified treatment in cases in which the therapeutic effect is attenuated during preoperative maintenance therapy, called loss of response (LOR), is unknown. Few studies have analyzed the relationship between preoperative anti-TNFα antibody treatment history and postoperative recurrence. The purpose of the present study was to examine this relationship.

Patients and methods

Patients

One hundred and fourteen consecutive patients with CD who underwent surgical bowel resection and anastomosis for CD related inflammatory indications of other than malignancy from 2009 to 2021 were included in this study. All patients underwent treatment and follow-up at Osaka University Hospital.

Assessment of clinical features

Gender, age at surgery, age at diagnosis, BMI, surgical history, lesion location, blood test results, and CD treatment history were collected retrospectively from the patients' records. The dosage of infliximab approved by the Japanese regulatory authorities for the treatment of CD is 5 mg per kg of body weight as a single intravenous infusion, administered again 2 weeks, 6 weeks, and 8 weeks after the initial dose. For adalimumab, 160 mg is injected subcutaneously for the first dose, 80 mg 2 weeks later, and 40 mg every 2 weeks thereafter. For patients with a diminished response to infliximab, doubling the dose, shortening the dosing interval to every 4–7 weeks, or switching to adalimumab are acceptable alternatives. For patients with a diminished response to adalimumab, the dose can be doubled or the treatment switched to infliximab.

The patients were divided into two groups to determine the relationship between preoperative use of anti-TNFα antibodies and postoperative recurrence. The TNFα Group was defined as patients who used anti-TNFα antibodies preoperatively, and the Non-TNFα Group was defined as patients who did not use anti-TNFα antibodies preoperatively. In addition, the TNFα Group was divided into two groups to evaluate the association between intensified treatment for preoperative anti-TNFα antibody attenuation and postoperative recurrence. The LOR Group consisted of patients who received double doses of anti-TNFα antibody, a shortened dosing regimen, or drug modification after weakening of the anti-TNFα antibody efficacy, whereas the Non-LOR Group consisted of patients who received a standard dose of anti-TNFα antibody before surgery (Fig. 1). In the introduction of biologics, anti-TNFα antibody were introduced first in all cases, and Ustekinumab, Vedolizumab and JAK inhibitors were not used prior to anti-TNFα antibody. The LOR for biologics is defined as a deviation from the state of remission after the introduction of biologics, i.e. IOIBD 0 or 1 and a state where both the erythrocyte sedimentation rate and CRP are within the institutional reference range, or when the attending

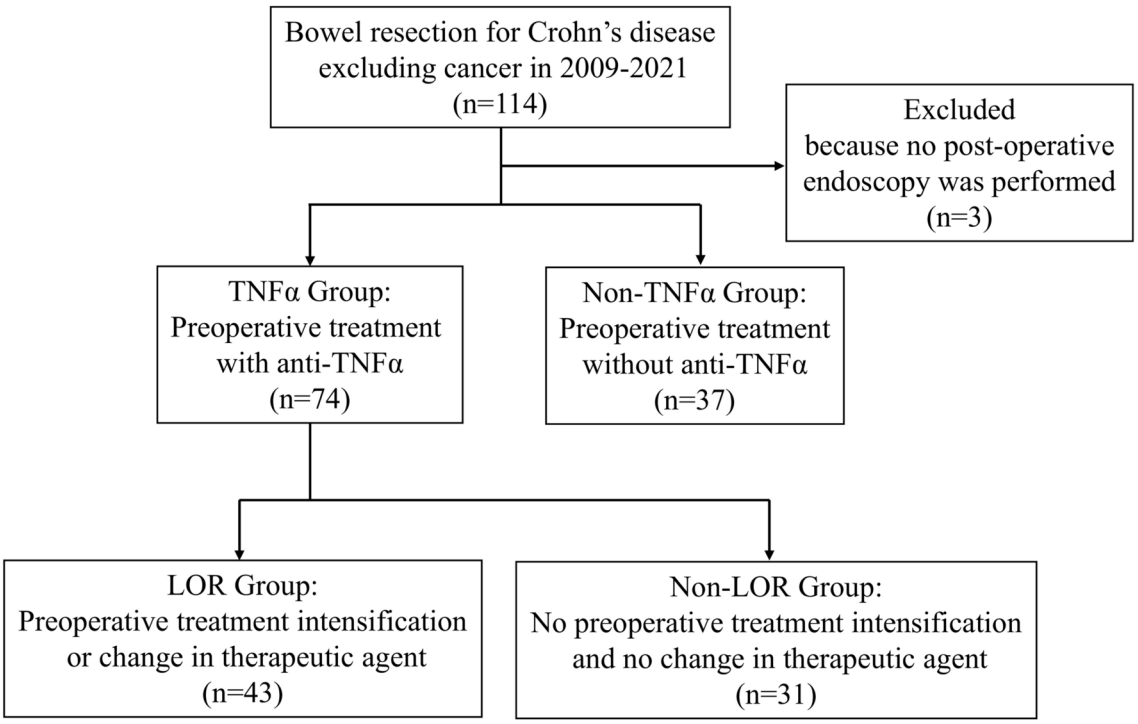

Fig. 1. Patient selection. Anti-TNFα, anti-tumor necrosis factor α; LOR, loss of response.

physician judges that there has been a relapse based on endoscopic examination. Our department's postoperative medical treatment policy was to not administer prophylactic anti-TNFα antibodies to the Non-TNFα Group and to resume the dose of anti-TNFα antibodies from before surgery in both the LOR and Non-LOR Groups, with treatment intensified according to the results of the first postoperative endoscopic examination.

Postoperative follow-up and diagnosis of recurrence

After surgery, patients were followed up as outpatients once every 1–3 months. As a rule, lower endoscopy, ileal endoscopy, and double-balloon endoscopy were performed 6–12 months after surgery, even in the absence of symptoms. Thereafter, endoscopy was performed every 1–2 years. The Crohn's Disease Activity Index (CDAI) was used to assess symptomatic recurrence, defined as CDAI ≥ 220. The Rutgeerts score (RS) was used to assess endoscopic recurrence, defined as RS ≥ i2[15,16].

Statistical analysis

Categorical data were compared using chi-squared or the Wilcoxon rank sum test. The Kaplan–Meier method and log rank test were used to compare endoscopic and symptomatic recurrence in the two groups and to calculate significant differences. $P < 0.05$ was considered significant. All statistical analyses were performed in JMP statistical software, package 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The characteristics of the 114 patients with CD who underwent surgical bowel resection and anastomosis for CD related inflammatory indications other than malignancy are provided in Table 1. The patients were mainly those who underwent initial surgery, and all patients who received biologics preoperatively were first treated with TNF agents; of those who received intensified biologic therapy before surgery after the TNF agents had diminished their efficacy, 11 patients switched to Ustekinumab and 2 patient switched to Vedolizumab. There were no cases of preoperative use of JAK inhibitors.

Characteristic	N = 114
Age at operation, years	39 (14–76)
Sex, male/female	88/26 (77.2%/22.8%)
Body mass index, kg/m^2	19.1 ± 2.8
Age group at diagnosis*	
A1	17 (14.9%)
A2	82 (71.9%)
A3	15 (13.2%)
Lesion location	
L1	54 (47.4%)
L2	10 (8.8%)
L3	48 (42.1%)
L4**	6 (5.3%)
Disease behavior	
B1	2 (1.8%)
B2	45 (39.5%)
B3	67 (58.8%)
Surgical history, primary/repeated	85/29 (74.6%/25.4%)
Preoperative albumin, mg/dL	3.5 ± 0.6
Preoperative CRP, mg/dL	1.2 ± 2.3
Preoperative CDAI	188.8 ± 101.9
Preoperative medication	
Anti-TNFα agent, +/−	74/37 (64.9%/35.1%)
Infliximab	67 (90.5%)
Adalimumab	32 (43.2%)
Switch to UST or VED after Anti-TNFα agent	13 (17.6%)
AZA · 6MP, +/−	43/71 (37.7%/62.3%)
Steroid, +/−	14/100 (12.3%/87.7%)
Interval to the first postoperative endoscopy, months	6 (1–27)

Table 1. Patient characteristics. Data are given as median (range), mean ± SD, or n (%). *According to Montreal classification. **Including cases of overlap with other locations. CRP, C-reactive protein; CDAI, Crohn's disease activity index; UST, Ustekinumab; ADA, Adalimumab; AZA, azathioprine; 6MP, 6-mercaptopurine; anti-TNFα, anti-tumor necrosis factor α.

Clinical features of the TNF groups

Anti-TNFα antibodies were used preoperatively in 74 patients. We found no differences between the TNFα and Non-TNFα Groups with respect to age at surgery, gender, BMI, preoperative CRP levels, preoperative CDAI, or corticosteroid use. However, there were significantly more cases of repeated surgery and preoperative albumin levels were significantly lower in the TNFα Group. Also, the number of patients using immunomodulatory drugs was significantly higher in the TNFα Group (Table 2).

Clinical features of the LOR groups

Of the 74 patients who used preoperative anti-TNFα antibodies, 43 received intensified treatment for decreased efficacy of the antibodies. We found no difference between the LOR and Non-LOR Groups in terms of age at surgery, gender, BMI, surgical history, preoperative albumin level, preoperative CRP level, preoperative CDAI, presence of immunomodulatory drugs or corticosteroid use (Table 3).

Endoscopic and symptomatic relapse and recurrence

The median follow-up period was 84 months. Figure 2 shows the endoscopic and symptomatic recurrence-free periods and the time elapsed without requiring reoperation for 111 patients.

The time to postoperative endoscopic recurrence was significantly shorter in the TNFα Group than the Non-TNFα Group ($p = 0.0055$; Fig. 3a). The time to postoperative symptomatic recurrence was not significantly different between the two groups (Fig. 3b). In addition, we found no predominant difference in time to postoperative endoscopic recurrence-free or time to symptomatic recurrence between the LOR and Non-LOR Groups (Fig. 4).

Discussion

The outcome of CD has improved dramatically with advances in medical therapy, especially biologic agents[17]. However, the emergence of a LOR to anti-TNFα antibodies has been problematic, with an attenuated therapeutic response reported to occur in approximately 37% of cases[18]. LOR is typically seen in 20% to 30% of patients, but approximately 10% of cases each year and nearly half of cases in 5 years have been reported to experience LOR[19]. The primary mechanism of LOR is thought to be a decrease in blood and tissue levels of anti-TNFα antibody. Anti-infliximab and anti-adalimumab antibodies have been reported as a possible cause[20,21]. As the main cause of LOR is a decrease in blood levels, the ACCENT I study increased the dose in 40 patients who

Characteristic	TNFα group n = 74	Non-TNFα group n = 37	*P* value
Age, years	38 (14–76)	42 (19–72)	0.3763
Male/female, n	57/17	28/9	0.8741
Body mass index, kg/m^2	19.0 ± 2.8	19.6 ± 3.0	0.2618
Age group at diagnosis,* n			
A1	14	3	
A2	56	23	
A3	4	11	
Lesion location, n			
L1	30	22	
L2	8	2	
L3	34	13	
L4**	4	2	
Disease behavior, n			
B1	2	0	
B2	36	9	
B3	36	28	
Surgical history, primary/repeated, n	53/21	33/4	0.0265
Preoperative albumin, mg/dL	3.4 ± 0.6	3.7 ± 0.5	0.0121
Preoperative CRP, mg/dL	1.1 ± 2.2	1.3 ± 2.6	0.5888
Preoperative CDAI	186.0 ± 98.8	194.6 ± 107.7	0.6886
Preoperative medication			
AZA · 6MP, +/−, n	36/38	6/31	0.0008
Steroid, +/−, n	12/62	2/35	0.1077

Table 2. Patient characteristics according to TNFα treatment. Data are presented as median (range) or mean ± SD unless otherwise noted. *According to Montreal classification. **Including cases of overlap with other locations. CRP, C-reactive protein; CDAI, Crohn's disease activity index; AZA, azathioprine; 6MP, 6-mercaptopurine.

Characteristic	LOR group n = 43	Non-LOR group n = 31	*P* value
Age, years	37 (18–76)	39 (14–68)	0.5546
Male/female, n	32/11	25/6	0.5299
Body mass index, kg/m^2	19.2 ± 2.7	18.6 ± 2.9	0.3785
Age group at diagnosis,* n			
A1	11	3	
A2	31	25	
A3	1	3	
Lesion location, n			
L1	13	17	
L2	4	4	
L3	25	9	
L4**	3	1	
Disease behavior, n			
B1	1	1	
B2	22	14	
B3	20	16	
Surgical history, primary/repeated, n	31/12	21/10	0.6862
Preoperative albumin, mg/dL	3.4 ± 0.5	3.4 ± 0.7	0.8207
Preoperative CRP, mg/dL	1.1 ± 1.7	1.1 ± 2.6	0.8780
Preoperative CDAI	182.7 ± 87.2	190.6 ± 112.5	0.7426
Preoperative medication			
Infliximab	40 (93.0%)	26 (83.9%)	
Adalimumab	26 (60.5%)	5 (16.1%)	
Switch to UST or VED after anti-TNFα agent	13 (30.2%)	0	
AZA · 6MP, +/−, n	24/19	12/19	0.1504
Steroid, +/−, n	10/33	2/29	0.0540

Table 3. Patient characteristics according to loss of response (LOR). Data are presented as median (range) or mean ± SD unless otherwise noted. *According to Montreal classification. **Including cases of overlap with other locations. CRP, C-reactive protein; CDAI, Crohn's disease activity index; UST, Ustekinumab; ADA, Adalimumab; AZA, azathioprine; 6MP, 6-mercaptopurine.

initially responded but had lost efficacy by week 54. To avoid a decrease in efficacy during maintenance therapy, 5 mg/kg infliximab was increased to 10 mg/kg, which restored efficacy in 36 patients (90%)[22].

In addition to evaluating clinical symptoms, endoscopic evaluation of postoperative recurrence is important[23]. After resection of the ileum, only 20% of CD patients are symptomatic 1 year postoperatively, but endoscopically recurrent lesions in the anastomotic ileum have been reported in 73% of cases[24]. Regarding recurrence after ileal resection and anastomosis, small aphthous ulcers appear on the ileal side of the anastomosis within the first postoperative year, and serpiginous ulcers and nodular thickening appear 1 to 3 years postoperatively. Anastomotic stenosis has been shown to occur within 3 to 10 years postoperatively[25]. The RS is used to evaluate postoperative endoscopy based on these observations. Symptomatic recurrence rates are low for i0 and i1 cases, but high for i2 to i4 cases.

In this study, we examined the preoperative anti-TNFα antibody treatment history and postoperative recurrence. As previously reported, endoscopic recurrence preceded symptomatic recurrence.

Preoperative serum albumin levels were significantly lower in the TNFα-treated group than the untreated group. Lower serum albumin levels are significantly correlated with increased clearance of infliximab, leading to a shorter half-life[26]. Low serum albumin levels also correlate with postoperative endoscopic recurrence in patients receiving preoperative anti-TNFα antibody therapy[27], consistent with a significantly higher incidence of endoscopic recurrence in the TNFα Group than in the Non-TNFα Group. In addition to low serum albumin levels, male sex and high BMI are known factors that increase the clearance of anti-TNFα antibodies[28].

One of the main causes of LOR is the appearance of antibodies to biological agents. Patients who develop LOR during preoperative anti-TNFα antibody therapy are considered to have emerging antibodies to anti-TNFα antibodies and are likely to relapse even with postoperative anti-TNFα antibody therapy.

This study has several limitations. First, it is a retrospective study conducted at a single institution with a small number of patients. Second, the timing of postoperative endoscopy in this study varied from patient to patient. Finally, this study did not measure antibody levels to biologics, a possible cause of LOR. Many new anti-TNFα antibodies have emerged to replace infliximab and adalimumab, as well as antibodies targeting cytokines and chemokines other than TNFα. Postoperative follow-up should consider the history of preoperative antibody therapy.

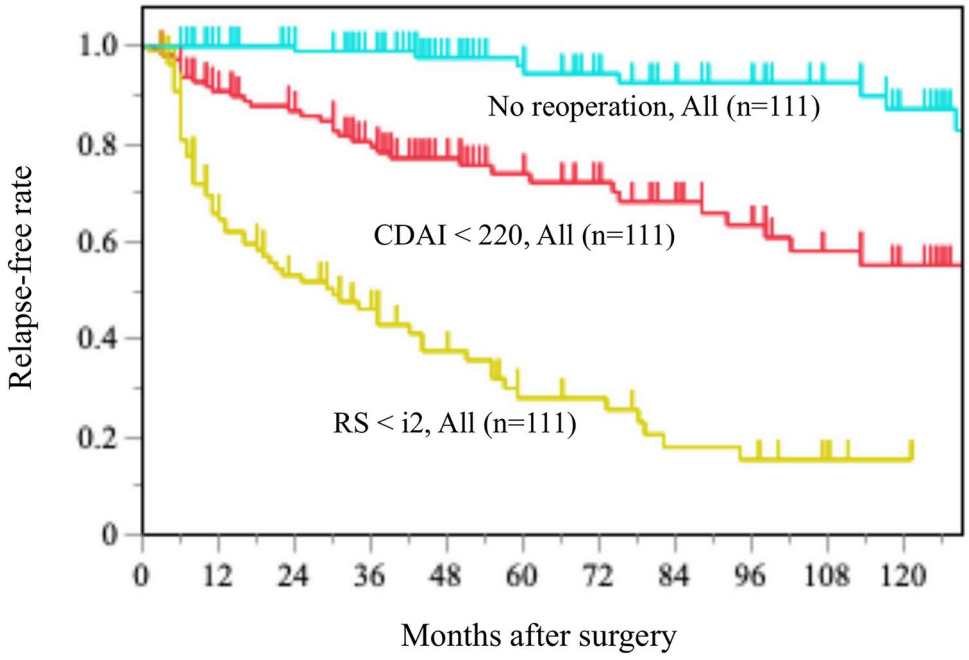

Fig. 2. Postoperative endoscopic and symptomatic relapse-free duration and operation-free duration. RS, Rutgeerts score; CDAI, Crohn's disease activity index.

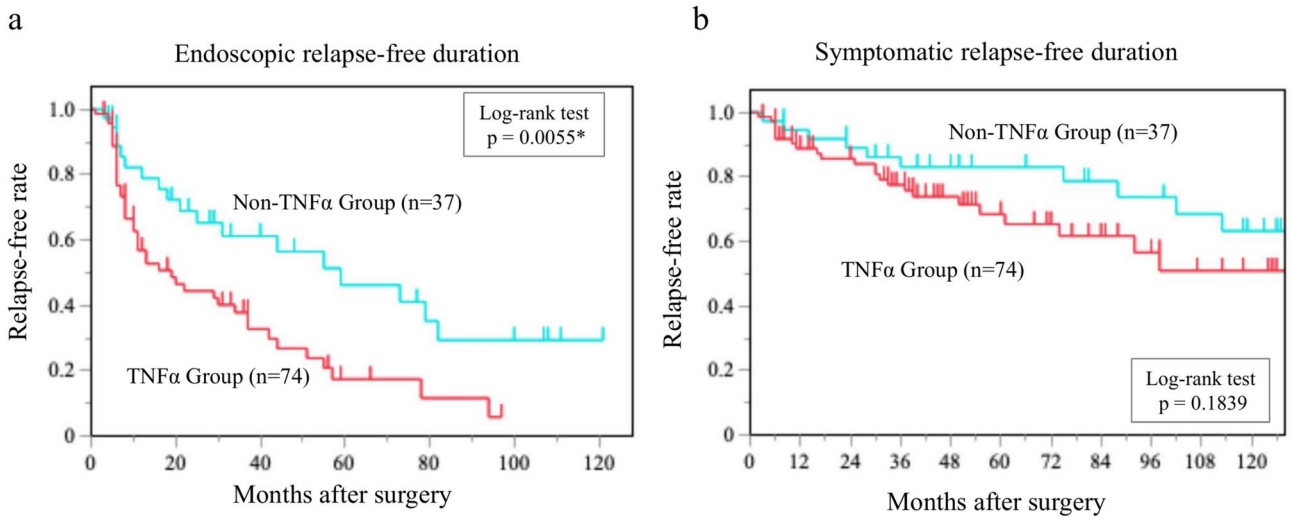

Fig. 3. Endoscopic and symptomatic relapse-free duration based on preoperative anti-TNFα agent use. Anti-TNFα, anti-tumor necrosis factor α.

In conclusion, patients who received preoperative anti-TNFα antibody therapy had a shorter time to endoscopic recurrence than those who did not receive the therapy.

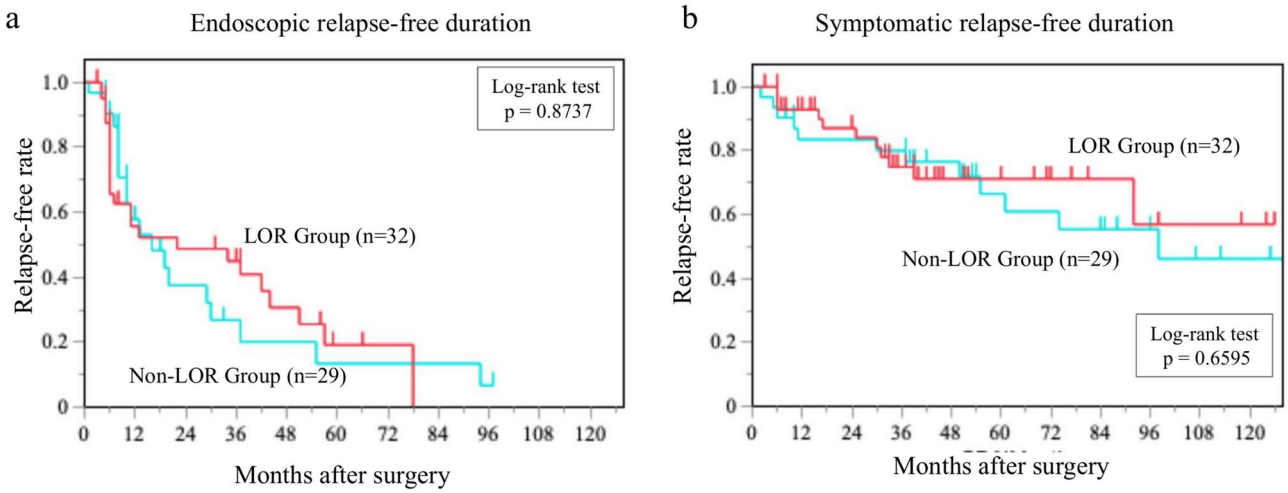

Fig. 4. Endoscopic and symptomatic relapse-free duration based on the loss of response (LOR) after preoperative anti-TNFα with intensified treatment.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to consent from participants but are available from the corresponding author on reasonable request.

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Author contributions
Y.S., T.O., and T.M. designed the study and wrote the manuscript. T.T., M.T., T.H., A.H., H.T., N.M., and M.U. performed data collection and analysis. Y.D. and H.E. approved the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
The Osaka University Clinical Research Review Committee approved this study (approval number: 15028-2). All patients provided written informed consent. If the patient was under 18 years of age, informed consent was obtained from the parent. All methods were performed in accordance with the relevant guidelines and regulations.

Additional information
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