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Utility of endoscopic diagnosis for postoperative small-bowel lesions in patients with Crohn's disease at double-balloon endoscopy

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ABSTRACT

Double-balloon endoscopy (DBE) has enabled precise diagnosis and endoscopic intervention deep within the small bowel. In this study, we determine the factor related to the risk of endoscopic and clinical recurrences in the diagnosis of postoperative lesions including anastomosis for the patients with Crohn's disease. Forty-eight patients (40 men and 8 women) had undergone small bowel resection previously and anastomotic sites were evaluated by Rutgeerts' endoscopic scoring. The factors related to endoscopic and clinical recurrences at anastomosed sites were investigated. The analyzed items included the disease type, anastomosis procedure, frequency of surgery, time to endoscopy after surgery, the presence or absence of treatment with 5-aminosalicylic acid (5-ASA), immunomodulators, steroids, maintenance administration of infliximab, and an elemental diet that required the ingestion of 900 kcal or more per day. Outcome of the anastomosed lesions was analyzed in the groups treated with and without postoperative anti-TNFα antibody including infliximab and adalimumab. DBE was performed 133 times, and 168 anastomosed lesions were observed for enrolled patients. Univariate analysis showed that time to DBE after surgery of 1.5-year or longer and the absence of 5-ASA administration were found to be significant factors leading to both endoscopic and clinical recurrences. The results of Kaplan-Meier estimate and the log rank test demonstrated that the clinical recurrence was avoided more often in the anti-TNFα antibody-treated group compared with the non-treated group. In conclusion, DBE was useful for accurate diagnosis of small-bowel lesions after surgery. Anti-TNFα antibody may help to decrease the postoperative recurrence rate of Crohn's disease.

Key Words: double-balloon endoscopy, Crohn's disease, biologics, small bowel, surgery

Abbreviations: double-balloon endoscopy (DBE), 5-aminosalicylic acid (5-ASA),

INTRODUCTION

Crohn's disease is a chronic inflammatory disease that manifests throughout the full-thickness of the gastrointestinal layer. Early diagnosis is difficult in many cases, and small-bowel lesions are often accompanied by fistula and stenosis on the first examination and require surgery.[1, 2] The

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reoperation rate is high, and internal therapy, based on evaluation of the small-bowel lesions and endoscopic treatment of the stenosis of the small intestine, may be important to avoid surgery.[3] Once healing of the intestinal mucosa has been achieved, the intestinal condition tends to be maintained thereafter in many reported cases.[4, 5] The effects of biological agents and immunomodulators in the treatment of Crohn's disease have been demonstrated, and a high therapeutic efficacy can be expected with multiple drug administrations when the pathology is accurately evaluated, even for intractable cases.[6] Double-balloon endoscopy (DBE) has enabled precise diagnosis and endoscopic intervention deep within the small bowel.[7, 8] Using DBE, endoscopic findings of Crohn's disease can be observed closely, facilitating understanding of the lesions. DBE also enables close observation of the anastomosed sites after surgery for Crohn's disease and after endoscopic balloon dilatation of the stenotic lesions.[9] The objective of this study was to retrospectively review patients who underwent evaluation of the anastomosed sites of the small bowel using DBE after surgery, and to elucidate the characteristics and factors involved in recurrence at the anastomosed sites.

PATIENTS AND METHODS

The subjects were Crohn's disease patients who underwent DBE assessment of the small bowel mucosa at the anastomosed sites following surgery at our hospital. DBE was performed as reported previously,[10, 11] and the findings were reviewed in the DBE database of our hospital, including endoscopic images, and medical records. The background demographics of the patients were also investigated. The condition of the anastomosed lesion site was evaluated in 5 steps, Grades 0–4, using the endoscopic scoring reported by Rutgeerts *et al.*,[12] and the following 2 items were investigated: Of the anastomosed lesions classified, those graded 2, 3, and 4 were regarded as endoscopic recurrence, and recurrence-related factors were investigated using univariate analysis. Of the anastomosed lesions classified, those graded 0, 1, 2, and 3 were regarded as clinical remission and the grade 4 lesions were regarded as clinical recurrence. These recurrence-related factors were investigated using univariate analysis.

The analyzed items included the disease type, anastomosis procedure, frequency of surgery, time to endoscopy after surgery, the presence or absence of treatment with 5-aminosalicylic acid (5-ASA), immunomodulators, steroids, maintenance administration of infliximab, and an elemental diet that required the ingestion of 900 kcal or more per day. Since the efficacy of anti-TNFα antibody has been reported recently,[13] the outcome of the anastomosed lesions was analyzed between the groups that were treated with and without postoperative anti-TNFα antibody.

RESULTS

Data from forty-eight patients at our hospital were reviewed (Table 1). At the time of the first admission to our hospital, the mean age was 37.4 years and the mean duration of illness was 9.3 years. There was a greater number of male patients, and the disease type was small bowel in 32 and small and large bowel in 16 patients, showing that there were more patients with the small bowel type. The mean number of surgeries was 1.4 times. The disease was symptomatic at the time of the first DBE in 31 patients, including abdominal pain and abdominal fullness, and remained asymptomatic in 17 patients. DBE was performed 133 times, and 168 anastomosed lesions were observed. The conditions of the anastomosed sites were classified according to the endoscopic score reported by Rutgeerts *et al.* (Figure 1).

Table 1 Characteristics of patients of whom anastomotic sites was evaluated by double-balloon endoscopy

Number of patients	48
Gender (male/female)	40 / 8
Age (y.o., mean±S.D.)	37.4±10.5
Disease duration (mean±S.D.)	9.3±6.2 years
Disease location (Ileal/Iliocolonic)	32 / 16
Post surgical history (times, mean±S.D.)	1.4±0.7

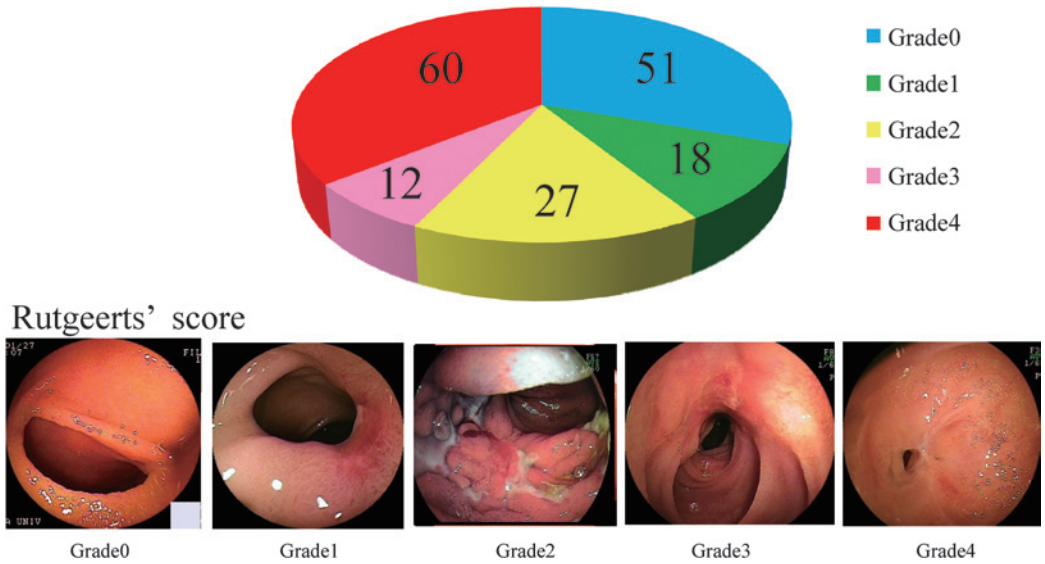

Fig. 1 Rutgeerts' scores of 168 anastomotic sites evaluated by DBE

The factors related to endoscopic recurrence at anastomosed sites were investigated. A time to DBE after surgery of 1.5-year or longer and the absence of 5-ASA administration were found to be significant factors leading to endoscopic recurrence (Table 2).

On analysis of factors leading to clinical recurrence, similar to endoscopic recurrence, a duration to DBE of 1.5-year or longer after surgery and the absence of 5-ASA administration were found to be significant (Table 3).

The 48 postoperative patients were divided into two groups, with and without administration of anti-TNFα antibody, which were comprised of 22 and 26 patients, respectively. The grade 4 outcomes based on the classification of Rutgeerts *et al.* were analyzed based upon these 2 treatment groups. The anti-TNFα antibodies were infliximab in 21 patients and adalimumab in 6 patients (5 patients overlapped). They included administration with irregular periods and on demand. The outcomes during the follow-up period (median duration: 51 months) were analyzed using the Kaplan-Meier estimate and the log rank test. The conditions leading to clinical recurrence were avoided more often in the anti-TNFα antibody-treated group compared with the non-treated group (Figure 2).

Table 2 Factors for affecting endoscopic recurrence (Rutgeerts score ≦1 vs. ≧2)

		Rutgeerts score≦1 (n=69)	Rutgeerts score ≧2 (n=99)	*P* value
Type	perforating type	23	34	0.8918
	non perforating type	46	65	
Operative procedure	End-to-end	53	81	0.6540
	Stricture plasty	13	13	
	others	3	5	
Previous surgery	≧3 times	11	19	0.5889
	<3times	58	80	
Postoperative period	**≧1.5 years**	42	87	**0.0128**
	<1.5 years	27	12	
Elemental diet *	+	43	53	0.3046
≧900 kcal/day	−	25	42	
5-aminosalicylic acid	+	68	85	0.0211
	−	1	14	
Steroid	+	10	14	0.9490
	−	59	85	
Immunomodulator	+	34	46	0.7197
	−	35	53	
Maintenance of Infliximab	+	5	5	0.5560
	−	64	94	

* Database lacked the descriptions about elemental diet in five patients.

Table 3 Factors for affecting Clinical recurrence (Rutgeerts score ≦3 vs.4)

		Rutgeerts score≦3 (n=108)	Rutgeerts score 4 (n=60)	*P* value
Type	perforating type	37	20	0.9033
	non perforating type	71	40	
Operative procedure	End-to-end	85	49	0.3481
	Stricture plasty	19	7	
	other	4	4	
Previous surgery	≧3 times	17	13	0.3383
	<3 times	91	47	
Postoperative period	≧1.5 years	60	50	0.0002
	<1.5 years	48	10	
Elemental diet *	+	63	33	0.9031
≧900 kcal/day	−	44	24	
5-aminosalicylic acid	+	102	51	0.0475
	−	6	9	
Steroid	+	13	11	0.2669
	−	95	49	
Immunomodulator	+	45	35	0.0394
	−	63	25	
Maintenance of Infliximab	+	7	3	0.6981
	−	101	57	

* Database lacked the descriptions about elemental diet in four patients.

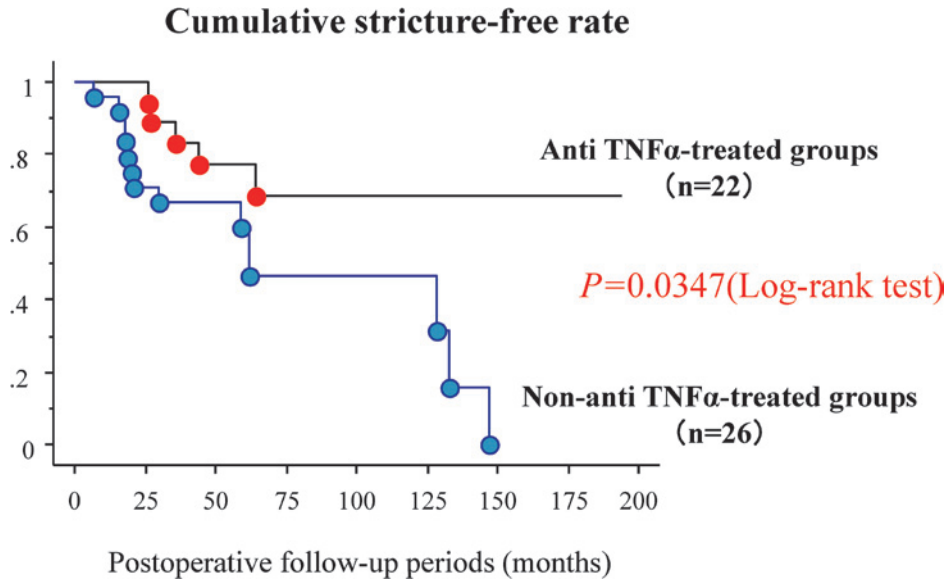

Fig. 2 Long-term outcome with or without anti-TNFα antibody (Follow-up Median: 51 months, Range: 5-194 months)

DISCUSSION

Crohn's disease patients frequently undergo intestinal resection, and surgery is performed for stenotic lesions in many cases. To avoid re-surgery, we propose the periodic evaluation of anastomosed sites and current lesions with endoscopy. Based upon our investigation of the 48 postoperative patients with Crohn's disease, whose course was followed using DBE at our department, 5-ASA may be effective as a base therapeutic drug, and it may be important to endoscopically evaluate anastomosed sites to determine the therapeutic effect using DBE within 1.5 years after surgery. As Figure 2 showed, the anti-TNFα antibodies were effective for postoperative patients to avoid small bowel stenosis, though the analysis for each lesion did not have same results (Table 2, 3). Ulcerative lesions were observed at most of the anastomosed sites in the group not treated with 5-ASA. Ulcer of the anastomosed region can develop due to the state of Crohn's disease or can be induced by mild ischemia following anastomosis, and 5-ASA was judged as effective for both conditions. If the anastomosed region has not been observed for a long time after surgery, the therapeutic strategy will be investigated based on symptoms. However, when symptoms become evident, the condition has already progressed to grade 4 of the classification established by Rutgeerts *et al.* in many cases. Early diagnosis of recurrence at the anastomosed region by endoscopy early after surgery can lead to the prevention of later reoperation. In addition, maintenance administration of anti-TNFα antibody after surgery may be effective in maintaining remission of the anastomosed lesion and preventing stenosis.[14] Improvement of postoperative treatment is essential for patients who have previously undergone surgery, because clinical activity may be or may have been high, however, the patients themselves may not consider it necessary due to the absence of symptoms. In such cases, the necessity of increasing treatment could be explained by showing them the endoscopic lesions.[15]

We adopted the classification established by Rutgeerts *et al.* for our evaluation of the anastomosed regions. However, this scoring system is limited to the evaluation of anastomosed

sites and their surroundings, which is not appropriate for evaluation of the entire small intestine after surgery. Indeed, in many cases, the ulcer tends to be limited to the anastomosed region even while the other intestinal region is in remission after ileocecal resection. However, the primary lesion may be present in regions other than the anastomosed region in patients with high disease activity.[16, 17] The establishment of a scoring system capable of evaluating the entire small intestine after surgery is anticipated. In conclusion, DBE was thought to be useful for the accurate diagnosis of small-bowel lesions after surgery.

Conflict of Interest: None declared.

REFERENCES

1) Blum E, Katz JA. Postoperative therapy for Crohn's disease. *Inflamm Bowel Dis*, 2009; 15: 463–472.
2) Peyrin-Biroulet L, Loftus EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol*, 2010; 105: 289–297.
3) Vaughn BP, Moss AC. Prevention of post-operative recurrence of Crohn's disease. *World J Gastroenterol*, 2014; 20: 1147–1154.
4) Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G. Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology*, 2010; 138: 463–468.
5) Hall B, Holleran G, Chin JL, Smith S, Ryan B, Mahmud N, McNamara D. A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. *J Crohns Colitis*, 2014; 8: 1601–1609.
6) Zimmerman LA, Shamberger RC, Valim C, Bousvaros A. The effect of immunomodulators and biologics on indication for surgical bowel resection in children with Crohn's disease. *Inflamm Bowel Dis*, 2014; 20: 1015–1020.
7) Nakamura M, Niwa Y, Ohmiya N, Miyahara R, Ohashi A, Itoh A, Hirooka Y, Goto H. Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in patients with suspected small-bowel bleeding. *Endoscopy*, 2006; 38: 59–66.
8) Nakamura M, Hirooka Y, Watanabe O, Yamamura T, Nagura A, Yoshimura T, Nakano A, Ando T, Ohmiya N, Goto H. Minimally invasive extraction of a foreign body from the small intestine using double-balloon endoscopy. *Nagoya J Med Sci*, 2015; 77: 189–194.
9) Ohmiya N, Arakawa D, Nakamura M, Honda W, Shirai O, Taguchi A, Itoh A, Hirooka Y, Niwa Y, Maeda O, Ando T, Goto H. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc*, 2009; 69: 84–93.
10) Honda W, Ohmiya N, Hirooka Y, Nakamura M, Miyahara R, Ohno E, Kawashima H, Itoh A, Watanabe O, Ando T, Goto H. Enteroscopic and radiologic diagnoses, treatment, and prognoses of small-bowel tumors. *Gastrointest Endosc*, 2012; 76: 344–354.
11) Nakamura M, Ohmiya N, Shirai O, Takenaka H, Morishima K, Miyahara R, Ando T, Watanabe O, Kawashima H, Itoh A, Hirooka Y, Goto H. Route selection for double-balloon endoscopy, based on capsule transit time, in obscure gastrointestinal bleeding. *J Gastroenterol*, 2010; 45: 592–599.
12) Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*, 1990; 99: 956–963.
13) Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*, 2015; 148: 344–354.
14) Beppu T, Ono Y, Matsui T, Hirai F, Yano Y, Takatsu N, Ninomiya K, Tsurumi K, Sato Y, Takahashi H, Ookado Y, Koga A, Kinjo K, Nagahama T, Hisabe T, Takaki Y, Yao K. Mucosal healing of ileal lesions is associated with long-term clinical remission after infliximab maintenance treatment in patients with Crohn's disease. *Dig Endosc*, 2015; 27: 73–81.
15) Kim DH, Park SJ, Park JJ, Yun YH, Hong SP, Kim TI, Kim WH, Cheon JH. Effect of follow-up endoscopy

on the outcomes of patients with inflammatory bowel disease. *Dig Dis Sci*, 2014; 59: 2514–2522.
16) Takenaka K, Ohtsuka K, Kitazume Y, Nagahori M, Fujii T, Saito E, Naganuma M, Araki A, Watanabe M. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. *Gastroenterology*, 2014; 147: 334–342.
17) Flamant M, Trang C, Maillard O, Sacher-Huvelin S, Le Rhun M, Galmiche JP, Bourreille A. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. *Inflamm Bowel Dis*, 2013; 19: 1390–1396.