# Findings of Retrograde Contrast Study Through Double-balloon Enteroscopy Predict the Risk of Bowel Resections in Patients with Crohn's Disease with Small Bowel Stenosis

Noriko Okazaki*, Toshihiro Inokuchi*, Sakiko Hiraoka*, Masayasu Ohmori*, Shiho Takashima*, Daisuke Takei*, Yuusaku Sugihara*, Masahiro Takahara*, Keita Harada*, Seiji Kawano*, Hiroyuki Okada*, Jun Kato**,

*Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, **Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan.

**Correspondence:**

Sakiko Hiraoka, M.D.

Department of Gastroenterology and Hepatology,

Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Phone: (+81)-86-235-7219, Fax: (+81)-86-225-5991

Email: sakikoh@cc.okayama-u.ac.jp

There are no funding received for this work from any organizations.

**Abbreviations**: CD, Crohn's disease; IBD, inflammatory bowel disease;

DBE, double balloon enteroscopy; ROC, receiver operating characteristic curve.

**Abstract**

***Backgrounds:*** Crohn's disease (CD) patients with small bowel strictures are at risk of surgery. Double-balloon enteroscopy (DBE) can evaluate the status of the small intestine, and retrograde contrast through the scope enables the surgeon to obtain information beyond the reach of the scope. This study aimed to examine whether a retrograde contrast study through DBE could be used as a predictor of subsequent surgery in CD patients with small intestinal strictures.

***Methods:*** The findings of DBE with retrograde contrast in 48 CD patients with small bowel strictures were examined.

***Results:*** Of the 48 patients, 14 (29%) underwent surgery for small intestinal strictures during a median observation period of 2.4 years (interquartile range: 1.4–3.7 years). According to the results of the multivariate analysis, a maximum length of strictures ≥ 20 mm and the ratio of the maximum diameter of prestenotic dilations to the diameter of the normal small intestine ≥ 1.4 were independent risk factors of surgery for small intestinal strictures (risk ratio = 7.6 [95% CI: 1.8-42.0], $p$ = 0.006; and risk ratio = 52.0 [95% CI: 3.5-2485.1], $p$ = 0.002, respectively). The latter predicted subsequent surgery with 92% sensitivity and 88% specificity. Cumulative surgery-free rates were discriminated significantly according to the presence or absence of these two risk factors (log-rank test: $p < 0.001$)

***Conclusions:*** Findings of retrograde contrast through DBE are helpful to predict risk of surgery in CD patients with small intestinal strictures.

**Keywords:** Crohn's disease, double-balloon enteroscopy, retrograde contrast

## Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that can involve the entire gastrointestinal tract and causes several complications, including intestinal and extra-intestinal disease.[1-3] Intestinal stricture is one of the most common intestinal complications in patients with CD, and it can reduce their quality of life because of symptoms of stenosis, which often necessitates surgery.[4, 5] Strictures occur in the small intestine more frequently than in the colon possibly due to its narrow diameter. Repetitive surgical interventions for recurrent strictures in the small intestine can lead to intestinal failure and malnutrition.[6] Despite recent advances in medical therapy and endoscopic balloon dilation, up to 30% of patients require at least one surgical resection within 10 years after diagnosis.[7] In this regard, accurate evaluation of small intestinal lesions and adequate assessment of risk for surgery are mandatory in clinical practice.

Although imaging modalities, including computed tomography (CT) enterography, magnetic resonance (MR) enterography and transabdominal ultrasound are useful for evaluation of small bowel status, the findings associated with the risk of surgery are rarely reported. Recent reports have demonstrated that MR imaging could detect critical strictures, and that detection of stenosis with the modality was a predictive factor for surgery.[8, 9] However, the positive predictive value (PPV) of stenosis detection with MR for surgery was low (less than 30%), indicating that the modality could not sufficiently predict the risk of surgery.

Double-balloon enteroscopy (DBE) has become common in recent decades and the usefulness for assessment of the small bowel has been reported.[10] DBE has unique advantages, in that histopathologic specimens can be obtained and performing therapeutic procedures such as balloon dilation for strictures is possible, in addition to reaching and observing the deep small intestine. However, DBE is a time and energy-consuming

procedure. Additionally, accessing the deep small intestine is difficult, particularly in patients with multiple surgeries, severe intra-abdominal adhesions, or strictures. When deep insertion into the small intestine is not allowed, information regarding the small intestine beyond the reach of the scope could be obtained by introducing retrograde contrast through the DBE scope. The procedure can be easily performed by injection of water-soluble contrast medium without additional operations or further equipment. However, the clinical relevance of retrograde contrast findings in CD patients has not been fully reported.

We hypothesized that retrograde contrast findings during DBE could predict the risk of surgery in CD patients. The aim of this study was to examine which findings of the retrograde contrast could be used as predictors of subsequent surgery in CD patients with small intestinal strictures.

## Materials and Methods

### *Patients*

Eighty-seven consecutive patients with CD who underwent DBE with retrograde contrast for evaluation of small intestinal status at Okayama University Hospital from March 2009 to May 2015 were considered eligible for this retrospective study. Of the 87 patients, a patient who was lost to follow-up, a patient who underwent surgery for perianal abscess, and a patient with incomplete retrograde contrast because of the stricture being too severe were excluded. In addition, 36 patients who had no strictures in the small intestine were excluded. Consequently, a total of 48 patients with stenosis in the small bowel were evaluated in the present study. Data regarding medical history, clinical findings, and findings of the retrograde contrast were obtained from electrical medical records of the hospital.

Patients were followed-up until the time of surgery associated with the small bowel strictures or until May 2016. The risk factors that affected the bowel resection after retrograde contrast were identified. In addition, the cumulative surgery-free rates were calculated according to the presence or absence of risk factors.

### *Procedure of retrograde contrast under DBE*

Retrograde contrast was carried out using the double-balloon enteroscope EN-450T5® (Fujifilm, Tokyo, Japan) with the DBE system by experienced endoscopists (S.K. and T.I). Carbon dioxide insufflation was employed during DBE and retrograde contrast.[11] The DBE scope was inserted into the proximal small intestine as far as the scope could reach using a retrograde approach, and the contrast study through the scope was performed after inflating the balloon at the distal end of the scope for prevention of backflow of the contrast medium. If necessary and possible, during the scope insertion,

DBE-assisted balloon dilation was performed for the small intestine strictures through which the scope could not pass, after assessing the characteristics of the stricture with retrograde contrast.

During the retrograde contrast, 200 mL of double-diluted meglumine diatrizoate® (Bayer, Leverkusen, Germany), a water-soluble contrast medium, was used. After filling the contrast medium, an appropriate amount of carbon dioxide gas was insufflated to gain the double-contrast figures of the small intestine until the Treitz ligament. To facilitate regurgitation of the medium, abdominal compression and change in body position were applied as appropriate. With these maneuvers, full inspection of the small bowel could be achieved for all subjects.

***Definitions of parameters on the retrograde contrast***

Within the reach of the enteroscope, a stricture was defined as the lesion through which the scope could not pass without balloon dilation. Beyond the reach of the scope, the lesion with a diameter less than 50% of the "normal" was counted as a stricture. Because the "normal" diameter of the small intestine varies widely among individuals, it was determined in each patient by measurement of the diameter of the small intestinal portion where the following criteria were fulfilled: procurement of definite retrograde contrast images (approximately within 50 cm of the stricture at the oral side), no evidence of inflammation, ulcers, and curing findings, and appearance of uniform Kerckring's folds. A maximum diameter of prestenotic dilation was defined as the most extended diameter located immediately at the oral side of the stricture. Stricture lengths were measured in all detected stenosis regardless of within or beyond the reach of the scope, based on retrograde contrast images.

According to DBE findings and retrograde contrast, following parameters were used for analysis: the number of strictures, minimum diameter of strictures, maximum length of strictures, maximum diameter of prestenotic dilations (M), and diameter of the normal small intestine (N; Figure 1). Additionally, the ratio of the maximum diameter to the diameter of the normal small intestine (M/N ratio) was calculated. These measurements were retrospectively performed by experienced endoscopists (N.O., and S.H.) based on the computerized film database, with the results of prognosis being blinded.

***Statistical analysis***

Patient characteristics and parameters based on DBE findings and retrograde contrast were compared using Fisher's exact test or Wilcoxon rank-sum test, as appropriate. Optimal cutoff values for continuous variables were determined using receiver operating characteristic (ROC) curve analysis, and sensitivity, specificity, PPV, negative predictive value (NPV), accuracy, and area under the curve (AUC) for subsequent surgery were calculated. In addition, the risk of bowel resection was assessed using Cox regression analysis with those parameters. Variables with a *p*-value below 0.05 in a univariate analysis were further tested in a multivariate analysis, and the risk ratios with 95% confidence intervals (CIs) were calculated. Survival analyses for the time without bowel resection were carried out using Kaplan-Meier method. Statistical comparison was carried out by log-rank test. A $p$-value $< 0.05$ was considered statistically significant. All statistical analyses were performed using JMP ver.12 pro software (SAS Institute, Cary, NC, USA).

***Ethical considerations***

This study was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. There were no conflicts of interest or sponsors of this study.

## Results

### *Patient characteristics*

DBE with or without balloon dilation, and retrograde contrast were performed safely for all subjects who underwent these procedures, and no adverse events including perforation and bleeding were observed. A total of 48 patients who showed small intestinal strictures with the DBE and retrograde contrast were examined. Patient characteristics are shown in Table 1. The median observation period after the retrograde contrast was 2.4 years (interquartile range (IQR): 1.4–3.7 years). Of these, 14 patients underwent surgery for small intestinal strictures, while the remaining 34 did not. The ratio of smokers was higher in patients with bowel resection (43% vs. 9%, $p = 0.01$). Thiopurine or corticosteroid use was less frequently observed in patients with bowel resection (7% vs. 50%, $p = 0.003$, and 0% vs. 21%, $p = 0.02$, respectively). Balloon dilation was performed for 25 patients (6 (43%) vs. 19 (56%), $p = 0.53$), with one to three dilatations for each patient (total 31 dilatations).

### *Findings of retrograde contrast through the DBE scope*

The retrograde contrast findings of the patients with and without surgery are shown in Table 2. There were significant differences in number of strictures (4 vs. 1, $p < 0.0001$), minimum diameter of strictures (4 mm vs. 6 mm, $p = 0.007$), maximum length of strictures (21 mm vs. 13 mm, $p = 0.003$), maximum diameter of prestenotic dilations (43 mm vs. 31 mm, $p = 0.005$), and M/N ratio (1.61 vs. 1.22, $p < 0.0001$) between patients with and without surgery for small intestinal strictures.

### *Sensitivity, specificity, and predictive values of the retrograde contrast findings for bowel resections*

The sensitivity, specificity, PPV, NPV, accuracy, and AUC of each parameter showing statistical significance for bowel resection are shown in Table 3. According to the AUC, M/N ratio was the best associated with subsequent surgery for small intestinal strictures.

***The univariate and multivariate analysis of variables associated with bowel resection***

The univariate and multivariate analyses of risk factors for bowel resection were performed using Cox regression analysis (Table 4). According to the results of the multivariate analysis, maximum length of strictures of ≥ 20 mm and M/N ratio of ≥ 1.4 were independent risk factors of surgery for small intestinal strictures (risk ratio = 7.6 [95% CI: 1.8-42.0], $p$ = 0.006; and risk ratio = 52.0 [95% CI: 3.5-2485.1], $p$ = 0.002, respectively). The diagnostic ability of the combination of these two parameters showed the lower AUC (0.79), with lower sensitivity and NPV (57.1% and 85%, respectively) and the best specificity and PPV (100% each).

***Cumulative surgery-free rate of CD patients with small intestinal strictures***

Cumulative surgery-free rate of the 48 subjects with small intestinal strictures was 76.4%, 73.6%, and 70.2% at 1, 2, and 3 years after the DBE procedure, respectively (Figure 2A). Surgery-free rates according to the presence or absence of the two significant risk factors differ significantly ($p$ < 0.001, log-rank test; Figure 2B). The one-year surgery-free rates of subjects with no risk factors, one risk factor, and two risk factors were 100%, 78.9%, and 12.5%, respectively.

## Discussion

A number of clinical and genetic factors have been reported to be associated with the development of strictures in patients with CD, including ileocolonic disease location, long disease duration, severe disease, and NOD2/CARD15 mutations.[8, 12] As risk factors for surgery, Solberg et al. identified terminal ileal location, stricturing or penetrating behavior, and age younger than 40 years at diagnosis.[13] Evaluation using DBE revealed that presence of fistula was significantly associated with the need for surgery as a long-term clinical outcome of strictures in CD patients.[14] Smoking was also shown to be a risk for endoscopic re-dilation or sugery.[15, 16] Moreover, a recent work demonstrated that detection of stenosis with MR enterography was a risk of surgery for small intestinal stenosis.[9]

Despite these previous reports, attempts for evaluation of surgical risk for small intestinal lesions by using imaging modalities have been scarce. In this study, we demonstrated that the findings of retrograde contrast using DBE could predict the risk of small bowel resection for strictures in CD patients. In particular, a maximum length of strictures $\geq$ 20 mm and an M/N ratio $\geq$ 1.4 proved to be significant risk factors for bowel resection in those patients.

Lesions in the small intestine can lead to intestinal complications, including stenosis and fistula more easily than colorectal lesions in CD patients, possibly due to the smaller caliber of the small intestine. Nevertheless, accurate evaluation of small intestinal lesions has been challenging because of its length and deep anatomic location, in contrast to the relative ease of inspection of the colorectum using colonoscopy. In recent years, several modalities, including CT or MR enterography, and video capsule endoscopy (VCE), have been developed, and the usefulness of these procedures in the evaluation of small intestinal lesions of CD have been reported.[17-19] However, the performance of these

methods has not always been satisfactory. Additionally, these modalities have limitations to their clinical use: requirement of specialized facilities and expert radiologists, risk of radiation exposure in CT, and risk of retention of VCE. Our methodology of DBE with retrograde contrast has the following advantages over those other modalities: the higher sensitivity for detection of strictures compared to MRI,[17] accurate measurement of each parameter associated with stricture because of direct injection of contrast medium at the closest position from stenosis, minimum risk of ileus because of retrograde injection of contrast medium, and feasibility of balloon dilatation for the narrowest strictures.

DBE is an effective method for assessment of small bowel lesions in patients with CD that allows observation of deep small bowel lesions where colonoscopy cannot reach.[20] In fact, it has been shown that findings of DBE were correlated with fecal calprotectin levels more precisely than those of ileocolonoscopy, suggesting that DBE yields a more accurate evaluation of inflammation in the small bowel.[21-23] In addition, DBE enabled not only direct observation of the mucosal status but also biopsies or other treatment procedures if needed. However, DBE sometimes cannot access the deep small intestine in cases with history of multiple surgeries, severe intra-abdominal adhesions and/or strictures, all of which occur frequently in CD patients.

Retrograde contrast study, which was applied in this report, can partly overcome such shortcomings of DBE. The procedure could be achieved relatively easily, by injecting water-soluble medium and air through the scope channel after just inflating the balloon at the distal end of the scope. Although it could provide detailed information of the portion of the small intestine where DBE scope could not reach, the clinical relevance of findings of this procedure has scarcely been reported.

In our study with retrograde contrast, two risk factors associated with strictures for small bowel resections were identified; the length of strictures and the diameters of

prestenotic dilations. First, long strictures have been shown to be a risk factor for surgical resections in CD patients. A previous report showing the prognosis of CD patients who underwent balloon dilation demonstrated that strictures were significantly longer in patients who received surgery after balloon dilation than in patients without surgery (7.5 cm vs. 2.5 cm, $p = 0.006$).[24] In this regard, Sunada et al precluded strictures that exceeded 50 mm in length from the indication of balloon dilation,[14] and others advocated that candidate lesions of balloon dilation were less than 4 cm with regard to potential efficacy.[25, 26] Hence, our criterion of 20 mm or longer strictures may appear to be too short to give up balloon dilation. However, most of those existing reports included colonic lesions evaluated with colonoscopy alone, and reports showing indications and outcomes of balloon dilation for strictures in the small intestine alone have been scarce.[24, 27, 28] Definite imaging of strictures in the deep small bowel that DBE cannot reach is responsible for determination of the short criterion of our study. In fact, a recent study indicated that shorter detection limit of small bowel stenosis with MR imaging (10 mm) is one of the criteria for higher risk of surgery.[9] Thus, the length of the small bowel stricture that could be treated using balloon dilation alone appears to be shorter than previously considered.

Prestenotic dilation, another risk factor identified in this study, is thought to occur due to chronic dysfunction of intestinal mobility. In fact, bowel stenosis with prestenotic dilation was more closely correlated with secondary loss of response to anti-tumor necrosis factor antibodies than bowel stenosis without prestenotic dilation.[29] However, the relationship between the degree of prestenotic dilation and risk of surgery has scarcely been reported, maybe because accurate evaluation of prestenotic dilation is difficult due to variability of normal diameters of the small intestine. The M/N ratio defined in the current

study may be ideal to evaluate prestenotic dilation, and having identified it as one of the risks of surgery would be very helpful in clinical practice.

Meanwhile, minimum diameter of strictures and the number of strictures were not identified as the risk of surgery. This suggests that even the narrowest stenosis and multiple strictures in the small intestine could be overcome by balloon dilation with DBE if the length of the stenosis is sufficiently short. Thus, balloon dilation for the small bowel stricture by using DBE appears to be a clinically useful procedure to avoid surgery, although the procedure requires specific techniques and skills. Furthermore, as an additional negative result of this study, it should be of note that obstructive symptoms are not always reliable when estimating the degree of the strictures.

The differentiation between inflammatory and fibrotic stenosis has been considered critical because medical treatments are indicated for inflammation, whereas fibrosis requires mechanical treatments including endoscopic balloon dilation or surgery.[30, 31] In fact, Holtmann et al reported that fibrotic strictures are unlikely to respond to anti-inflammatory medical treatment.[32] In this regard, our two criteria, maximum length of strictures ≥ 20 mm and an M/N ratio ≥ 1.4, may reflect fibrotic strictures. To verify this concept, further studies are required in the future.

This study has limitations that are common to retrospective studies performed in a single center. The number of evaluated patients was small. Because of these limitations, multivariate analysis was not reliable enough with wide 95% CIs even in variables with statistical significance. However, the surgery-free rate of our patients (76% at one year) was equivalent to reported surgery-free rates after DBE-assisted balloon dilation (60% - 87.3% at 1 year),[14, 20, 33, 34] indicating that our study was reasonable and conducted appropriately. In this regard, our results should be validated in a prospective manner in the

future. Lastly, the results might be more reliable if the findings of retrograde contrast had been compared with other imaging modalities.

In conclusion, the present study showed that findings of retrograde contrast through DBE could identify small intestinal strictures with high risk of surgery. In particular, patients who showed strictures with a length of 20 mm or more and prestenotic dilation with this modality are at extremely high risk for bowel resection and should be considered to undergo surgery without performing balloon dilation.

## References


1. van Hogezand RA, Witte AM, Veenendaal RA, et al. Proximal Crohn's disease: review of clinicopathologic features and therapy. *Inflamm Bowel Dis.* 2001;7:328-337.
2. Lescut D, Vanco D, Bonniere P, et al. Perioperative endoscopy of the whole small bowel in Crohn's disease. *Gut.* 1993;34:647-649.
3. Otterson MF, Lundeen SJ, Spinelli KS, et al. Radio-graphic underestimation of small bowel stricturing in Crohn's disease: a comparison with surgical findings. *Surgery.* 2004;136:854-860.
4. Futami K, Arima S. Role of strictureplasty in surgical treatment of Crohn's disease. *J Gastroenterol.* 2005;40:35-39.
5. Dietz DW, Laureti S, Strong SA, et al. Safety and longterm efficacy of stricteureplasty in 314 patients with obstructing small bowel Crohn's disease. *J Am Coll Surg.* 2001;192:330-338.
6. Greenstein AJ, Zhang LP, Miller AT et al. Relationship of the number of Crohn's strictures and strictureplasties to postoperative recurrence. *J Am Coll Surg.* 2009;208:1065-1070.
7. Bernstein CN Jr, Loftus EV, Ng SC, et al. Hospitalizations and surgery in Crohn's disease. *Gut.* 2012;61:622-629.
8. Abreu MT, Taylor KD, Lin YC, et al. Mutation in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology.* 2012;123:679-688.
9. Takenaka K, Ohtsuka K, Kitazume Y, et al. Magnetic resonance evaluation for small bowel strictures in Crohn's disease: comparison with balloon enteroscopy. *J Gastroenterol.* 2016 Nov 15. [Epub ahead of print]

10. Rahman A, Ross A, Leighton JA, et al. Double-balloon enteroscopy in Crohn's disease: findings and impact on management in a multicenter retrospective study. *Endoscopy.* 2015;47:352-376.
11. Hirai F, Beppu T, Nishimura T, et al. Carbon dioxide insufflation compared with air insufflation in double-balloon enteroscopy: a prospective, randomized, double-blind trial. *Gastrointestinal Endoscopy.* 2011;73:743-749.
12. Rieder F, Zimmermann EM, Remzi FH, et al. Crohn's disease complicated by strictures: a systematic review. *Gut.* 2013;62:1072-1084.
13. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol.* 2007;5:1430-1438.
14. Sunada K, Shinozaki S, Nagayama M, et al. Long-term outcomes in patients with small intestinal strictures secondary to Crohn's disease after double-balloon endoscopy-assisted balloon dilation. *Inflamm Bowel Dis.* 2016;22:380-386.
15. Sabatc JM,Villarejo J, Bouhnik Y, et al. Hydrostatic balloon dilation of Crohn's strictures. *Aliment Pharmacol Ther.* 2003;18:409-413.
16. Hoffmann JC, Heller F, Faiss S, et al. Through the endoscope balloon dilation of ileocolonic strictures: prognostic factors, complications, and effectiveness. *Int J Colorectal Dis.* 2008;23:689-696.
17. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. *Gastroenterology.* 2014;147:334–342.
18. Greenup AJ, Bressler B, Rsenfeld G, et al. Medical imaging in small bowel crohn's disease-computer tomography enterography, magnetic resonance enterography, and

ultrasound: “Which one is the best for what?” *Inflamm Bowel Dis.* 2016;22:1246-1261.

19. Leighton JA, Gralnek IM, Cohen SA, et al. Capsule endoscopy is superior to small-bowel follow-through and equivalent to ileocolonoscopy in suspected crohn’s disease. *Clin gastroenterol hepatol.* 2014;12:609-615.
20. Fukumoto A, Tanaka S, Yamamoto H, et al. Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc.* 2007;66:108-112.
21. Inokuchi T, Kato J, Hiraoka S, et al. Fecal immunochemical test versus fecal calprotectin for prediction of mucosal healing in Crohn’s disease. *Inflamm Bowel Dis.* 2016;22:1078-1085.
22. Sipponen T, Kärkkäinen P, Savilahti E, et al. Correlation of fecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther.* 2008;28:1221-1229.
23. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol.* 2010;105:162-169.
24. Mueller T, Rieder B, Bechtner G, et al. The response of Crohn’s strictures to endoscopic balloon dilation. *Aliment Pharmcol Ther.* 2010;31:634-639.
25. Min Chen, Bo Shen. Endoscopic Therapy in Crohn’s Disease: Principle, Preparation, and Technique. *Inflamm Bowel Dis.* 2015;21:2222–2240.
26. Hassan C, Zullo A, De Francesco V, et al. Systematic review: Endoscopic dilation in Crohn's disease. *Aliment Pharmacol Ther.* 2007;26:1457-1464.
27. Bharadwaj S, Fleshner P, Shen B. Therapeutic armamentarium for stricturing Crohn’s disease: medical versus endoscopic versus surgical approaches. *Inflamm Bowel Dis.*

2015;21:2194–2213.

28. Ferlitsch A, Reinisch W, Puspok A, et al. Safety and efficacy of endoscopic balloon dilation for treatment of Crohn's disease strictures. *Endoscopy.* 2006;38:483–487.
29. Eder P, Michalak M, Katulska K, et al. Magnetic resonance enterographic predictors of one-year outcome in ileal and ileocolonic Crohn's disease treated with anti-tumor necrosis factor antibodies. *Sci Rep.* 2015;5:10223.
30. Fornasa F, Benassuti C, Benazzato L. Role of magnetic resonance enterography in differentiating between fibrotic and active inflammatory small bowel stenosis in patients with Crohn's disease. *J Clin Imaging Sci.* 2011;1:35.
31. Soyer P, Boudiaf M, Sirol M, et al. Suspected anastomotic recurrence of Crohn's disease after ileocolic resection: evaluation with CT enteroclysis. *Radiology.* 2010;254:755-764.
32. Holtmann MH, Neurath MF. Anti-TNF strategies in stenosing and fistulizing Crohn's disease. *Int J Colorectal Dis.* 2005;20:1-8.
33. Pohl J, May A, Nachbar L, et al. Diagnostic and therapeutic yield of push-and-pull enteroscopy for symptomatic small bowel Crohn's disease strictures. *Eur J Gastroenterol Hepatol.* 2007;19:529-534.
34. Despott EJ, Gupta A, Burling D, et al. Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). *Gastrointest Endosc.* 2009;70:1030-1036.

## Figure Legends

**Figure 1. Retrograde contrast through DBE and schematic diagram of evaluated parameters.**

(A) Minimum diameter of stricture, (B) maximum length of stricture, (M) maximum diameter of prestenotic dilation, and (N) diameter of normal small intestine with retrograde contrast were measured in each case. White dashed-circle indicated the inflated balloon at the end of the scope.

**Figure 2. Kaplan-Meier analysis of cumulative surgery-free rates of the patients**

**(A) Cumulative surgery-free rate of all the 48 patients with small intestinal strictures.**

Cumulative surgery-free rates of all the subjects were 76.4%, 73.6%, and 70.2% at 1, 2, and 3 years after the DBE procedure, respectively.

**(B) Cumulative surgery-free rates according to the presence or absence of significant risk factors identified by multivariate analysis.**

Surgery-free rates of subjects with no risk factor, one risk factor, and two risk factors differed significantly, and one-year surgery free-rates of those subjects were 100%, 78.9%, and 12.5%, respectively.

**Table 1. Clinical characteristics of the study population.**

| Patients (n = 48) | CD patients with bowel resection (n = 14) | CD patients without bowel resection (n = 34) | *p*-value |
|---|---|---|---|
| **Gender (Male / Female)** | 11 / 3 | 19 / 15 | 0.20 |
| **Age (years)** * | 36 (29-41) | 39 (33-44) | 0.42 |
| **Age at diagnosis (years)** * | 24 (22-35) | 30 (24-39) | 0.29 |
| **Duration of disease (years)** * | 6.7 (3.1-12.6) | 5.6 (0.2-11.2) | 0.68 |
| **Disease location** | | | |
| L1: ileal / L3: ileocolonic | 6 (43%) / 8 (57%) | 22 (65%) / 12 (35%) | 0.21 |
| **Disease behavior** | | | |
| B2: structuring / B3: penetrating | 9 (64%) / 5 (36%) | 25 (74%) / 9 (26%) | 0.20 |
| **Perianal disease** | 6 (43%) | 15 (44%) | 1.00 |
| **Smoking** | 6 (43%) | 3 (9%) | 0.012 |
| **History of surgery** | 6 (43%) | 16 (47%) | 1.00 |
| **Obstructive symptoms** | 11 (79%) | 16 (47%) | 0.059 |
| **Endoscopic balloon dilation** | 6 (43%) | 19 (56%) | 0.53 |
| **Medications** | | | |
| 5-aminosalycylic acid | 13 (93%) | 31 (91%) | 0.85 |
| Elemental diet | 10 (71%) | 27 (79%) | 0.56 |
| Thiopurine | 1 (7%) | 17 (50%) | 0.0025 |
| Corticosteroids | 0 (0%) | 7 (21%) | 0.021 |
| TNF-alpha antagonist | 5 (36%) | 18 (53%) | 0.27 |
| **Blood examinations** | | | |
| White blood cells (/$mm^3$) * | 5000 (4213-6453) | 5080 (4080-6450) | 0.90 |
| Hemoglobin (g/dL) * | 13.6 (12.8-14.7) | 12.6 (11.7-13.8) | 0.11 |
| Albumin (g/dL) * | 4 (3.6-4.4) | 3.9 (3.5-4.3) | 0.93 |
| C-reactive protein (mg/dL) * | 0.24 (0.14-0.98) | 0.15 (0.04-0.30) | 0.10 |

*median (IQR)

**Table 2. Comparison of the findings of retrograde contrast through DBE between CD patients with and without bowel resection.**

| The findings of retrograde contrast | CD patients with bowel resection (n = 14) | CD patients without bowel resection (n = 34) | *p*-value |
|---|---|---|---|
| Number of strictures* | 4 (3-5) | 1 (1-5) | < 0.0001 |
| Minimum diameter of strictures (mm)* | 4 (3-4) | 6 (3-9) | 0.007 |
| Maximum length of strictures (mm)* | 21 (16-27) | 13 (4-50) | 0.003 |
| Maximum diameter of prestenotic dilation (mm)* | 43 (34-47) | 31 (22-56) | 0.005 |
| Diameter of normal small intestine (mm)* | 24 (22-27) | 26 (24-28) | 0.20 |
| M/N ratio* | 1.6 (1.5-1.7) | 1.2 (1.1-1.3) | < 0.0001 |

*median (IQR)
M, maximum diameter of prestenotic dilation
N, normal diameter of small bowel

**Table 3. Sensitivity, specificity, predictive values and AUC for bowel resection.**

| | Number of strictures (≥ 3) | Minimum diameter of strictures (≤ 5 mm) | Maximum length of strictures (≥ 20 mm) | M (≥ 42 mm) | M/N (≥ 1.4) |
|---|---|---|---|---|---|
| Sensitivity (%) | 85.7 | 92.9 | 64.3 | 57.1 | 92.9 |
| Specificity (%) | 73.5 | 55.9 | 73.5 | 88.2 | 88.2 |
| PPV (%) | 57.1 | 46.4 | 50.0 | 66.7 | 76.5 |
| NPV (%) | 92.6 | 95.0 | 83.3 | 83.3 | 96.8 |
| Accuracy (%) | 77.1 | 58.3 | 70.8 | 79.2 | 89.6 |
| AUC | 0.85 | 0.75 | 0.78 | 0.76 | 0.91 |

M, maximum diameter of prestenotic dilation
N, normal diameter of small bowel
PPV, positive predictive value
NPV, negative predictive value
AUC, area under the receiver operating characteristic curve

**Table 4. Univariate and multivariate analysis of variables associated with bowel resection using Cox regression model.**

| Risk factors | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Risk ratio (95% CI) | *p*-value | Risk ratio (95% CI) | *p*-value |
| **Smoking** | 4.7 (1.5-13.6) | 0.009 | 0.4 (0.09-1.5) | 0.16 |
| **Obstructive symptoms** | 3.3 (1.1-14.8) | 0.04 | 0.3 (0.05-2.1) | 0.23 |
| **Medications during the study periods** | | | | |
| Thiopurine (no) | 11.1 (2.2-201.9) | 0.001 | 2.3 (0.2-54.1) | 0.48 |
| **Retrograde contrasting** | | | | |
| Number of strictures (≥ 3) | 10.4 (2.8-67.2) | 0.0001 | 1.6 (0.3-11.5) | 0.60 |
| Minimum diameter of strictures (≤ 5 mm) | 11.7 (2.3-210.7) | 0.001 | 1.3 (0.1-30.7) | 0.85 |
| Maximum length of strictures (≥ 20 mm) | 3.7 (1.3-12.2) | 0.02 | 7.6 (1.8-42.0) | 0.006 |
| M/N ratio (≥ 1.4) | 40.8 (8.0-744.7) | < 0.0001 | 52.0 (3.5-2485.1) | 0.002 |

CI, confidence interval
M, maximum diameter of prestenotic dilation
N, normal diameter of small bowel

**Figure 1.**

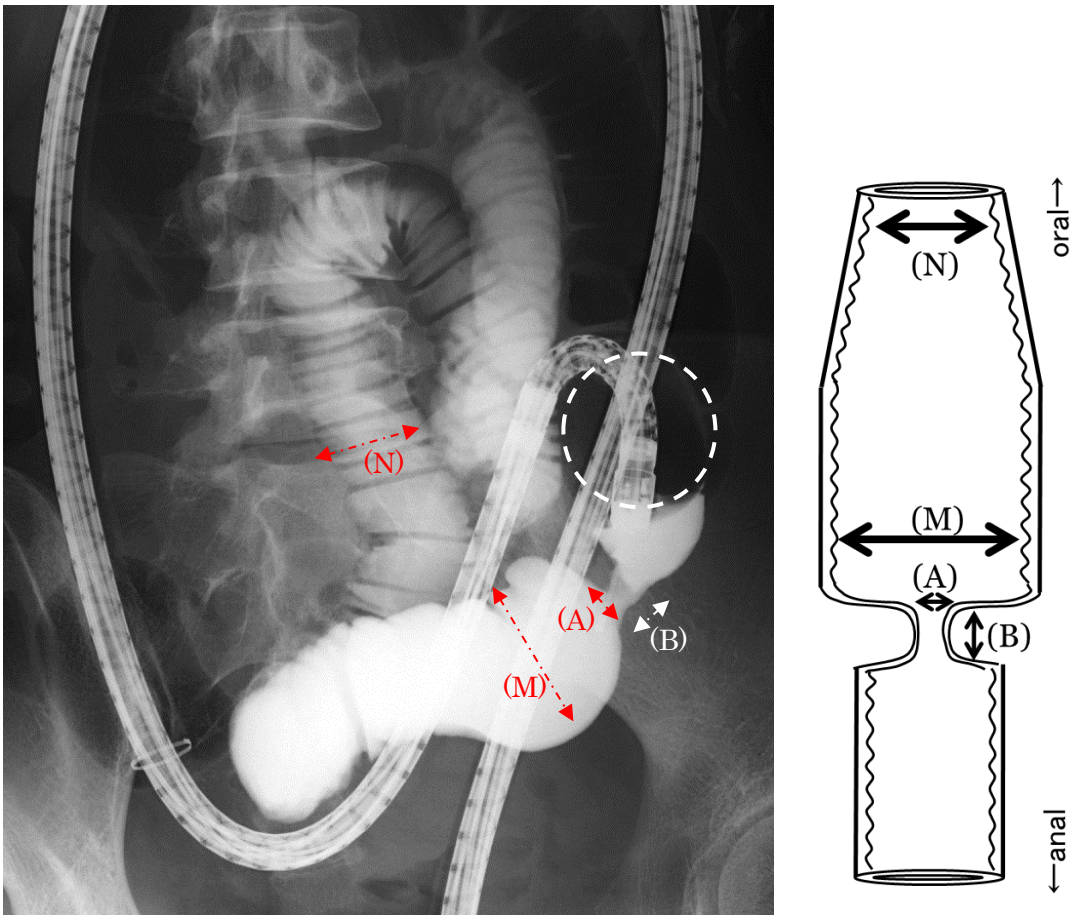
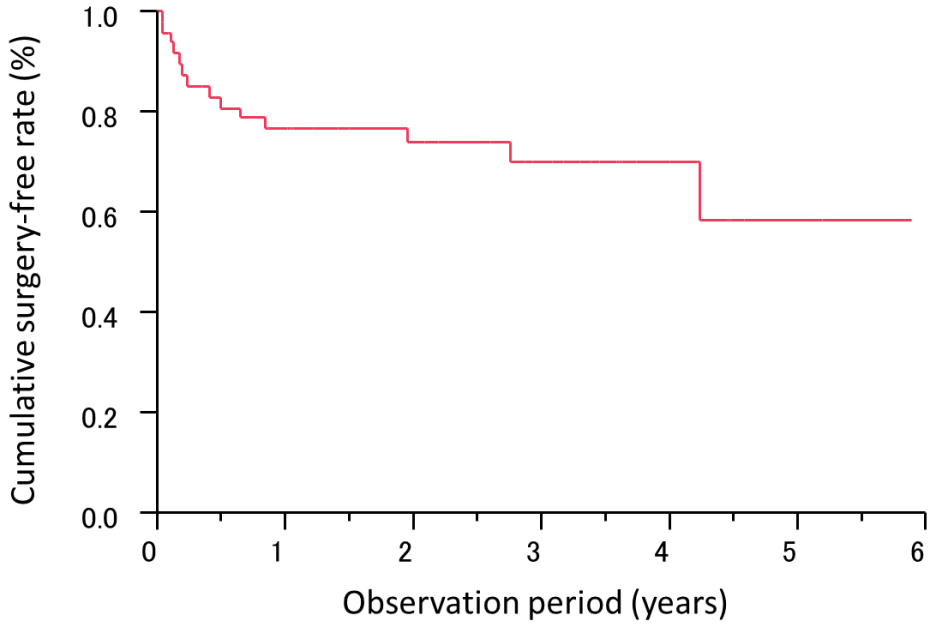
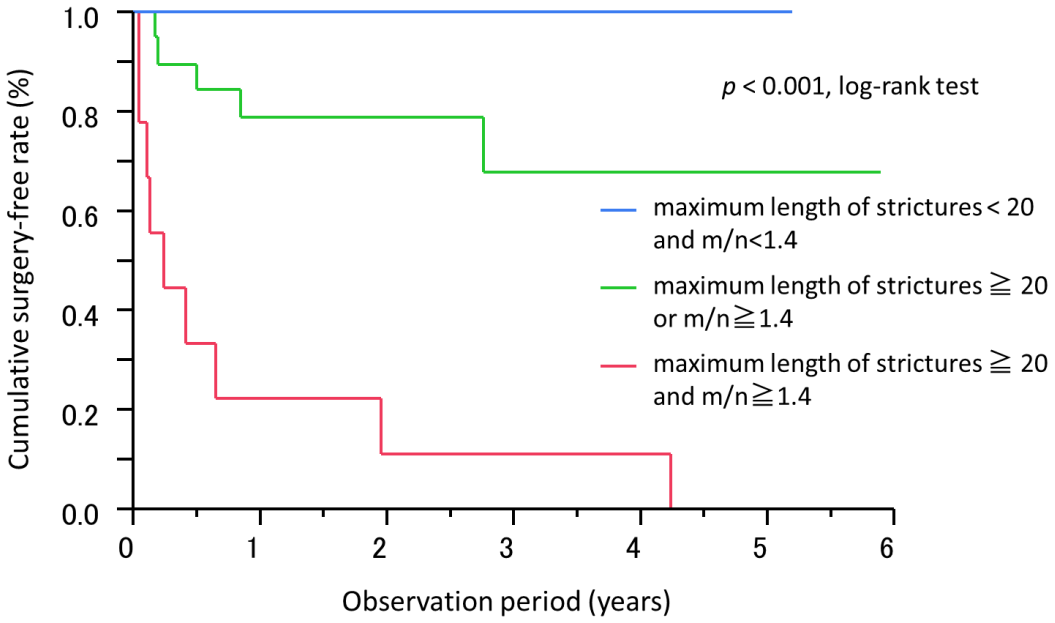


Figure 2.


Cumulative surgery-free rate (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Observation period (years)

**(A)**


Cumulative surgery-free rate (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Observation period (years)
p < 0.001, log-rank test
maximum length of strictures < 20 and m/n<1.4
maximum length of strictures ≧ 20 or m/n≧1.4
maximum length of strictures ≧ 20 and m/n≧1.4

**(B)**