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【 ORIGINAL ARTICLE 】

Analysis of the Risk Factors of Surgery after Endoscopic Balloon Dilation for Small Intestinal Strictures in Crohn's Disease Using Double-balloon Endoscopy

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Abstract:

Objective Balloon-assisted endoscopy enables access to and treatment of strictures in the small intestine using endoscopic balloon dilation (EBD); however, the long-term outcomes of EBD have not been sufficiently evaluated. This study evaluated the long-term outcomes of EBD in Crohn's disease to identify the risk factors associated with the need for subsequent surgical intervention.

Methods We retrospectively analyzed patients with Crohn's disease who had undergone EBD with double-balloon endoscopy (DBE) for small intestinal strictures at a single center between 2006 and 2015. The long-term outcomes were assessed based on the cumulative surgery-free rate following initial EBD.

Results Seventy-two EBD with DBE sessions and 112 procedures were performed for 37 patients during this period. Eighteen patients (48.6%) required surgery during follow-up. Significant factors associated with the need for surgery in a multivariate analysis were multiple strictures (adjusted hazard ratio, 14.94; 95% confidence interval, 1.91-117.12; p=0.010). One patient (6.7%) required surgery among 15 who had single strictures compared to 17 (77.3%) among 22 patients with multiple strictures.

Conclusion In a multivariate analysis, the presence of multiple strictures was a significant risk factor associated with the need for surgery; therefore, a single stricture might be a good indication for EBD using DBE for small intestinal strictures in Crohn's disease patients.

Key words: Crohn's disease, double balloon endoscopy, endoscopic balloon dilation, inflammatory bowel disease, small intestinal stricture

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Introduction

Crohn's disease is a chronic and refractory disorder of the gastrointestinal tract characterized by transmural inflammation, which can lead to intestinal strictures, one of the most common complications of this disease. About one-third of patients with Crohn's disease experience a stricture (1-3). As it is difficult to resolve severe strictures using pharmacotherapy alone, severe intestinal strictures require surgical intervention. A population-based cohort study revealed that the risk of surgery 10 years after a diagnosis of intestinal stricture was 38-55% (4). However, re-strictures often develop after surgical resection. The recurrence rate among patients examined within 1 year after undergoing surgery was 72% (5), and 31.4% and 61.2% of patients underwent reoperation requiring intestinal surgery within 5 and 10 years of the first, respectively (6). The emergence of through-the-scope (TTS) balloons in the 1980s has allowed intestine-conserving therapies using endoscopic balloon dilation (EBD) as alternative therapies to surgery (7-12). A systematic review reported that the technical success rate of EBD

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was 71-100%, the clinical efficacy rate was 53-100%, and major complications occurred in 0-18% of reported cases (13). Most data described in these studies and a review were collected from strictures localized in the colon or at a previous ileocolonic anastomosis using conventional ileocolonoscopy strictures, although the most frequent site of stricture requiring intestinal resections is the small intestine (14). Therefore, further evidence supporting the conservative management of small intestinal strictures is necessary.

Balloon-assisted endoscopy techniques such as double-balloon endoscopy (DBE) were developed (15) in the 2000s and are becoming a key modality for evaluating the small intestinal involvement of Crohn's disease with greater diagnostic yield than conventional modalities such as fluoroscopic enteroclysis (16-18). DBE has shown that 88.9% of patients with deep small intestinal involvement proximal to the terminal ileum had no involvement of the terminal ileum (19), indicating that the evaluation and treatment using balloon-assisted endoscopy may be more useful in the management of small intestinal Crohn's disease than conventional ileocolonoscopy. More recently, several series have demonstrated the efficacy of EBD using DBE for small intestinal strictures (16, 20-25). However, few reports have evaluated the long-term outcomes of EBD using DBE (22, 23, 25).

The purpose of this study was to evaluate the long-term outcomes of EBD for small intestinal strictures in patients with Crohn's disease using DBE to identify the risk factors associated with the need for subsequent surgical intervention.

Materials and Methods

Patients

In this study, we retrospectively examined 37 consecutive patients with Crohn's disease (31 males, 6 females) who underwent EBD using DBE for small intestinal strictures in the Department of Gastroenterology at the Osaka City University Hospital from April 2006 to May 2015. The diagnosis of Crohn's disease was based on clinical, endoscopic, and histopathological findings, according to the criteria of the Research Committee on Inflammatory Bowel Disease in Japan (26). Disease location and behavior were classified according to the Montreal classification (27). An intestinal stricture was defined as persistent narrowing through which an endoscope could not be passed, or a narrowing with radiographic pre-stenotic dilation as detected by a water-soluble contrast agent (Gastrografin®; Bayer Holding, Osaka, Japan) during DBE. The length of the strictures was measured with contrast radiography with a water-soluble contrast agent. The longest stricture was measured if there were multiple strictures. A stricture of less than 10 mm was defined as a short stricture. A session of EBD was defined as a series of EBDs during one DBE procedure. The demographic and clinical characteristics of patients at initial EBD are summarized in Table 1. Information regarding the demographic and clinical characteristics and the endoscopic and surgical procedures was obtained from the patients' medical records.

Indications and procedure of EBD

The indications for EBD at our hospital were as follows: (1) small intestinal strictures causing obstructive symptoms; (2) a stricture length ≤5 cm; (3) no ulcer; (4) no severe curvature of the stricture; and (5) no fistula or abscess around the stricture (22). All patients with symptomatic strictures who met these indications and provided their informed consent to the procedure first underwent EBD at our hospital. Contrast radiography using a water-soluble contrast agent with DBE was performed to detect fistulas around the strictures prior to EBD. If ulcers existed around the stricture, re-examination was done after treatment with biologics (infliximab or adalimumab) for six months to one year in order to determine whether or not EBD could be performed. Endoscopic dilation was performed using DBE (EN-450 T5; Fujifilm Medical, Tokyo, Japan) and TTS dilation balloons with a diameter of 12-15 mm (CRE balloon catheter; Boston Scientific, Natick, USA) under conscious sedation with midazolam and pentazocine. The balloon was positioned across the stricture and filled with diluted Gastrografin® under direct vision to a pressure of 1 to 3 atm, with the pressure maintained for 1 to 2 minutes. In patients with multiple strictures, we sometimes were unable to complete the dilation of all of the strictures during a single EBD session in order to avoid an excessively long procedure time or because of difficult accessibility.

Clinical outcomes

Procedure-related complications were defined as intestinal perforation and active bleeding requiring surgery or blood transfusion. The long-term outcome was assessed as the cumulative surgery-free rate after initial EBD. Surgery was performed for strictures that were not resolved by medical or endoscopic therapy, for intestinal perforation caused by subsequent EBD, or for spontaneous perforation.

Statistical analyses

Continuous variables were presented as the median and interquartile range. Patients were followed from the date of initial EBD to surgery or until the end of October 2015 if no surgery was performed. The cumulative surgery-free rate was illustrated with a Kaplan-Meier plot, and a Cox regression model was used for the analysis of the cumulative surgery-free rate. The data were presented as the hazard ratios (HRs) with 95% confidence intervals (CIs). Variables with $p \leq 0.15$ in a univariate analysis were entered into a multivariate analysis. A p value less than 0.05 was regarded as statistically significant. The software program SPSS 19.0 (IBM, Tokyo, Japan) was used for the statistical analyses.

Table 1. Baseline Characteristics at Initial Endoscopic Balloon Dilation.

Number of patients	37
Gender: male/female	31/6
Age at diagnosis, median (interquartile range)	24.7 (20.5–28.4) years
Age at initial dilation, median (interquartile range)	35.0 (31.8–37.9) years
Disease duration at initial dilation, median (interquartile range)	10.0 (5.5–14.0) years
Smoker, n (%)	7 (18.9%)
Disease location at initial dilation, n (%)	
Ileal (L1)	21 (56.8%)
Colonic (L2)	0 (0%)
Ileocolonic (L3)	16 (43.2%)
Behaviour at initial dilation, n (%)	
Non-stricturing, non-penetrating (B1)	0 (0%)
Stricturing (B2)	28 (75.7%)
Penetrating (B3)	9 (24.3%)
Presence of jejunal stricture(s)	5 (13.5%)
Presence of peri-anal disease, n (%)	13 (35.1%)
Pre-stenotic dilatation, n (%)	31 (83.8%)
Type of stricture, n (%)	
de novo	31 (83.8%)
anastomosis	6 (16.2%)
Number of strictures, n (%)	
Single	15 (40.5%)
Multiple (two or more)	22 (59.5%)
Length of strictures, n(%)	
Short	15 (40.5%)
Long	22 (59.5%)
Concomitant therapies at initial dilation, n (%)	
Steroids	2 (5.4%)
Immunomodulators (azathioprine or 6-mercaptopurine)	11 (29.7%)
Biologics (infliximab or adalimumab)	20 (54.1%)
Follow-up time, median (interquartile range)	27.1 (1.6–59.3) months

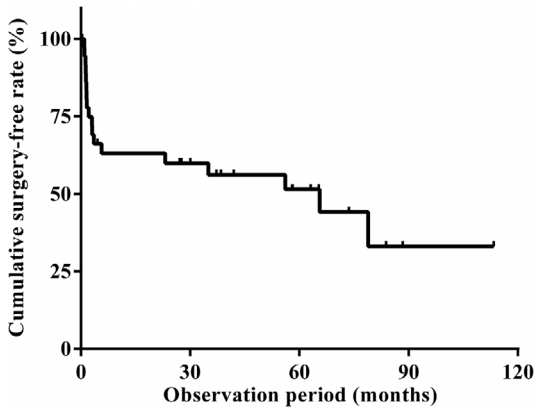

Figure 1. The cumulative surgery-free rates among all subjects were 63.1%, 59.9%, and 56.2% at 1, 2, and 3 years, respectively (the Kaplan-Meier method).

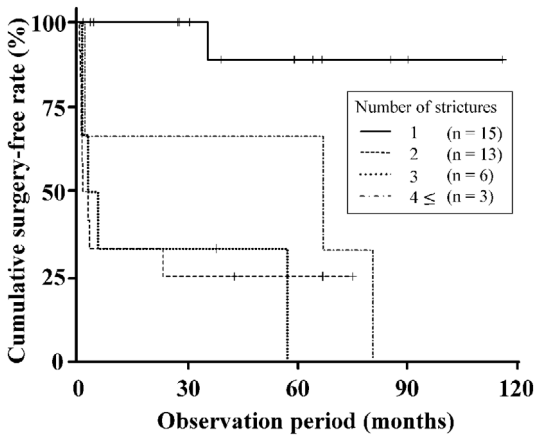

Figure 2. The cumulative surgery-free rates of endoscopic balloon dilation according to the number of strictures (the Kaplan-Meier method).

Ethical considerations

This study was approved by the ethics committee of Osaka City University Graduate School of Medicine. All patients provided their informed consent to undergo the procedure.

Results

The data from 37 patients were available for the analyses. The mean number of strictures subjected to EBD in the in-

Table 2. Cox Regression Analysis of Risk for Subsequent Surgery (Surgical Bowel Resection or Stricture-plasty) during Follow-up after Initial Dilation.

	No. of events	Rate	Unadjusted HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Gender						
Male, n=31	14	0.45				
Female, n=6	4	0.67	1.49 (0.49–4.57)	0.483		
Age at diagnoisis						
<25 years, n=19	10	0.53				
25≤ years, n=18	8	0.44	1.04 (0.41–2.65)	0.936		
Age at initial dilation						
<40 years, n=31	16	0.52				
40≤ years, n=6	2	0.33	0.71 (0.16–3.14)	0.638		
Smoking habit at dilation						
Non-smoker, n=30	15	0.50				
Smoker, n=7	3	0.43	0.87 (0.25–3.03)	0.828		
Disease duration at initial dilation						
<10.0 years, n=18	7	0.39				
10≤ years, n=19	11	0.58	1.88 (0.72–4.90)	0.199		
Disease location at initial dilation						
Ileal (L1), n=21	9	0.43				
Ileocolonic (L3), n=16	9	0.56	1.66 (0.66–4.21)	0.284		
Behaviour at initial dilation						
Stricturing (B2), n=28	14	0.50				
Penetrating (B3), n=9	4	0.44	1.37 (0.44–4.30)	0.593		
Presence of jejunal stricture(s)						
No, n=32	13	0.41				
Yes, n=5	5	1.00	3.69 (1.27–10.68)	0.016	1.37 (0.42–4.48)	0.606
Presence of peri-anal disease						
No, n=24	11	0.46				
Yes, n=13	7	0.54	1.47 (0.56–3.86)	0.439		
Pre-stenotic dilatation						
No, n=6	1	0.17				
Yes, n=31	17	0.55	4.75 (0.63–35.73)	0.131	3.68 (0.47–28.93)	0.215
Type of stricture(s)						
de novo, n=31	17	0.55				
Anastomosis, n=6	1	0.17	0.33 (0.04–2.49)	0.281		
Number of stricture(s)						
Single, n=15	1	0.07				
Multiple (two or more), n=22	17	0.77	19.79 (2.61–150.06)	0.004	14.94 (1.91–117.12)	0.010
Length of stricture(s)						
Short, n=15	7	0.46				
Long, n=22	11	0.50	1.76 (0.67–4.63)	0.250		
Steroid treatment at initial dilation						
No, n=35	17	0.49				
Yes, n=2	1	0.50	0.93 (0.12–7.34)	0.944		
Immunmodulators (azathioprine or 6-mercaptopurine) at initial dilation						
No, n=26	12	0.46				
Yes, n=11	6	0.55	1.14 (0.43–3.04)	0.798		
Biologics (infliximab or adalimumab) at initial dilation						
No, n=17	11	0.65				
Yes, n=20	7	0.35	0.46 (0.18–1.19)	0.108	0.59 (0.19–1.77)	0.342

HR: hazard ratio, CI: confidence interval

itial session was 1.4 (range, 1-3). Overall, 72 EBDs with DBE sessions and 112 procedures were performed, and the mean number of dilation sessions per patient was 2.0 (range, 1-7) during this period. A detailed overview of the patients' characteristics is given in Table 1. The median duration of follow-up (time from the initial EBD to the end of follow-up or surgery) was 27.1 months (interquartile range, 1.6-59.3 months). Eighteen patients (48.6%) required surgery

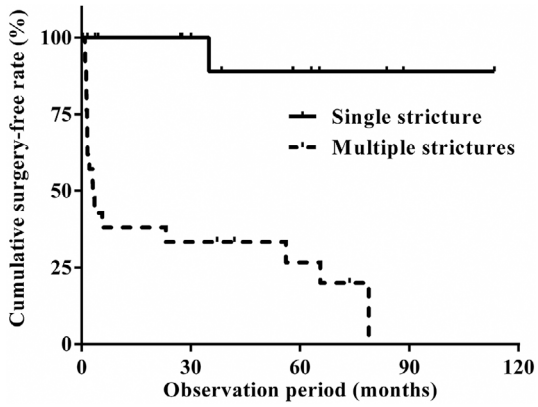

Figure 3. The cumulative surgery-free rates of endoscopic balloon dilation at 3 years were 88.9% and 33.3% with single and multiple (two or more) strictures, respectively (the Kaplan-Meier method).

during follow-up. The causes of surgery were as follows: perforation caused by subsequent EBD (n=3), spontaneous perforation (n=2), remaining strictures that could not be treated by EBD because of contraindications such as ulcer or curvature of stricture (n=2), remaining strictures which could not be approached by DBE (n=7), and persistent or recurrent abdominal symptoms resistant to medical therapy or EBD (n=4). One of the cases of spontaneous perforation had malignant strictures of the ileum (28). The cumulative surgery-free rates among all patients were 63.1% (1 year), 59.9% (2 years), and 56.2% (3 years) (Fig. 1).

Risk factors significantly associated with the need for subsequent surgery on an unadjusted analysis were multiple (≥2) strictures (HR, 19.79; 95%CI, 2.61-150.06; p=0.004) and the presence of jejunal strictures (HR, 3.69; 95%CI, 1.27-10.68; p=0.016). Regarding the number of strictures, we analyzed the cumulative surgery-free rates according to the number of strictures. Patients with two, three, and four or more strictures tended to experience poorer outcomes than those with a single stricture (Fig. 2). Therefore, the outcomes were compared between the patients with a single stricture and patients with two or more strictures. No other clinical variables, such as the sex, age at diagnosis, age at initial EBD, smoking habit, disease duration at initial EBD, disease location at initial EBD, disease behavior at initial EBD, presence of perianal disease, presence of pre-stenotic dilation, type of strictures (*de novo* or anastomosis), length of the stricture, or concomitant medication use with steroids, immunomodulators (azathioprine or 6-mercaptopurine) or biologics (infliximab or adalimumab), showed a statistically significant association with the outcome (Table 2).

A Cox regression model was used to assess the risk factors for subsequent surgery. Candidate factors associated with the need for subsequent surgery on a multivariate analysis were the presence of multiple strictures, no use of biologics, the presence of jejunal strictures, and the presence of pre-stenotic dilation. We tested for interactions among these four factors.

The increased risk associated with the presence of multiple strictures remained after adjustment for other factors (adjusted HR, 14.94; 95%CI, 1.91-117.12; p=0.010), and none of the other three factors was associated with a significantly increased risk of subsequent surgery (Table 2). Seventeen patients (77.3%) among those who had multiple strictures at initial EBD required subsequent surgery compared to 1 patient (6.7%) among 15 who had single strictures (HR, 19.79; 95%CI, 2.61-150.06; p=0.004) (Table 2). The cumulative surgery-free rate of EBD at 3 years was 88.9% with a single stricture and 33.3% with multiple strictures (Fig. 3). There were no significant differences in the clinical background between the patients with and without operation (Table 3).

In terms of complications, perforations occurred during 3 of 112 procedures overall (2.7% per procedure). Regarding the three patients who experienced perforations caused by EBD, none were receiving steroid therapy. One patient was receiving infliximab and had two strictures in the ileum; 15-mm dilation was successfully performed for one stricture, but perforation occurred with 12-mm dilation at the site of EBD for the other stricture. In another patient, free-air appeared on abdominal radiography after the EBD procedure with 15-mm dilation. Surgery was performed, and the strictures were removed; however, the site of perforation was not detected on surgery or a pathological examination. The third patient, who was receiving infliximab and azathioprine, had three strictures in the ileum and had undergone two sessions of EBD in the past. Although 15-mm dilation was thought to have been successfully performed, free-air was detected on computed tomography (CT) the following day. These three patients were all successfully treated with surgical resection.

Discussion

Recent studies have shown that the short-term success and safety of EBD using DBE for small intestinal strictures are similar to the efficacy for colon and ileocolonic anastomosis using conventional ileocolonoscopy (16, 20-25). Although few studies have evaluated the long-term outcomes of EBD for small intestinal strictures by DBE (22, 23, 25), the long-term efficacy is likely to be similar to that of conventional ileocolonoscopy. In the present study, the cumulative surgery-free rates were 63.1% (1 year), 59.9% (2 years), and 56.2% (3 years). These rates were lower than those found in previous reports (23, 25). This difference might be caused by variations in the patient populations and indications for surgery. Surgical treatment was usually chosen for the cases that still had active ulcers after treatment with biologics in our hospital.

To our knowledge, two risk factors for surgery after EBD using DBE for small intestinal Crohn's disease have been reported: stricture with fistula (25) and unsuccessful dilation (22, 23). As strictures with fistula were a contraindication to EBD in our series, no cases with these strictures at initial EBD were included. An analysis of the risk factors

Table 3. Clinical Background of Patients with Multiple Strictures with Operation and without Operation.

	With operation (n=17)	Without operation (n=5)	p value
Gender (M/F)	13/4	5/0	0.535
Age, median (interquartile range)	34.2 (30.8–37.0) years	37.4 (32.4–37.7) years	0.649
Disease duration, median (interquartile range)	7.4 (6.7–9.3) years	10.1 (5.0–13.1) years	0.820
Smoker (yes/no)	3/14	1/4	1
Location at initial dilation (Ileal (L1)/Ileocolonic (L3))	8/9	4/1	0.323
Behaviour at initial dilation (Stricturing (B2)/Penetrating (B3))	13/4	4/1	1
Pre-stenotic dilatation (yes/no)	16/1	4/1	0.411
Type of stricture (*de novo*/anastomosis)	16/1	3/2	0.117
Number of strictures, mean (range)	2.7 (2–5)	2.2 (2–3)	0.266
Length of strictures, (short/long)	7/10	0/5	0.135
Concomitant therapies at initial dilation			
Steroids (yes/no)	1/16	0/5	1
Immunomodulators (azathioprine or 6-mercaptopurine) (yes/no)	5/12	2/3	1
Biologics (infliximab or adalimumab) (yes/no)	6/11	3/2	0.609

associated with subsequent surgery using a multivariate analysis revealed that the presence of multiple strictures had a hazard ratio of 14.94. Only 1 patient (6.7%) among the 15 with single strictures required surgery compared to 17 patients (77.3%) among the 22 with multiple strictures during follow-up. This risk factor might be caused by technical issues (e.g., difficulty maintaining the endoscope across the stricture in the deep small intestine), difficulty completing EBD for all strictures (e.g., the presence of a stricture with a contraindication or difficult accessibility included in multiple strictures), difficulty in evaluating the presence of an ulceration or a fistula on strictures located in the deep small intestine, or a high risk of perforation with repeated EBD.

The two retrospective studies to date analyzing the long-term outcomes of EBD for small intestinal strictures by DBE detected no association between the number of strictures and subsequent operations (23, 25). Our results are not in line with the findings of these reports. This discrepancy might occur due to differences in the definition of long-term outcomes and in the number of strictures. For example, one report assessed the cumulative redilation-free rate after EBD as a long-term outcome (23), whereas we evaluated the cumulative surgery-free rate. We felt that the cumulative surgery-free rate was more suitable as a long-term outcome after EBD than the cumulative redilation-free rate, because we pre-emptively carried out redilation to avoid relapse of the obstructive symptoms at periodic follow-up DBE if we detected re-strictures, even in patients without recurrence of obstructive symptoms. Regarding the number of strictures, we counted the total number of strictures detected by endoscopy or radiography during the DBE procedure, regardless of the performance of EBD, whereas a previous report counted the number of strictures successfully treated by EBD (25), which might include other potential strictures. Taken together, the total number of strictures, including those not treatable by EBD, might be more useful for predicting the long-term outcome than the number of strictures treated by EBD. Another report, which counted the number of strictures by small bowel enteroclysis and/or abdominal CT prior to DBE (23), also detected no association between the number of strictures and the long-term outcome. As DBE has a higher diagnostic yield than fluoroscopic enteroclysis (16) or CT, which is relatively unreliable for detecting low-grade obstructions (29), we felt it more suitable to evaluate the number of strictures during DBE.

EBD should be considered as a first-line treatment for small intestinal strictures in Crohn's disease patients in order to reduce the number of surgeries over the patient's lifetime, unless EBD is difficult to perform. However, as is often the case with patients with multiple strictures, performing EBD for all strictures is difficult, and complications may occur more frequently than in patients with a single stricture; therefore, patients with multiple strictures should be considered for surgical intervention on a case-by-case basis. As a multivariate analysis showed that, with the exception of the number of strictures, none of the factors in our series, including smoking habit, presence of jejunal strictures, concomitant medications, type of strictures, disease location, disease behavior, or a longer disease duration, had any impact on the probability of subsequent surgery, EBD can be considered a valuable strategy in the management of single strictures in the small intestine in Crohn's disease patients. However, the case with inflammation-associated cancer suggests the need for careful malignancy surveillance, especially for patients with a long disease duration.

Several limitations associated with the present study warrant mention. One limitation is related to the sensitivity of DBE for detecting small bowel strictures in Crohn's disease patients. Enteroscopy is generally preferred for identifying intestinal damage, such as strictures (30). However, an examination of the entire small intestine of patients with Crohn's disease using balloon-assisted enteroscopy can be difficult (31, 32), resulting in the mistaken detection of only a single stricture in patients with multiple strictures. Computed tomography enterography (CTE) or magnetic resonance enterography (MRE) are also useful modalities for

identifying extramural changes, such as abscesses, fistulas, and strictures (33-35). In this study, not all patients with EBD were evaluated by CTE or MRE, although it would preferable to perform such evaluations prior to EBD. Another limitation of this study is its retrospective nature and relatively small cohort. Performing further large prospective cohort studies will help evaluate the key predictors of long-term EBD success. As subsequent EBDs were required for some patients, our study did not indicate any direct relationship between initial EBD and its effectiveness against strictures. Nevertheless, EBD can be performed repeatedly, helping postpone subsequent surgery.

In conclusion, we showed that patients with single strictures had better outcomes than patients with multiple strictures, suggesting that a single stricture might be a good indication in Crohn's disease patients with small intestinal obstruction.

The authors state that they have no Conflict of Interest (COI).

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