（表紙）

表　　題　クローン病による小腸狭窄に対する内視鏡的バルーン拡張術後の再狭窄に影響する因子の検討

(Efficacy of endoscopic balloon dilation therapy on CD related small bowel strictures)

論 文 の 区 分　博士課程

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Abbreviations

ALB	Albumun
BMI	Body mass index
CAST	Calibrated small-caliber-tip transparent
CD	Crohn's disease
CRP	C-rective protein
DBE	Double-balloon endoscopy
EBD	Endoscopic balloon dilation
ESR	Erythrocyte sedimentation rate
HGB	Hemoglobin
IBD	Inflammatory bowel disease
ICV	Ileo-cecal valve
NoU	No-ulcer
UD	Ulcer-developed
UH	Ulcer-healed
UR	Ulcer-remaining

Chapter 1. Introduction

1.1.Inflammatory bowel disease

Inflammatory bowel disease (IBD) represents a group of non-curable as well as non-preventable chronic inflammatory gastrointestinal disorders including following two major types: Crohn's disease (CD) and ulcerative colitis. IBD is characterized by repeated episodes of clinical remission and relapse and has relatively low mortality rate. But it has an enormously negative impact on patients' quality of life by disturbing nutritional health, restricting daily life activity, and weakening financial stability and has been a global health-care problem. Before 2000's, it was known mainly as a disease of wealthy countries of North America, Europe, and Oceania [1]. Since the start of the 21st century, IBD has become a worldwide disease with speeding up incidence in the countries of Asia, South America, and Africa, where the traditional special lifestyle of the population has been influenced greatly by westernized lifestyle [2]. The increasing incidences are linked to the continuous increase on the number of patients with IBD-related complications. Among IBDs, CD develops more serious and frequent long-term complications compared to other types.

1.2. CD

Crohn's disease is a chronic inflammatory gastrointestinal disorder and mostly affects the distal small intestine and colon. The incidence of CD was reported with dramatical increase in many Asian countries: Japan, Korea, and Hong Kong during the last few decades [1, 3] and is expected to rise more in the next decade [4]. However, the etiology of CD is largely unclear. Interaction between genetics, environmental risk factors, and intestinal microflora resulting in dysregulated immunological response are key components of the pathogenesis of CD. Genetic predispositions make a host more vulnerable to CD, and several

genes (NOD2 / CARD15, IL23R, ATG16L1, LRRK2, IRGM, HLA, STAT3, JAK2, and others) have been studied well to respect CD and significant strong associations were reported [5-7]. Environmental factors such as a westernized diet, which is characterized by an increased intake of calories derived from some macronutrients including simple carbohydrates (found in processed foods and sweets) and long-chain fatty acids (found in dairy products, meat, bakery and deep fried products) and low consumption of fiber, sedentary lifestyle and disturbed sleep are capable to increase risk of CD by triggering metabolic inflammation [8, 9] in hosts' intestine.

In clinical practice, CD is categorized by the Montreal classification, which is the international classification developed in 2005 at the Montreal world congress of Gastroenterology to assess and diagnose IBD [10]. According to this classification, CD has various age of onset (A), disease location (L) and behavior (B) [11]. For instance, few population-based studies reported that 57% of the patients were are diagnosed as CD between age of 17- 40 years (A2) while 9-11.4% and 32-34% of patients were younger than 17 years old (A1) and older than 40 years old (A3) at the time of diagnosis [12, 13]. Another study revealed that the mean age of patients at the diagnosis was 25.2 years. The location of CD disease is classified as ileal (L1), colonic (L2), ileocolonic (L3), and isolated upper disease (L4) by the above classification. Because CD specific changes can involve any part of gastrointestinal tract from mouth to the anus. But distal ileum and colon are most vulnerable parts to the CD. For instance, several studies found that rate of patients with ileal (L1) and colonic (L2) were higher with 38-45% and 32-45% at the time of diagnosis compared to the rate of those patients had ileocolonic (L3) and isolated upper disease (L4) CD with 14-19% and 0.3-4%, respectively [12, 13]. CD specific intestinal lesions include segmentally located

longitudinal and irregular shape ulcer, aphthae, cobble-stone appearance of mucosa lesions Depending on the presence of CD specific lesions on intestinal wall and intestinal complications, disease behavior is classified as follows: non-stricturing (B1), stricturing (B2), and penetrating (B3) types. At the time of disease onset, majority of patients (81.4%) are diagnosed with B1 and the proportion of patients with B2 (4.6%) and B3 (14.3%) increase gradually over the time after initial diagnosis [13].

1.3. Crohn's disease related intestinal stricture

As many previous studies revealed, multiple and controverse pathways are responsible to promote fibrogenesis in intestine and increase the risk of stricture formation with time during CD. Basically, as consequences of dysregulated healing and relapses of CD specific lesions, which are transmural inflammation, deep longitudinal ulcerations, or irregular ulcers in gastrointestinal tract, fibrotic changes can develop through the full thickness of intestinal wall including the mucosa, submucosa, muscularis propria, and serosa layers. This will result in transmural thickening and stiffening with narrowness of the intestinal lumen leading to strictures (Fig. 1), which is one of the most common long-term complications of CD [7, 14]. In population based cohorts, most of the patients had inflammatory and non-stricturing behaviors 5-15% of newly diagnosed patients with CD already developed strictures at the time of disease onset [12-14] and the cumulative rate of stricture formation increases from 11-14% to 21-35% five years after the initial diagnosis [15, 16]. Frequency and severity of strictures range from single to multiple and mild to severe and they affect presence of obstructive symptoms. Severe strictures as well as the appearance of multiple strictures that are mostly found in small bowel can cause acute and severe obstructive symptoms and become the common risk factor for CD-associated surgery. Since the ileum has the narrowest diameter of

lumen in small bowel compared to those other parts including duodenum and jejunum, it is considered as the most vulnerable part to CD related strictures. For instance, a recent single center study reported that the dominant causes of initial surgery among patients with CD were strictures and fistulas that located in ileum (38.6%) and terminal ileum [16-18].

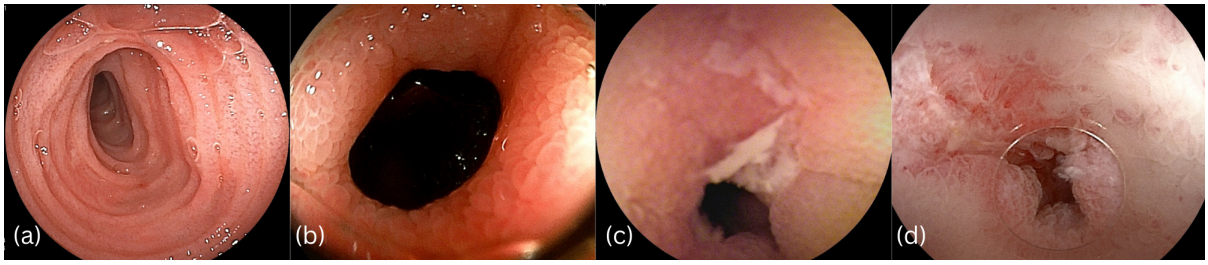

Figure 1. Lumens of small bowel. a) Normal lumen; b) Stricture; c, d) Stricture with ulceration.

During recent decades, medical treatments of CD has been achieved great advances, but specific anti-fibrotic drugs to prevent or to treat intestinal fibrotic strictures are not available now. Despite the current era of biologics, a significant portion of the patients has been required surgery and mostly performed operations for CD are identified as ileo-colonic resection due to strictures[17]. Accordingly, CD is be a common cause of short bowel syndrome, accounting for 18% of adult patients, who were monitored for over 20 years due to the short bowel syndrome [19]. The cumulative rate of initial surgery at 5, 10, 15, and 20 years from the diagnosis were 32%, 55%, 70%, and 82%, respectively [16]. If patients with CD underwent initial surgical resection for strictures, subsequent operations are often required, with a 5-year second surgery risk of 24.2% [20], and repeated resections of the small bowel can lead to short bowel syndrome, which is one of the major causes of chronic intestinal failure [21]. Chronic intestinal failure strongly affects patients' quality of life and its management is challenging for medical care providers, facilities, and patients. Fortunately, endoscopic

balloon dilation (EBD) has been emerged an alternative to surgery [22] to prevent related complications.

1.4. Endoscopic balloon dilation and restenosis

EBD is a minimally invasive treatment modality to dilate stricture in the intestine. It has been known as a safe and effective treatment for uncomplicated (stricture without abscess, fistula, severe angulation, and big ulcer) and short-length strictures (< 5cm) [23, 24] in IBD patients since early 2000's along with the spread of double balloon endoscopy (DBE) in clinical practice because DBE is one of the very few options to reach deep small intestine and EBD is performed mostly for small bowel strictures with assistance of DBE. Effectiveness of EBD is evaluated its short and long term success rates. In several studies, high rates of technical success, which was defined as passing through stricture immediately after dilation, were reported with 86.7-97.1% [25-27]. But then, long-term efficacy of EBD was indicated mostly as symptom-free rate or surgery-free rate previously [25, 28, 29]. In detail, surgery-free rates in 1, 3 and 5 years after EBD were high with 87.3-93.8%, 73-81.1% and 73.5% [25, 30-32] with tendency of gradual decrease. Recent retrospective studies showed that anastomotic and ileo-cecal valve stricture, long-stricture, presence of active endoscopic inflammation and internal fistula, and intolerance of elemental diet were identified as possible risk factors for surgery after EBD [30, 33, 34].

Generally, repeat interventions after EBD are required because of restenosis, which is a determination of recurrence of obstructive symptoms. A multi-center retrospective study detected 26.7% of recurrence of stricture after 2 months of EBD in patients with small bowel de novo strictures [27]. Another systematic review reported 35.9%, 62.1%, and 75.9% of

restenosis rate after 6, 12, 24 months after EBD. These higher rates of recurrence did not consider actual changes on the strictures and asymptomatic strictures.

In fact, stricture refers to a decrease of the normal diameter of intestinal lumen. Significant increases or decreases in diameter of strictures are observed after scheduled DBE with EBD that has been performed routinely in patients with CD-related small bowel strictures in our institution in recent years. Therefore, we believe that objective evaluation of stricture diameter is important to assess the outcome of EBD by detecting exact improvement and restenosis, to identify factors affecting outcomes, and to improve the effectiveness of EBD in the patients with small intestinal strictures.

1.5.Aims of the study

In this study, we aimed to evaluate efficacy of EBD for patients with CD with small intestinal strictures by detecting endoscopic restenosis and to identify factors causing restenosis.

Chapter 2. Methods

2.1. Patients

This retrospective cohort study initially reviewed data of all patients with stricturing CD, who are under-follow-up and underwent at least one-time scheduled DBE with EBD at Jichi Medical University Hospital between January 2016 and October 2021.

To set inclusion criteria for current study, we should consider the endoscopic management implemented in our institution. A scheduled DBE monitoring has started to be performed annually for the most patients with CD undergoing maintenance therapy in our institution since early 2000. A DBE with a short interval (less than 7 months) is performed for patients just after initial induction therapy or switching the biologics and for patients who failed

sufficient EBD for all strictures. Except for these patients, we perform DBE annually (with interval longer than 7 months) to monitor and optimize medications. Moreover, the short interval (less than 7 months) can be too short to progress restenosis and evaluate it. If a stricture is found during the DBE, diameter of stricture is measured as well as EBD is performed for it. Although we started to measure stricture diameter by using a Calibrated and small-caliber-tip transparent (CAST) hood in 2009, all measured diameters were not well and sufficiently noted on the examination reports before January 2016. Furthermore, in our institution, EBD is performed for the strictures that met the following indications for it: short (length is no longer than 5cm) fibrotic strictures, through which the scope or over-tube could not be passed regardless of the presence of obstructive symptoms in patients and a stricture without ulcer, fistula, and severe angulation and/or a stricture with tiny ulcer. In contrast, contraindications to EBD were determined as strictures with deep ulcers, fistulas, or abscesses and long or severely angulated strictures because they have high risk of perforation due to dilation. According to these compositions of the endoscopic management for CD patients, the inclusion criteria of this study were determined as follows:

(1) patients with ileal (L1) or ileocolonic (L3) CD;
(2) patients with only *de novo* fibrotic stricture(s) in the small bowel;
(3) patients underwent two DBE sessions with an interval of 7 months or longer (1^{st} session: EBD and 2^{nd} session; follow-up);
(4) all strictures and ulcers were evaluated by DBE in the two sessions mentioned in inclusion criteria (3);
(5) all strictures met the indications for EBD and treated by EBD in the EBD session mentioned in inclusion criteria (3)

Exclusion criteria were determined as: patients, who did not meet inclusion criteria, patients with unreachable strictures, and patients underwent two sessions of DBE performed with short (< 7 months) and long interval (> 24 months).

Initially we found 113 patients with stricturing CD, who underwent DBE with CAST hood for EBD and then those 65 patients did not meet the inclusion criteria were excluded (Fig. 2).

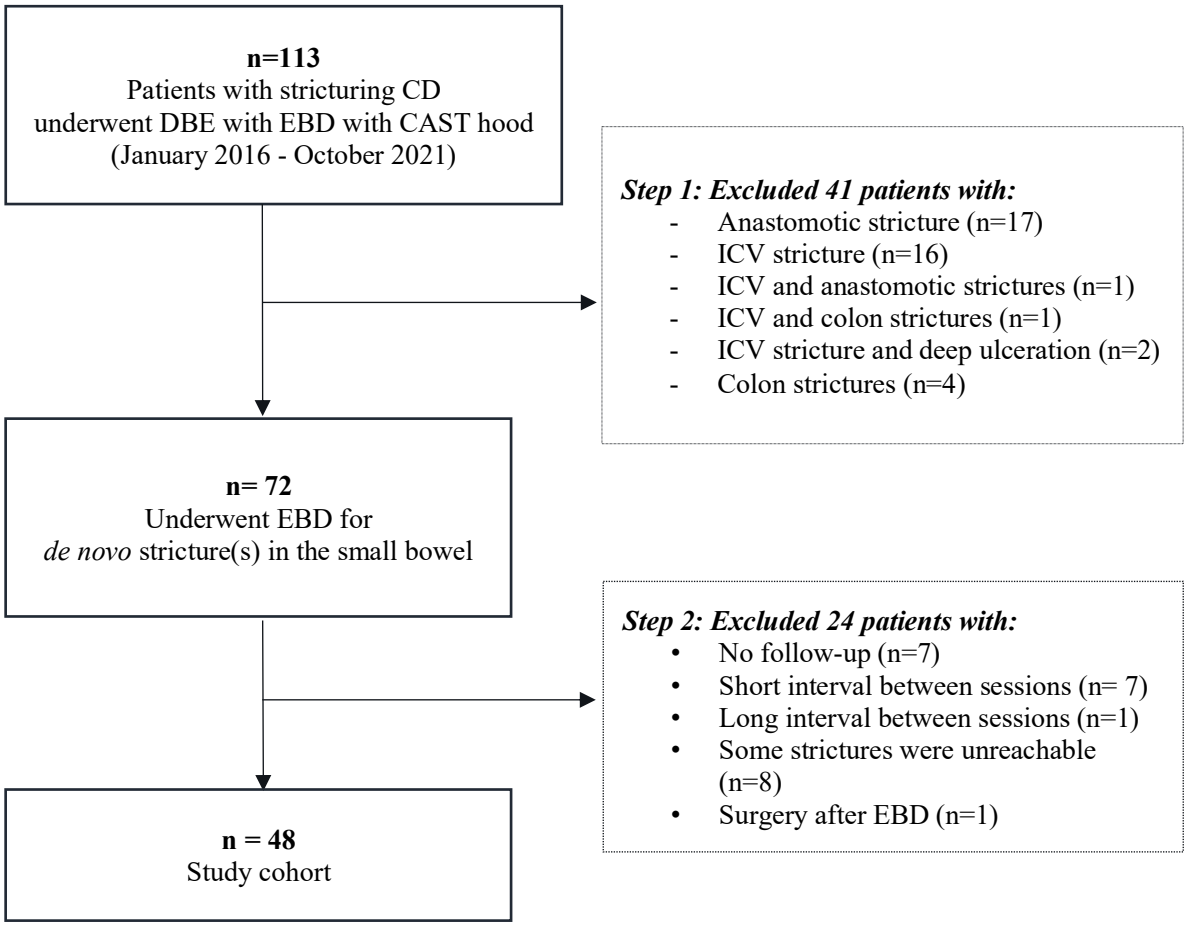

Figure 2. Study flowchart. Among 113 screened patients, 65 were excluded from the study after two exclusion steps, and 48 were analyzed. CD; Crohn's disease, DBE; double-balloon endoscopy, EBD; endoscopic balloon dilation, CAST hood; calibrated small-caliber-tip transparent hood, ICV; ileocecal valve

2.2. Sessions and procedures

As involved in the inclusion criteria, all patients underwent two sessions of DBE that were defined as the EBD session and follow-up session during the study timeframe. A session is a description of a series of DBE examinations performed during one hospitalization of each patient. At the EBD session, all detected lesions, including stricture and ulceration, were evaluated endoscopically, and all strictures were treated by EBD. While, at the follow-up session, all the lesions were evaluated, and EBD was performed as indicated.

2.2.1. Double balloon endoscopy

Double balloon endoscopy is one of the balloon-assisted endoscopic modalities to diagnose and treat small intestinal diseases, which was invented by Professor Hironori Yamamoto in 2000 in Japan. Since DBE can reach the deep small intestine, where other techniques are unreachable, ileal or ileocolonic type CD patients are monitored regularly by this modality in many institutions in Japan including our Endoscopy center. DBE system consists of several components such as a long scope, a balloon attachable on the tip of the scope, an over-tube with a balloon, connecting tubes for a scope and balloon controller, and filters and DBE examination is performed under sedation through both oral and anal routes.

Before all examinations of each DBE session of this study, patients gave written informed consent for DBE examination, EBD procedure, and conscious sedation with Midazolam, a short-acting benzodiazepine[35], and Pethidine, an opioid analgesic [36]. All endoscopic examinations and procedures were performed by experienced endoscopists under the direct supervision of experts using a therapeutic-type DBE (EI-580BT or EN-580T, Fujifilm Corporation, Tokyo, Japan) with an over-tube (TS-13140 or TS-13101, Fujifilm Corporation) and a CAST hood under fluoroscopic guidance if it was needed. The minimal water exchange method was used during all procedures for smooth insertion and a clear view

of the intestinal lumen. Small intestinal lesions: ulcer and stricture were evaluated carefully in both sessions of DBE. An ulcer was defined as a mucosal defect, not depending on size or depth. This study considered very tiny mucosal defects around the stricture. A stricture was defined as a narrowed intestinal lumen that the endoscope or over-tube cannot pass through and was classified as severe (diameter ≤ 7 mm), moderate (diameter 8-10 mm), and mild (diameter ≥ 11mm) based on its diameter.

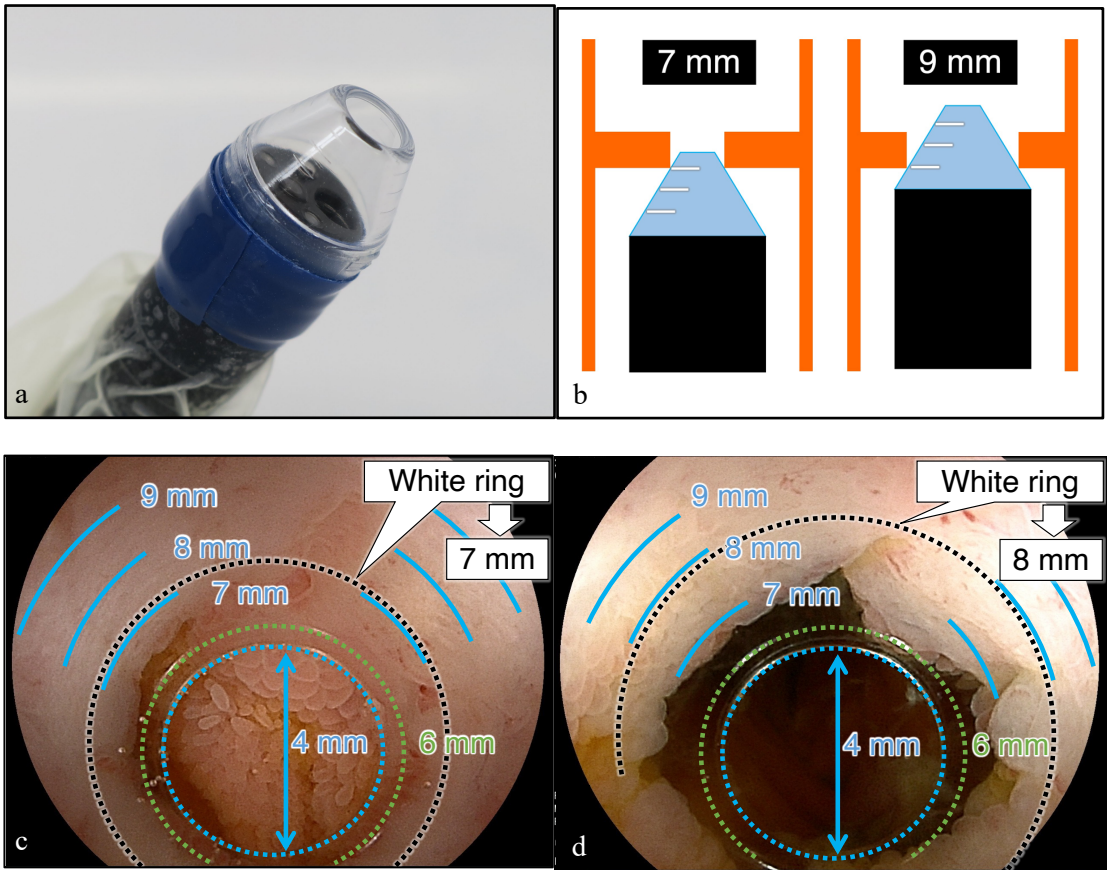

Figure 3. Calibrated small-caliber-tip transparent (CAST) hood.

A CAST hood attached to the tip of the scope. b) Measurement of the inner diameter by wedging the CAST hood to the stricture. c and d) Calibration lines on the wall of the CAST hood are highlighted in green and blue. The white ring indicates the narrowest part of the stricture. The inner diameter is read as 7 mm (c) and 8 mm (d).

2.2.2. Measuring stricture diameter

Detecting a stricture, the diameter was measured with assistance of a CAST hood (Top corporation, Tokyo, Japan), which was designed for DB to select the proper size of dilation balloon for EBD and to assess the effectiveness of EBD for this study. A CAST hood, which was designed to overcome difficulty to measure diameter of stricture accurately, can fit the therapeutic-type DBE and has calibration lines (7, 8, 9 mm) and other landmarks (orifice: 4 mm, edge: 6 mm, outer ring: 10mm) that allow precise measurement of stricture diameter. Reaching a stricture, we advanced a tip of scope to the stricture lumen and pressed the CAST hood into the orifice of stricture with gentle force, so that mucosal "white ring", which is the identification of the narrowest part of the fibrotic stricture, is seen (Fig. 1c) [37, 38] and was compared to the lines and landmarks of the hood.

Strictures with a diameter of less than 11 mm are easily measured in this technique. But diameters of mild strictures were estimated by the ability of the CAST hood attached scope and over-tube with outer diameters of 11 mm and 13.2 mm, respectively, to pass through the stricture.

2.2.3. Endoscopic balloon dilation

When a stricture was found, EBD was performed to pass through the stricture and observe further areas of the small intestine. After measuring diameter of a stricture, an endoscopic guidewire (Revowave, Piolax, Kanagawa, Japan) and appropriate-sized through-the-scope balloon catheter (CRE balloon catheter, Boston Scientific, MA, USA) were inserted and positioned properly under fluoroscopic guidance. Then dilation balloon was pressurized with dilute contrast (Gastrographin, Bayer, Osaka, Japan) up to target size and was kept as dilated for one minute. After dilating up to 13.5 mm, the over-tube, with a diameter of 13.2

mm, was safely advanced beyond the stricture. Other subsequent strictures were measured and treated with EBD using the same techniques. A balloon catheter 12-15 mm in diameter was generally used for moderate and mild strictures. Although EBD for mild strictures was not necessary to pass the endoscope (diameter 11mm), it was often performed to pass the over-tube depending on needs. A balloon catheter 10-12 mm in diameter was mainly used for severe strictures. Although most strictures were dilated up to 15 mm, some severe strictures were dilated up to 12 mm in this study. All strictures were dilated at the EBD session.

2.3. Outcome evaluation

Endoscopic findings at both sessions were compared to assess the effect of one session of EBD. Additionally, according to the aim of the study, we should evaluate that those treated strictures improved or failed to restenosis. But our patients had different number strictures in the EBD and follow-up sessions and it was difficult to recognize and compare diameter of same strictures to detect restenosis. Therefore, concerning a change on diameter of the narrowest strictures found at the time of EBD and follow-up sessions in each patient was the most proper way to identify restenosis in this study. So, patients were divided into two groups in accordance with the change in diameter of the narrowest stricture, an "improvement" group with a change of +2 mm or more and a "restenosis" group with a change of +1 mm or less. In addition, the factors associated with restenosis after EBD were analyzed.

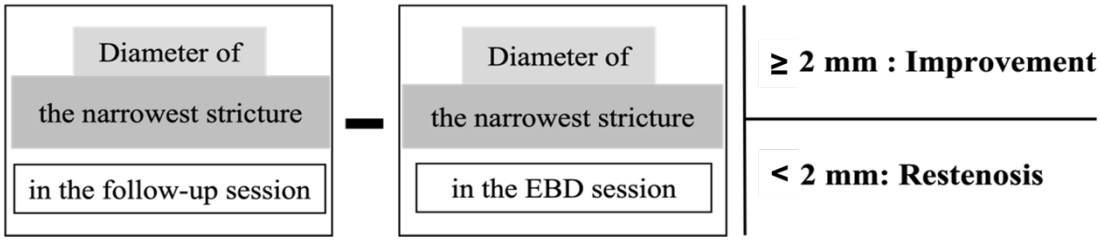

Figure 4. Definitions of improvement and restenosis of stricture after EBD

2.4. Statistical analysis

All statistical analyses were performed using STATA 16.1 (StataCorp, Texas, USA). Fisher's exact test was used for group comparison of categorical variables. Student's t-test or a paired t-test was used to compare quantitative variables. Logistic regression analysis was used to identify factors associated with restenosis. Variables with a *p-value* < 0.1 in univariate analysis were included in the multivariate analysis. *P-value* < 0.05 was considered statistically significant.

2.5. Ethical consideration

This study was approved by the Institutional Ethical Review Board of Jichi Medical University (The board approval number: 20-163 and 21-162) and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Chapter 3. Results

3.1. Background characteristics of patients

Between January 2016 and October 2021, one hundred and thirteen patients, who had stricturing type Crohn's disease, underwent DBE with EBD in the Endoscopy center at the Jichi medical university. After the initial review of data, we excluded 41 patients with an anastomotic stricture (n=17), ileocecal valve (ICV) stricture (n=16), either of ICV and anastomotic strictures (n=1), either of ICV and colon strictures (n=1), either of ICV stricture and deep ulceration (n=2) and colon strictures (n=4). Then another 24 patients were excluded to missed follow-up session (n=7), short and long interval between sessions (n= 8), scope unreachable strictures (n=8) and surgery after EBD session (n=1) and 48 patients remained in the study analysis (Fig 2).

General characteristics and clinical findings of the remaining 48 patients (37 male and 11 female) in the study are shown in Table 1. According to the Montreal classification for CD, most patients (n=34, 71%) were diagnosed as CD when they were 17-40 years old, while 8.3% (n=4) and 21% (n=10) of the patients were diagnosed under 16 and over 40 years old.

Table 1. Patients' characteristics

Factor	All	Restenosis n = 32	Improved n = 16	*P* value
Gender (male: female)	37:11	24:8	13:3	0.73
Age (years), median (range)				
at diagnosis of Crohn's disease	30 (14-72)	32 (15-72)	28.5 (14-50)	0.46
at first EBD in the disease course	36.5 (17-74)	38 (17-74)	32 (18-50)	0.25
at EBD session of the study	39.5 (17-81)	40.5 (17-81)	35 (18-53)	0.08
Age at diagnosis, n (%)				
A1: below 16 years	4 (8.3)	2 (6.3)	2 (13)	
A2: between 17 and 40 years	34 (71)	22 (69))	12 (75)	0.5
A3: above 40 years	10 (21)	8 (25)	2 (13)	
Overall period from initial diagnosis, years, mean (SD)				
to the first EBD of the disease course	4.5 ± 6.4	4.9 ± 7.0	3.6 ± 5.2	0.53
to the EBD session of the study	7.9 ± 7.1	9.3 ± 7.6	5.3 ± 5.1	0.07
History of EBD before the study, n (%)	30 (63)	24 (75)	6 (38)	0.01*
Number of previous EBDs, mean (SD)	3.1 ± 3.8	3.8 ± 3.7	1.8 ± 3.7	0.08
Period between the sessions, (months), mean (SD)	12.8 ± 3.3	11.9 ± 2.6	14.7 ± 3.8	0.005*
Mean body mass index, kg/m^2, mean (SD)	21.1 ±3.1	21.0 ± 2.8	21.4 ± 3.8	0.6
Patients with history of smoking	15 (31)	10 (67)	5 (33)	1.0
Never smoker	33 (69)	22 (67)	11 (33)	
Patients with abdominal symptoms				
before EBD session, n (%)	11	7 (64)	4 (36)	0.1
before follow-up session, n (%)	9	4 (44)	5 (56)	0.8

SD; standard deviation, EBD; endoscopic balloon dilation, (*) indicates statistical significance

The median age of patients at the time of diagnosis, at the very first EBD of disease course, and at the EBD session of the study were 30 (range 14-72) years, 36.5 (range 17-74) years, and 39.5 (range 17-81) years, respectively.

Mean BMI was in normal (21.1 ± 3.1 kg/m^2) range among all patients, and the rate of patients with underweight (BMI <18.5 kg/m^2) and overweight (BMI >25 kg/m^2) were 14.6% (n=7) and 10.4% (n=5), respectively. A history of smoking, one of the risk factors for CD, was positive in 15 (31%) patients, while 33 (69%) patients were identified as a never smoker. Before the study time, 63% of patients (n=30) had history of EBD with 4.9 ± 3.8 times of frequency and underwent the first EBD in 4.5 ± 6.4 years of diagnosis.

All patients were subjects of scheduled endoscopic follow-up monitoring for CD in our institution due to small bowel stricture(s). Accordingly, the mean interval between EBD and follow-up sessions of DBE in this study was 12.8 ± 3.3 months with a range of 7 to 21 months. Most patients were clinically and serologically in remission during the study period. For instance, the number of patients who complained of abdominal symptoms, including mild pain and bloating, was 11 (23%) and 9 (19%) in the EBD and follow-up sessions, respectively (Table 2).

Moreover, mean values of the most useful markers to indicate the activity of CD such as hemoglobin (HGB), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin (ALB), were normal in all patients (Table 2). In addition, the laboratory data before both sessions revealed that increased CRP and ESR were found only in 2 (4%) vs. 6 (12.5%), 11 (23%) vs. 7 (14.6%), while decreased HGB and ALB were detected in 27 (56%) vs. 20 (41.6%) and 10 (21%) vs. 14 (29%) patients, respectively (Table 2).

All patients underwent conservative treatment, based on the evidence-based clinical practice guidelines for inflammatory bowel disease in Japan [39]. At the time of the EBD session, the number of patients who were treated with biologics and immunomodulators was 34 (71%) and 27 (56%), respectively, and an elemental nutrition diet was taken by most of the patients (n=39, 81%). Medical treatment was modified in 15 patients (31%) after the EBD session due to the presence of ulcers and severe strictures, including the introduction of biologics (n=5) and a dose escalation of immunomodulators and/or biologics (n = 7) (Table 3).

Table 2. Laboratory data before the sessions

Factors	**All** n=48	**Restenosis** n = 32	**Improved** n = 16	***P* value**
Laboratory data at EBD session, mean (±SD)				
Hemoglobin, g/dL	13.5 ± 1.4	13.4 ± 1.3	13.7 ± 1.4	0.5
Erythrocyte sedimentation rate, mm/h	8.5 ± 9.8	8.5 ± 10.6	8.3 ± 8.2	0.9
C-reactive protein, mg/dL	0.06 ± 0.1	0.07 ± 0.1	0.04 ± 0.05	0.5
Serum albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.4	0.1
Laboratory data at follow-up session, mean (±SD)				
Hemoglobin, g/dL	13.8 ± 1.3	13.7 ± 1.3	13.9 ± 1.2	0.52
Erythrocyte sedimentation rate, mm/h	6.4 ± 6.4	6.3 ± 7.1	6.7 ± 5.0	0.84
C-reactive protein, mg/dL	0.09 ± 0.3	0.1 ± 0.3	0.08 ± 1.5	0.73
Serum albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	0.38

SD; standard deviation, EBD; endoscopic balloon dilation

3.2. Procedure-related adverse event

Of 120 DBE procedures performed on the 48 study patients, no patients exhibited obvious obstructive symptoms or required surgery during the interval between the EBD and the follow-up session. Post-procedural bleeding was observed after two procedures, and

these two patients were treated conservatively. Perforation or acute pancreatitis were not observed.

Table 3. Medical treatments before and after the EBD session

Medications	**All patients** n=48	**Restenosis** n = 32	**Improved** n = 16	***P* value**
Medical treatments before EBD session, n (%)				
Elemental nutrition	43 (90)	28 (88)	15 (94)	0.5
5-aminosalycilic acid	41 (85)	27 (84)	14 (88)	0.8
Systemic steroids	8 (17)	4 (6)	4 (25)	0.3
Immunomodulators	27 (56)	17 (53)	10 (63)	0.5
Biologics	34 (71)	22 (69)	12 (75)	0.7
Medical treatments after EBD session, n (%)				
Elemental nutrition	43 (90)	29 (91)	14 (88)	1.0
5-aminosalycilic acid	40 (83)	26 (81)	14 (88)	0.7
Systemic steroids	6 (13)	2 (6.2)	4 (25)	0.09
Immunomodulators	27 (56)	17 (53)	10 (63)	0.76
Biologics	39 (81)	26 (81)	13 (81)	1.0
Treatment modified after EBD session, n (%)	15 (31)	10 (31)	5 (31)	1.0

EBD; endoscopic balloon dilation

3.3. Endoscopic findings and outcomes of EBD

To assess the effectiveness of EBD, endoscopic findings, including the presence of stricture and ulceration, the number of all detected strictures, and the diameter of stricture from the two sessions, were compared. The total number of detected strictures in all patients during the EBD session detected decreased from 162 to 149 at the follow-up session. A significant decrease in the mean number of strictures per patient decreased from 3.4 to 3.0 ($p = 0.04$) was observed along with a decrease in the frequency of severe and moderate strictures. The number of strictures decreased in 10 (33%) patients, while six patients became

stricture free. Additionally, the number of patients with ulcerative strictures decreased from 24 (50%) to 19 (40 %).

Based on the measurement, the mean diameter of all strictures detected increased significantly from 8.7 mm to 9.8 mm (p = 0.0004) in the follow-up session. The number of severe (diameter ≤ 7 mm) and moderate (8-12 mm) strictures decreased from 57 to 40 and from 75 to 46, respectively (Table 4).

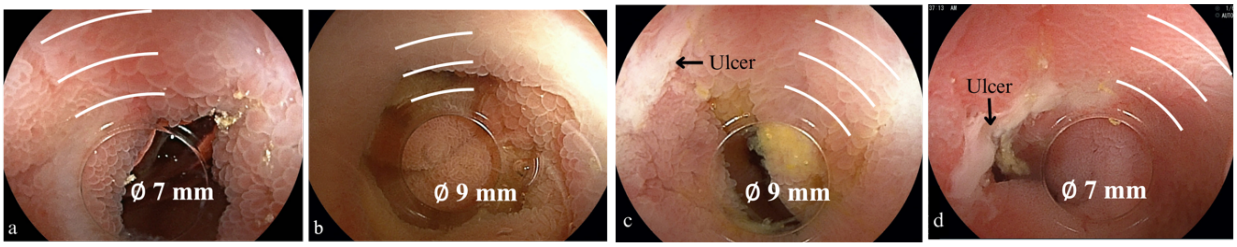

Figure 5. Small bowel strictures with different diameters. a, b) Improvement of stricture with mucosal healing from 7 mm to 9 mm in diameter. c, d) Restenosis of stricture with tiny ulcer from 9 mm to 7mm in diameter.

We found that the mean diameter of the narrowest stricture of all patients increased significantly from 7.6 mm to 8.7 mm (+1.1 mm, p = 0.0001). Of those all patients, 32 (67 %) resulted restenosis and 16 (33%) had improved diameter based on our definition of restenosis. Therefore, we compared all general and clinical data based on restenosis and improvement groups (Table 1, 2, 3 and 5). Despite the history of previous EBD, the period between two sessions of DBE, and the number of patients with the presence of ulceration in the EBD, there were no significant differences observed among general characteristics between the groups. Restenosis patients had a history of undergoing significantly more EBD procedures (3.8 vs. 1.8, $p = 0.01$) and a shorter interval between the sessions (11.9 vs. 14.7 months, $p = 0.005$).

Table 4. Endoscopic findings at the sessions of DBE

Findings	EBD session	Follow-up session	*P* value
Number of all strictures in all patients, n	162	149	
Number of strictures per patient, n (%)	3.4 ± 3.0	3.0 ± 3.2	0.04*
Patients by number of strictures, n (%)			
with multiple strictures	36 (75.0)	30 (62.5)	0.002*
with single stricture	12 (25.0)	12 (25.0)	
with no stricture	0	6 (12.5)	
Number of patients with severe stricture, n (%)	27 (56.3)	21 (43.8)	
Mean diameter of strictures, mm, mean (SD)			
All detected strictures	8.7 ± 2.2	9.8 ± 2.7	0.0004*
All strictures in each patient	8.6 ±2.0	9.8 ± 2.4	<0.0001*
The narrowest strictures	7.6 ± 2.1	8.7 ± 2.7	0.0001*
Number of strictures in each diameter group, n (%)			
Severe (diameter ≤ 7 mm)	57 (35.2)	40 (26.8)	
Moderate (diameter 8-10 mm)	75 (46.3)	46 (30.9)	
Mild (diameter ≥ 11 mm)	30 (18.5)	63 (42.3)	
Presence of ulceration on site of the stricture, n (%)			
Patients with ulcer	24 (50.0)	19 (39.6)	0.17
Patients with no ulcer	24 (50.0)	29 (60.4)	

Data are presented as n (%) or mean ± standard deviation, EBD; endoscopic balloon dilation, (*) indicates statistical significance

The number of patients with ulceration in the follow-up session was significantly higher in the restenosis group compared to the improved group (17 vs. 2, $p = 0.01$) (Table 5).

In addition, 75% of the patients with ulcers at the EBD session (18/24) and 90% of those at the follow-up session (17/19) developed restenosis. Although there were no significant differences in the frequency of multiple and severe strictures between the two groups, 69% of patients with multiple strictures (25/36) and 74% of patients with severe strictures (20/27) developed restenosis.

Table 5. Endoscopic findings in patients with restenosis and improvement after EBD

Findings	**Restenosis** n=32	**Improved** n=16	***P* value**
Number of strictures per patient in the EBD session	3.5 ± 3.3	3.1 ± 2.2	0.61
Number of patients with multiple strictures in the EBD session	25 (78.1)	11 (68.8)	0.5
Number of patients with presence of ulcer in the EBD session	18 (56.2)	6 (37.5)	0.36
Number of patients with presence of ulcer in the follow-up session	17 (53.1)	2 (12.5)	0.01
Presence of severe stricture in the EBD session	20 (62.5)	7 (43.8)	0.24

Data are presented as n (%) or mean ± standard deviation, EBD; endoscopic balloon dilation

Univariate analysis revealed that the history of previous EBD, the interval between the EBD and the follow-up session, and the presence of ulcers at the follow-up session were significantly related to the development of restenosis (Table 6). Multivariate analysis showed the presence of ulcers at the follow-up session was positively associated with endoscopic restenosis (odds ratio 9.4; 95% CI 1.51-58.4, p = 0.01), and a long interval between EBD and the follow-up session was negatively associated with restenosis (odds ratio 0.7; 95% CI 0.49-0.93, p = 0.02) (Table 6).

Table 6. Univariate and multivariate analysis for factors of restenosis

Factors	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Gender (male)	0.69	0.16 - 3.06	0.6			
Age						
at the diagnosis of Crohn's disease	1.02	0.97 -1.07	0.45			
at the first EBD during disease course	1.03	0.98 -1.09	0.25			
at the EBD session of the study	**1.05**	**0.99 - 1.11**	**0.09**	1.02	0.96 -1.09	0.4
Overall period from initial diagnosis, years						
to the first EBD during disease course	1.03	0.93 -1.15	0.5			
to the EBD session of the study	**1.12**	**0.98 - 1.28**	**0.09**	1.0	0.83 - 1.1	0.6
History of EBD before the study (>1 time)	**5.0**	**1.37 - 18.1**	**0.01**	1.8	0.36 - 8.5	0.15
Number of previous EBDs	**1.2**	**0.97 - 1.46**	**0.09**	1.3	0.9 -1.5	0.2
Period between EBD and follow-up session, months	**0.7**	**0.57 - 0.9**	**0.02**	**0.7**	**0.49 - 0.9**	**0.02**
Laboratory data in the EBD session						
Hemoglobin	0.97	0.937 - 1.02	0.3			
Erythrocyte sedimentation rate	0.97	0.93 -1.02	0.3			
C-reactive protein	2.99	0.04 - 25.3	0.6			
Serum albumin	0.93	0.81-1.06	0.9			
Treatment modification after the EBD session (yes)*	1	0.27-3.63	1.0			
Concomitant treatments after the EBD session (yes)*						
Elemental diet	0.93	0.16 - 6.1	1.0			
5-aminosalycilic acid	0.61	0.11- 3.5	0.6			
Systemic steroids	0.29	0.04 -1.95	0.2			
Immunomodulators	0.68	0.19 - 2.32	0.5			
Biologics	0.82	0.18 - 3.7	0.8			
Endoscopic findings						
Multiple strictures in the EBD session (yes)*	1.62	0.2 - 6.2	0.5			
Number of strictures per patient in the EBD session	1.05	0.85 -1.31	0.6			
Presence of ulcer in the EBD session	2.14	0.62 - 7.3	0.2			
Presence of ulcer in the follow-up session (yes)*	**7.9**	**1.54 - 40.7**	**0.01**	**9.4**	**1.51 - 58.4**	**0.01**
Diameter of stricture in the EBD session	0.85	0.63 - 1.14	0.3			
Presence of severe stricture in the EBD (diameter ≤ 7 mm) (yes)*	2.8	0.8 - 9.59	0.1			

EBD; endoscopic balloon dilation, OR; odds ratio, CI; confidence interval, * reference = no

Based on the presence of ulcers, patients were categorized into four groups, ulcer-remaining (UR, n = 16), ulcer-developed (UD, n = 3), ulcer-healed (UH, n = 8), and no-ulcer (NoU, n = 21) (Fig. 6). Among them, only the no-ulcer group, that is patients with complete mucosal healing throughout the study period, showed significant improvement in the mean diameter of the narrowest strictures (7.4 to 9.1, +1.7 mm, p = 0.001) (Fig. 6).

However, there were variations in changes of diameter within each group, suggesting that other factors affected them. The ratios of restenosis were 88% (n = 14) in ulcer-remaining, 100% (n = 3) in ulcer-developed, 50% (n = 4) in ulcer-healed, and 52% (n = 11) in the no-ulcer groups.

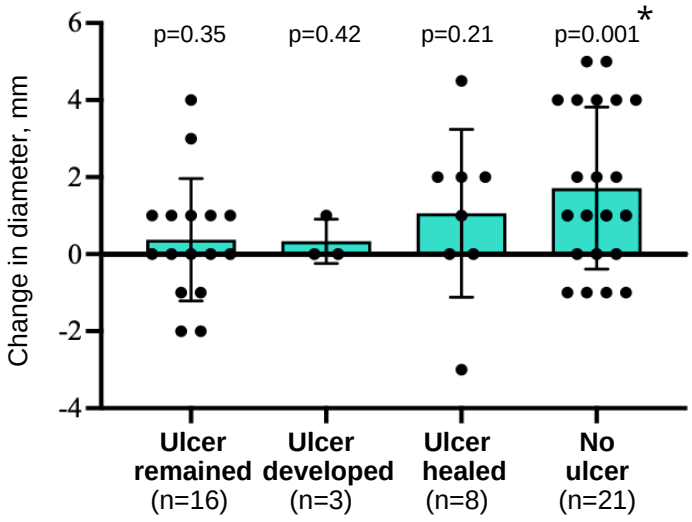

Figure 6. Changes in diameter of the narrowest strictures.
Each dot represents the changes in the diameter in each patient. Bars and error bars represent mean and SD, respectively. The asterisk indicates p-value <0.05. Paired t-test was used.

Chapter 4. Discussion

None of the evidence of endoscopic changes on treated strictures after EBD were reported among plenty of previous studies accounted to the success rate and safety of EBD. This study aimed to evaluate the efficacy of EBD in patients with stricturing CD by detecting endoscopic restenosis and identifying factors associated with the restenosis after one-time EBD on small intestinal strictures based on the precise measurements of stricture diameter, and we found EBD was an effective treatment, but the rate of recurrence of stricture was high.

A recent sharp increase in incidences of IBD including CD among the population of relatively newer regions like Asian countries reminds healthcare workers that continuous efforts for the management of CD are needed despite the great achievements regarded to medical treatment. CD can negatively affect patients' quality of life because it is a lifelong, chronic and relapsing inflammatory condition derived from unknown etiology and multifactorial pathogenesis. More than half of the patients with CD are diagnosed between the second to third decade of their life [12], but this rate was identified as higher (71%) among the patients in our study. In accordance with the natural history of CD, the patients are at risk of intestinal complications, the most common of which is small bowel stricture. About one-third of patients will develop intestinal strictures within five years of the initial diagnosis of CD [16], and it will increase up to 50% 20 years after diagnosis [40]. Patients in the present study had small bowel strictures only and they underwent the first EBD of their disease course in 6.5 years of initial diagnosis. This result indicates a relatively shorter period to develop severe stricture requiring intervention and supports previously reported knowledge that the strictures located in the small bowel, the narrowest part of the

gastrointestinal tract, are an independent risk for CD-related surgery [16, 17]. Once initial surgery has been performed in patients with stricture-forming CD, subsequent operations will be required in a fourth of patients within five years [20], and repeated resections lead to short bowel syndrome. Therefore, endoscopic follow-up is suggestable management to prevent surgical interventions and has been implicated in many facilities across Japan.

EBD, whose high rate of long-term success and low complication rate have been demonstrated in numerous studies, is a less invasive and effective alternative option to surgery [25, 30, 34, 41, 42]. Therefore, EBD is widely used as first-line therapy for CD-related small intestinal strictures to prolong the surgery-free interval for patients. In this study, we assessed outcomes of EBD performed in our institution and found a significant decrease in the number of all detected strictures and patients with multiple strictures around one year after EBD. In accordance with long-term outcomes after EBD, symptom-free remission rate and surgery-free rate, all of whom are based on presence of obstructive symptoms, were assessed mostly in previous studies [25, 28, 29]. However, in practice, eating habits and adherence to elemental diet therapy in patients can affect the presence of obstructive symptoms, as well as the surgery-free rate, which might depend on the intentions of the patient and the treating physician. Although there is lack of published evidence, over 20 years of experience of EBD in our institution, the experts in the field did not find strong relationship between diameters of strictures and intensity of presence of obstructive symptoms. And our results indicated that small fraction (19-23%) of our patients had obstructive symptoms including only mild abdominal pain and distension when they have small bowel strictures. Therefore, objective evaluation of stricture is necessary to assess the long-term efficacy of EBD to improve effectiveness of the treatment.

Due to the difficulty in measuring the inner diameter of intestinal strictures accurately, changes in the diameter of strictures were not evaluated to explain the primary outcome of EBD in previous reports. To the best of our knowledge, current study is the pioneer to precisely evaluate changes in the diameter of gastrointestinal strictures after EBD using a CAST hood, which was specifically designed hood attachable on tip of DBE to simplify the measurement of the inner diameter of an intestinal stricture during DBE. As a result of these measurements, a significant improvement in stricture diameter was demonstrated in the present study. For instance, all detected strictures among all patients and individual patient significantly improved in their mean diameter by more than 1 mm after a mean of 12.8 months following dilation. Additionally, the number of detectable strictures decreased because of the increase in diameter.

However, a high rate of repeat dilation after EBD due to the recurrence of stricture (restenosis), which is mostly identified based on the obstructive symptoms, was reported frequently. It has taken our attention to create more objective definition of restenosis in this study to assess outcome of EBD. Either of identifying and comparing each discrete stricture one-to-one in both sessions to define restenosis was difficult as well as impossible because many patients had multiple strictures, and the number of detectable strictures was different at the two sessions. Therefore, the change in diameter of only the narrowest stricture in each patient at the two sessions was considered. As a result, the rate of patients with restenosis in 7 to 21 months of the meantime after EBD was high (n=32, 67%), which was like the results from other studies that used a different definition of restenosis. For instance, as reported by Bettenworth et al, 73% of those 1463 patients underwent EBD required repeat dilation after 24 months, and the study considered only recurrence of symptoms as a restenosis [40].

Another systematic review reported 35.9%, 62.1%, and 75.9% of restenosis rate after 6, 12, 24 months after EBD. But these high rate of restenosis does not indicate that EBD is ineffective therapy. The present study assessed the effect of only one session of dilation and found a significant increase in diameters of strictures, which is a compatible result to our almost twenty years of experience of scheduled DBE follow-up with maintenance EBD for CD patients. It can be supported by the report released by Bamba et al. As they suggested, a scheduled maintenance EBD is an effective procedure to prevent surgery in patients with stricturing CD because the appropriate interval of EBD after initial dilation extended symptom-free-time of symptomatic patients [32]. Same as we do, several facilities across Japan perform annually scheduled DBE monitoring with prophylactic EBD for patients with CD, even whose strictures are in remission.

Since we found that restenosis, which is condition require repeat dilation, occurs in the significant part of the patients, defining the risk factor for restenosis was important. In fact, risk factors for restenosis are not defined yet due to lack of objective evaluation of the diameter of stricture. From beginning of the study, we hypothesized that ulceration might negatively affect efficacy of EBD and found patients with presence of ulcer in the follow-up session had a higher risk of developing restenosis according to the univariate and multivariate analysis. In clarification, patients with presence of ulcer in the follow-up session (n=19) were either of whom ulcer remained (UR patients) and developed (UD patients) after EBD session and 16 (84%) of them were patients belonged to UR group. Conversely, patients with complete mucosal healing, who belonged to NoU group, had a significantly increased rate of improvement in the diameter of the narrowest stricture after EBD. Moreover, our other results showed that the maximum improvement of the narrowest

stricture (+1.7 mm) was observed among patients in the NoU group, while UR, UD, and UH groups including patients who had small ulcerations at either any or both sessions of the study, did not show significant improvement. All these findings are supported by result those reported by Hibiya et al. The presence of an ulcer at the site of stricture was described as a possible risk factor for needing repeat dilation and surgical resection after EBD on the study that involved 98 patients, 64.3% of whom had an ulcer at the stricture site. And ulcers at a stricture had a significantly higher risk of requiring surgery than those with mucosal healing (hazard ratio 4.84, 95% confidence interval 1.58-14.79)[43]. In the present study, we believed that not regarding to its size, ulcerations (<5mm) adversely affected the outcomes after EBD, because the patients had only tiny ulcer around the stricture. According to these results, maintaining complete mucosal healing is crucial to improve the long-term outcomes of EBD.

Moreover, time of interval between the sessions was negatively associated with endoscopic restenosis. This result was like those reported by Bamba et al. In detail, an EBD interval shorter than 446 days increases the presence of some gastrointestinal symptoms. Although there was no significant difference, the endoscopic findings of those in the improved group at the EBD session tended to be better than those in the restenosis group, which might affect the physician's decision regarding the examination interval.

A systematic review by Schulberg et al. concluded that effective anti-inflammatory drug therapy combined with optimal endoscopic therapy for strictures provides the most effective non-surgical treatment of strictures[44]. However, in clinical practice, clinical decision-making to prevent restenosis was often difficult in patients with CD and small and shallow ulcers with clinical and serological remission. The results of the present study have made

clinical decision-making to prevent restenosis more straightforward. Complete mucosal healing should be achieved and maintained by individualized modification of medical treatment using annual DBE according to the treat-to-target strategy.

This study has several limitations. First, it is a single-center retrospective study with a limited number of patients. However, EBD procedures and endoscopic evaluation criteria should be uniform across all patients for reliable results. Secondly, we have chosen the diameter of the narrowest stricture in each patient as the basis of the analysis. However, it was challenging to identify and compare each discrete stricture one-to-one at the two sessions because strictures that had greatly improved could not be detected.

Chapter 5. Conclusion

In conclusion, EBD is an effective treatment for CD-related small bowel strictures when patients maintain complete mucosal healing.

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