Yamamoto Hironori (Orcid ID: 0000-0002-3601-1153)
Yano Tomonori (Orcid ID: 0000-0002-0160-432X)
Araki Akihiro (Orcid ID: 0000-0001-6308-9290)
Esaki Motohiro (Orcid ID: 0000-0002-1195-0074)
Ohmiya Naoki (Orcid ID: 0000-0002-7651-402X)
Oka Shiro (Orcid ID: 0000-0002-6602-7199)
Nakase Hiroshi (Orcid ID: 0000-0003-2848-6586)
Bamba Shigeki (Orcid ID: 0000-0002-4108-5894)
Hosoe Naoki (Orcid ID: 0000-0002-4516-5648)
Mitsui Keigo (Orcid ID: 0000-0001-9880-4143)
Watanabe Kenji (Orcid ID: 0000-0002-3781-4724)
Fujishiro Mitsuhiro (Orcid ID: 0000-0002-4074-1140)



# Guidelines for endoscopic balloon dilation in treating Crohn's disease-associated small intestinal strictures (Supplement to the Clinical Practice Guidelines for Enteroscopy)

Hironori Yamamoto, Tomonori Yano, Akihiro Araki, Motohiro Esaki, Kazuo Ohtsuka, Naoki Ohmiya, Shiro Oka, Hiroshi Nakase, Shigeki Bamba, Fumihito Hirai, Naoki Hosoe, Tomoki Matsuda, Keigo Mitsui, Kenji Watanabe, Haruhiko Ogata, Shinichi Katsuki, Takayuki Matsumoto, Mitsuhiro Fujishiro, Kazuma Fujimoto, Haruhiro Inoue

Japan Gastroenterological Endoscopy Society

Correspondence: Hironori Yamamoto, M.D., Ph.D.

Department of Medicine, Division of Gastroenterology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.

E-mail: ireef@jichi.ac.jp; tel: +81-285-58-7347; fax: +81-285-40-6598

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/den.14429

## Abstract

Balloon-assisted enteroscopy allows endoscopic treatments in the deeper segments of the small bowel. Endoscopic balloon dilation has become a popular minimally invasive alternative for the treatment of Crohn's disease-associated small intestinal strictures. As a supplement to the Clinical Practice Guidelines for Enteroscopy, the Japan Gastroenterological Endoscopy Society's Working Committee has developed the present "Guidelines for endoscopic balloon dilation in treating Crohn's disease-associated small intestinal strictures," based on new scientific techniques and evidence. The guidelines cover standard procedures for the insertion route of the balloon endoscope, bowel preparation, indications, procedure-related complications, efficacy, target diameter and duration, management of multiple strictures, and the current state of combined and alternative treatments. Unresolved future research questions are also listed in this guideline.


**Keywords:** balloon-assisted endoscopy, Crohn's disease, small intestinal stricture, endoscopic balloon dilation

## Introduction

Crohn's disease, a chronic inflammatory bowel disease (IBD), is characterized by transmural inflammation in the gastrointestinal (GI) tract and may lead to discontinuous deep ulcers. Repeated cycles of recurrence and remission of Crohn's disease may cause strictures, fistulas, or perforations in the GI tract. Advanced GI tract strictures may result in intestinal obstruction, inhibiting oral intake.

In the past, it was difficult to reach the site of small intestinal strictures with an endoscope, and intestinal resection and/or stricture-plasty were commonly

performed surgically. However, surgical treatment cannot completely cure Crohn's disease, and repeated surgical resections for recurrent strictures increase the risk of developing short bowel syndrome, particularly in cases where multiple strictures are distributed over long segments of the small intestine and require more extensive resections.

Introduction of balloon-assisted enteroscopy (BAE) has enabled endoscopic treatments, including endoscopic balloon dilation (EBD), in the deeper segments of the small bowel. EBD has recently been widely recognized as a minimally invasive treatment for Crohn's disease-associated small intestinal strictures; however, guidelines for a standard EBD procedure have not been established.

In 2015, the Japan Gastroenterological Endoscopy Society developed the Clinical Practice Guidelines for Enteroscopy.[1] Although these guidelines described the indications for EBD, detailed EBD methodology was not mentioned. Therefore, the committee was asked to develop "Guidelines for endoscopic balloon dilation in treating Crohn's disease-associated small intestinal strictures" as an addendum to the Clinical Practice Guidelines. A motorized-spiral enteroscope (PowerSpiral®; Olympus) was approved in Japan in 2021; however, sufficient evidence is lacking at present regarding its efficacy and safety for treating small intestinal strictures or ulcers in patients with Crohn's disease, and hence, has been excluded from the new EBD guidelines.

The guidelines were developed according to the *Minds Handbook for Clinical Practice Guideline Development 2017*[2] to ensure that they were rooted to evidence-based medicine (**Table 1**), and were written in the clinical questions (CQ) format. High-level evidence in this field is scarce, which necessitated relying on the consensus of experts. Nevertheless, we hope that the guidelines will be helpful for

clinicians in the treatment of patients with Crohn's disease-associated small intestinal strictures.



Table 1. Strength of recommendation and evidence level

| |
|---|
| Grade of recommendation |
| 1: Strongly recommend |
| 2: Weakly recommend (propose) |
| Nothing: Cannot make a clear recommendation or determine the strength of recommendation |
| Evidence level |
| A (strong): Very confident that the estimated treatment effect is sufficient to support the recommendation |
| B (moderate): Moderately confident that the estimated treatment effect is sufficient to support the recommendation |
| C (weak): Limited confidence that the estimated treatment effect is sufficient to support the recommendation |
| D (very weak): Almost no confidence that the estimated treatment effect is sufficient to support the recommendation |

## Procedure for the development of the Guidelines

### 1) Committee members

The Japan Gastroenterological Endoscopy Society (JGES) entrusted 13 gastrointestinal endoscopists to form the committee that developed the new EBD guidelines. After examining the guidelines closely, the development committee and chairperson settled on the final proposal. Three gastrointestinal endoscopists formed an evaluation committee and evaluated the guidelines (**Table 2**).

Table 2. Members of committees for developing the Guidelines for endoscopic balloon dilation in treating Crohn ′ s disease-associated small intestinal strictures (Supplement to the Clinical Practice Guidelines for Enteroscopy).

| | |
|---|---|
| Japan Gastroenterological Endoscopy Society Guideline Committee | |
| Board Chairperson | Haruhiro Inoue (Digestive Diseases Center, Showa University Koto Toyosu Hospital) |
| Managing Director | Kazuma Fujimoto (Department of Internal Medicine, Faculty of Medicine, International University of Health and Welfare) |
| Committee Chairperson | Mitsuhiro Fujishiro (Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo) |
| Working Committee | |
| Committee Chairperson | Hironori Yamamoto (Department of Medicine, Division of Gastroenterology, Jichi Medical University) |
| Development Committee Chairperson | Tomonori Yano (Department of Medicine, Division of Gastroenterology, Jichi Medical University) |
| Committee members | Akihiro Araki (Health Management Center, Toranomon Hospital) |
| | Motohiro Esaki (Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Saga University) |
| | Kazuo Ohtsuka (Department of Endoscopy, Tokyo Medical and Dental University) |
| | Naoki Ohmiya (Department of Advanced Endoscopy, Fujita Health University) |

| | |
|---|---|
| | Shiro Oka (Department of Gastroenterology and Metabolism, Hiroshima University Hospital)<br>Hiroshi Nakase (Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine)<br>Shigeki Bamba (Division of Digestive Endoscopy, Shiga University of Medical Science Hospital)<br>Fumihito Hirai (Department of Gastroenterology, Fukuoka University School of Medicine)<br>Naoki Hosoe (Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine)<br>Tomoki Matsuda (Digestive Endoscopy Center, Sendai Kousei Hospital)<br>Keigo Mitsui (Department of Gastroenterology, Nippon Medical School)<br>Kenji Watanabe (Center for Inflammatory Bowel Disease, Division of Internal Medicine, Hyogo College of Medicine) |
| Evaluation Committee Chairperson | Haruhiko Ogata (Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine) |
| Committee members | Takayuki Matsumoto (Division of Gastroenterology, Department of Internal Medicine, Iwate Medical University)<br>Shinichi Katsuki (Digestive Disease Center, Otaru Ekisaikai Hospital) |
| Cooperating Organizations | Japanese Society for Inflammatory Bowel Disease; Japanese Gastroenterological Association; Japanese Society of Gastroenterology; Japanese Society of Small Intestinal Disease; Grants from the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease |

Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare



**2) Evidence level, the strength of recommendation, and statement**

A total of 13 important questions were posed regarding indications, exclusion criteria, procedures, procedure-related complications, combined treatments, and alternative methods that could influence the course of patient management. A literature review was conducted in February 2020 on PubMed, which included studies published between January 2000 and January 2020. The following queries were searched:

(English[Language])AND("2000/01/01"[Date - Publication]:"2020/01/31"[Date - Publication]) AND (Crohn's disease) AND ((endoscopic balloon dilation) OR (endoscopic balloon dilatation) OR (endoscopic treatment) OR (endoscopic therapy) OR (endoscopic management)) AND ((stenosis) OR (stricture) OR (strictures) OR (structuring) OR (narrowing))

The search queries provided a total of 610 results; 160 were chosen based on their titles. For topics with insufficient literature support, literature that was not found due to search leakage, and literature from outside the queried period, materials were searched for and added manually, where appropriate. After reviewing the literature, selecting the most important materials, and integrating experts' opinions, a response was drafted for each question featuring a leading statement and explanatory notes.

The development committee assigned a recommendation level to the evidence level for each piece of literature and statement based on the Minds Recommendation Grades (**Table 1**).

According to the evidence level, the resulting statements and explanatory notes were classified into the following three categories:

1. *Background questions (BQs):* those for which conclusions were already clear or a consensus had already been reached in previous guidelines.
2. *Clinical questions (CQs):* those that affect the treatment course and for which recommendations and evidence levels can be determined based on a comprehensive literature search.
3. *Future research questions (FRQs):* those for which recommendation and evidence level cannot be determined, even with the current comprehensive literature search (no evidence; a task for future research).

The development committee voted on each statement drafted according to the modified Delphi method; 1–3, 4–6, and 7–9 votes were considered non-consensus, unsatisfactory, and consensus, respectively. Statements with seven or more votes were chosen, and CQs with seven or more votes were recorded as recommendations. After implementing the appropriate revisions based on evaluations received from the evaluation committee, the completed draft of the Guidelines was presented to the JGES committee members for public comments. The Guidelines were completed following discussion of the public comments.

### 3) Scope of the Guidelines

The Guidelines are intended to be used by clinicians who will perform EBD for

patients with Crohn's disease-associated small intestinal strictures. Although the Guidelines represent a standard method, the individual patients' wishes, age, comorbidities, and social circumstances must also be carefully considered before the procedure.

**Statement of conflicts of interest related to the content of this paper**

Each development committee and evaluation committee member was asked to provide a statement with information regarding any conflicts of interest they may have by listing each corporation or organization from which they received some form of compensation for the guidelines.

These included remuneration (1 million JPY or more), stock options (1 million JPY or more, or 5% or more), patent royalties (1 million JPY or more), lecturer's fees (etc.) (500,000 JPY or more), manuscript fees (500,000 JPY or more), research funding or grants (1 million JPY or more), scholarship grants (etc.) (1 million JPY or more), endowed courses provided by a corporation/organization (1 million JPY or more), and provision of materials not directly related to research (50,000 JPY or more).

Hironori Yamamoto (lecturer's fee: Fujifilm, Fujifilm Medical; endowed courses: Fujifilm, Fujifilm Medical), Tomonori Yano (endowed courses: Fujifilm, Fujifilm Medical); Motohiro Esaki (lecturer's fee: AbbVie, Mitsubishi Tanabe Pharma, EA Pharma, Janssen Pharmaceuticals, Takeda Pharmaceutical Co. Ltd.; scholarship grants: AbbVie, Mitsubishi Tanabe Pharma, EA Pharma); Naoki Ohmiya (lecturer's fee: EA Pharma; research funding/grants: the Japanese Society of Gasteroenterology, the Japanese Gastroenterological Association, the Ministry of Internal Affairs and Communications, Nippon Kayaku, EA Pharma, AbbVie, Mylan

EPD, Daiichi Sankyo, Ajinomoto Bio-Pharma, the Okawa Foundation for Information and Telecommunications, the Suzuken Memorial Foundation, the University of Miyazaki, the Watanabe Foundation; scholarship grants: Nippon Kayaku, Takeda Pharmaceutical Co. Ltd., Bristol Myers Squibb, Eli Lilly Japan, Mitsubishi Tanabe Pharma); Hiroshi Nakase (lecturer's fee: Mitsubishi Tanabe Pharma, Janssen Pharmaceuticals, Takeda Pharmaceutical Co. Ltd., AbbVie, Pfizer, Daiichi Sankyo, Celgene, JIMRO, Kissei Pharmaceutical, EA Pharma, Mochida Pharmaceutical Co. Ltd., Nippon Kayaku, Kyorin Pharmaceutical Co. Ltd.; research funding/grants: HOYA, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical Co. Ltd., AbbVie; scholarship grants: AbbVie, Nippon Kayaku, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Co. Ltd., Bayer, EA Pharma, Eisai Co. Ltd., Otsuka Pharmaceutical); Shigeki Bamba (lecturer's fee: Janssen Pharmaceuticals); Fumihito Hirai (lecturer's fee: AbbVie, EA Pharma, Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma, Mochida Pharmaceutical Co. Ltd., Janssen Pharmaceuticals; research funding/grants: Eli Lilly Japan, Janssen Pharmaceuticals; scholarship grants: AbbVie, AYUMI Pharmaceutical Corporation, Asahi Kasei Medical, EA Pharma, Eisai Co. Ltd., Otsuka Pharmaceutical, Kissei Pharmaceutical, Mochida Pharmaceutical Co. Ltd.; endowed courses: AbbVie, EA Pharma, JIMRO, Kyorin Pharmaceutical Co. Ltd., Zeria Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma), Naoki Hosoe (research funding/grants: Olympus, Covidien Japan); Kenji Watanabe (lecturer's fee: AbbVie, EA Pharma, Kissei Pharmaceutical, Pfizer, Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical Co. Ltd., Mochida Pharmaceutical Co. Ltd.; research funding/grants: EA Pharma, Takeda Pharmaceutical Co. Ltd.; scholarship grants: AbbVie, EA Pharma, Mitsubishi Tanabe Pharma; endowed courses: AbbVie,

EA Pharma, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical Co. Ltd., Zeria Pharmaceutical Co. Ltd., JIMRO, Otsuka Pharmaceutical Factory, Asahi Kasei Medical, Mochida Pharmaceutical Co. Ltd.); Takayuki Matsumoto (lecturer's fee: Mitsubishi Tanabe Pharma, AbbVie, EA Pharma, Janssen Pharmaceuticals, Kyorin Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Nippon Kayaku, Pfizer; scholarship grants: Mitsubishi Tanabe Pharma, Nippon Kayaku); Haruhiko Ogata (lecturer's fee: Takeda Pharmaceutical Co. Ltd.; scholarship grants: Kyorin Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma, AbbVie, Mochida Pharmaceutical Co. Ltd.); Mitsuhiro Fujishiro (lecturer's fee: Olympus, Fujifilm; research funding/grants: Olympus, Fujifilm); Kazuma Fujimoto (scholarship grants: Daiichi Sankyo).

**Funding**

The Japan Gastroenterological Endoscopy Society covered expenses related to development of these Guidelines.

References

1. Yamamoto H, Ogata H, Matsumoto T et al. Clinical practice guidelines for enteroscopy. *Dig. Endosc* 2017; 29: 519–46.
2. Kojimahara N, Nakayama T, Morizane T et al. *Minds Handbook for Clinical Practice Guideline Development 2017*. Tokyo: MINDS Guideline Center, Japan Council for Quality Health Care, 2017. (in Japanese).

# Guidelines for endoscopic balloon dilation in treating Crohn's disease-associated small intestinal strictures

## General statement

### 1) Significance of performing endoscopic balloon dilation (EBD)

EBD ameliorates symptoms due to obstruction, and even if restenosis occurs, EBD can be repeated. EBD would not lead to short bowel syndrome if surgical resection can be avoided. Therefore, EBD is highly beneficial for improving the long-term prognosis of patients with Crohn's disease

Relapse of Crohn's disease is thought to be related to bacterial overgrowth due to stagnant enteral content[1) 2)]; therefore, EBD may help prevent a relapse if it improves the enteral content stagnation.

References

1. Ricci JERJ, Chebli LA, Ribeiro TCDR et al. Small-intestinal bacterial overgrowth is associated with concurrent intestinal inflammation but not with systemic inflammation in Crohn's disease patients. *J Clin Gastroenterol* 2018; 52: 530-6.
2. Cohen-Mekelburg S, Tafesh Z, Coburn E et al. Testing and treating small intestinal bacterial overgrowth reduces symptoms in patients with inflammatory bowel disease. *Dig Dis Sci* 2018; 63: 2439-44.

### 2) Balloon-assisted enteroscopy (BAE) insertion route

BAE can be performed with either transoral or transanal approach. The insertion

route should be chosen based on accessibility to the stricture. Crohn's disease-associated small intestinal strictures tend to occur in the ileum, and hence, the transanal approach is often chosen.

Adhesions or deformities in the ileum obstruct access to the stricture via the transanal approach. In such cases, the transoral approach may be used as it does not require passing through the large intestine and deformities in the ileum. Thus, the insertion route should be chosen based on the findings of previous examinations of the patient.

When there are multiple strictures spread over a long segment of small intestine and it is impossible to perform EBD on all strictures using one insertion route alone, both BAE insertion routes should be used.

### 3) Bowel preparation

Patients' oral intake should be limited, starting one or two days prior to the procedure; allow oral liquid food or an elemental diet, and instruct patients to stop consuming any medications that can easily remain in the GI tract, such as controlled-release formulations of 5-aminosalicylic acid (5-ASA).

When preparing the bowel for retrograde insertion, obstructive symptoms may appear if the whole-bowel preparation solution is administered in its entirety on the morning of treatment. It is therefore advisable to split the dosage and distribute the drug slowly over a more extended period, such as half on the day before and half on the day of treatment.[1)] Further, the preparation should be discontinued if the patient complains of a feeling of fullness. In patients with severe strictures, bowel preparation only using a high-pressure enema can also be considered.

If computed tomography (CT) scan or magnetic resonance (MR) imaging is

performed in the presence of the bowel cleansing agent in the small intestine, a CT/MR enterography image can be obtained.[2] This can help understand the distribution of lesions and confirm the presence or absence of fistulas and abscesses.

References

1. Nett A, Velayos F, McQuaid K. Quality bowel preparation for surveillance colonoscopy in patients with inflammatory bowel disease is a must. *Gastrointest Endosc Clin NAm* 2014; 24: 379-92.
2. Sagami S, Kobayashi T, Kikkawa N et al. Combination of colonoscopy and magnetic resonance enterography is more useful for clinical decision making than colonoscopy alone in patients with complicated Crohn's disease. *PLoS One* 2019; 14: e0212404.

### 4) Procedure-related complications

In a systematic review of the results of performing EBD on Crohn's disease-associated small intestinal strictures, the incidence rates of perforation, severe hemorrhage, and significant procedure-related complications requiring surgery were 3.21% on a per-patient basis and 1.82% on a per-procedure basis.[1] The incidence rate of perforation, which should be most assiduously avoided, was found to be 0–10% in several observational studies.[2] [3] While steroid therapy is a known risk factor for perforation in observation and EBD in colonoscopy[4], clarity on its risk in EBD for small bowel strictures using BAE is lacking. However, the indications for EBD include the absence of deep ulcers and fistulae [5] [6]; thus, it is important to assess the activity at the stricture site before performing the procedure. In addition, one must work delicately and add pressure gently in the initial stages of dilating the balloon

to prevent perforations.[7) 8)] For severe strictures, accommodations are necessary, such as choosing a smaller initial balloon size.

The frequency of severe hemorrhage is low, at 0–3.2%.[3) 5) 9)–15)] EBD is a procedure with a high risk of hemorrhage, and the patient's medical history of anticoagulant should be obtained. Discontinuation of anticoagulant should be considered prior to the procedure according to the guidelines.[16) 17)] Nonetheless, no cases requiring surgical treatment have been reported, and patients usually recover from hemorrhage with conservative treatment.

Pancreatitis was found in approximately 0.2% of cases of BAE performed orally[18)]; special attention should be required for patients undergoing prolonged transoral EBD procedures.

References

1. Bettenworth D, Bokemeyer A, Kou L et al. Systematic review with meta-analysis: efficacy of balloon-assisted enteroscopy for dilation of small bowel Crohn's disease strictures. *Aliment Pharmacol Ther* 2020; 52: 1104-16.
2. Hirai F. Current status of endoscopic balloon dilation for Crohn's disease. *Intest Res* 2017; 15: 166-73.
3. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
4. Navaneethan U, Kochhar G, Phull H et al. Severe disease on endoscopy and steroid use increase the risk for bowel perforation during colonoscopy in inflammatory bowel disease patients. *J Crohns Colitis* 2012; 6: 470–5.
5. Hirai F, Beppu T, Sou S et al. Endoscopic balloon dilatation using double-balloon

endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010; 22: 200-4.

6. Shen B, Kochhar G, Navaneethan U et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol* 2020; 5: 393-405.
7. Hirai F, Beppu T, Matsui T. Endoscopic balloon dilation of intestinal strictures in Crohn's disease. *J Gastroenterol* 2012; 109: 386-92.
8. Chen M, Shen B. Endoscopic therapy in Crohn's disease: principle, preparation, and technique. *Inflamm Bowel Dis* 2015; 21: 2222-40.
9. 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: 380-6.
10. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. *Dig Endosc* 2014; 26: 545-51.
11. Fukumoto A, Tanaka S, Yamamoto H et al. Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc* 2007; 66(3 Suppl): S108-12.
12. 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: 529-34.
13. Ohmiya N, Arakawa D, Nakamura M et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc* 2009; 69: 84-93.

14. 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: 1030-6.

15. Gill RS, Kaffes AJ. Small bowel stricture characterization and outcomes of dilatation by double-balloon enteroscopy: a single-centre experience. *Therap Adv Gastroenterol* 2014; 7: 108-14.

16. Fujimoto K, Fujishiro M, Kato M et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig. Endosc* 2014; 26: 1-14.

17. Kato M, Uedo N, Hokimoto S et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 Appendix on anticoagulants including direct oral anticoagulants. *Dig. Endosc* 2018; 30: 433-40.

18. Xin L, Liao Z, Jiang YP et al. Indications, detectability, positive findings, total enteroscopy, and complications of diagnostic double-balloon endoscopy: a systematic review of data over the first decade of use. *Gastrointest Endosc* 2011; 74: 563–70.

## 5) Definition of efficacy

At present, no high-quality, evidence-based study exists that defines the efficacy of EBD. Previous studies have reported short-term efficacy rates ranging between 36–100%, particularly when efficacy was defined as the endoscope being able to pass through the stricture or disappearance of abdominal symptoms caused by the stricture (disappearance of abdominal pain, post-EBD food intake, etc.).[1)–17)] Regarding long-term efficacy, the definition of "long-term" differs among reports (the

average period of observation was 6–10 months). The scope of the term efficacy is equally broad, ranging from avoiding surgery or the need for repeated EBD to the complete absence of recurrent abdominal symptoms caused by GI tract strictures. When measured by the rate of preventing the need for a repeated EBD (some overlap was detected), the long-term efficacy rate is reported to be 46–93%.[1)–17)] The post-EBD surgical conversion rate can be considered the most important long-term efficacy indicator. Bettenworth et al.[17)] reported 12- and 24-month post-EBD cumulative surgery rates of 30.1% and 42.9%, respectively. In contrast, the meta-analysis by Morar et al. showed a cumulative surgery rate of 75% within 5 years.[18)] A multi-center retrospective study on 305 cases in Japan[19)] reported surgical conversion rates of 26.0%, 45.6%, and 55.7% at 1, 5, and 10 years post-EBD, respectively, which means that EBD in Japan yields a relatively favorable surgical avoidance rate as compared to Europe and the US.

The two possible situations that would require surgical procedures are as follows: (i) EBD is not indicated for the lesions and (ii) insufficient EBD treatment effect. Of these, the former is described later with respect to the indications for / exclusion of EBD and the latter is described here. Three prospective studies[2) 6) 8)] have described the long-term results of EBD for intestinal strictures in Crohn's disease, but the criteria for conversion to surgical procedures were unclear. Similarly, the criteria in retrospective studies varied considerably, including the continuance or recurrence of abdominal symptoms, procedural failure, existence of new strictures in the intestine proximal to the stricture, presence of fistulas proximal to the stricture, the patient's wishes, and doctors' advice. Hence, it is necessary to examine the long-term efficacy of EBD in the setting of certain criteria for transition to surgical treatment.

References


1. Couckuyt H, Gevers AM, Coremans G et al. Efficacy and safety of hydrostatic balloon dilatation of ileocolonic Crohn's strictures: a prospective long term analysis. *Gut* 1995; 36: 577-80.
2. Fukumoto A, Tanaka S, Yamamoto H et al. Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc* 2007; 66 (3 Suppl): S108-12.
3. Hassan C, Zullo A, De Francesco V et al. Systematic review: endoscopic dilatation in Crohn's disease. *Aliment Pharmacol Ther* 2007; 26: 1457-64.
4. 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: 689-96.
5. Mueller T, Rieder B, Bechtner G et al. The response of Crohn's strictures to endoscopic balloon dilation. *Aliment Pharmacol Ther* 2010; 31: 634-9.
6. Scimeca D, Mocciaro F, Cottone M et al. Efficacy and safety of endoscopic balloon dilation of symptomatic intestinal Crohn's disease strictures. *Dig Liver Dis* 2011; 43: 121-5.
7. Gustavsson A, Magnuson A, Blomberg B et al. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn's disease. *Aliment Pharmacol Ther* 2012; 36: 151-8.
8. de'Angelis N, Carra MC, Borrelli O et al. Short- and long-term efficacy of endoscopic balloon dilation in Crohn's disease strictures. *World J Gastroenterol* 2013; 19: 2660-7.
9. Atreja A, Aggarwal A, Dwivedi S et al. Safety and efficacy of endoscopic dilation for primary and anastomotic Crohn's disease strictures. *J Crohns Colitis* 2014; 8:

392-400.

10. Greener T, Shapiro R, Klang E et al. Clinical outcomes of surgery versus endoscopic balloon dilation for stricturing Crohn's disease. *Dis Colon Rectum* 2015; 58: 1151-7.

11. Taida T, Nakagawa T, Ohta Y et al. Long-term outcome of endoscopic balloon dilatation for strictures in patients with Crohn's disease. *Digestion* 2018; 98: 26-32.

12. Lee HW, Park SJ, Jeon SR et al. Long-term outcomes of endoscopic balloon dilation for benign strictures in patients with inflammatory bowel disease. Gut Liver 2018; 12: 530-6.

13. Nishida Y, Hosomi S, Yamagami H et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn's disease using double-balloon endoscopy. *Intern Med* 2017; 56: 2245-52.

14. Guo F, Huang Y, Zhu W et al. Efficacy and safety of endoscopic balloon dilation for upper gastrointestinal strictures of Crohn's disease. *Dig Dis Sci* 2016; 61: 2977-85.

15. Asairinachan A, An V, Daniel ES et al. Endoscopic balloon dilatation of Crohn's strictures: a safe method to defer surgery in selective cases. *ANZ J Surg* 2017; 87: E240-4.

16. Kanamori A, Sugaya T, Tominaga K et al. Endoscopic balloon dilation for stenotic lesions in Crohn's disease. *Turk J Gastroenterol* 2017; 28: 117-24.

17. Bettenworth D, Gustavsson A, Atreja A et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017; 23: 133-42.

18. Morar PS, Faiz O, Warusavitarne J et al. Systematic review with meta-

analysis: endoscopic balloon dilatation for Crohn's disease strictures. *Aliment Pharmacol Ther* 2015; 42: 1137-48.

19. Bamba S, Sakemi R, Fujii T et al. A nationwide, multi-center, retrospective study of symptomatic small bowel stricture in patients with Crohn's disease. *J Gastroenterol* 2020; 55: 615-26.

## Detailed discussion

BQ1: Is it permissible to perform EBD on strictures with inflammation or ulcers?

| Statement: Strictures with inflammation or ulcers are not a contraindication for EBD. However, EBD should be avoided in lesions with deep ulcers. |
|---|

### Commentary:

A meta-analysis of 3,213 procedures for 1,463 cases across 33 studies performed between 1991 and 2013 indicated that inflammation in the stricture area was unrelated to long-term prognosis.[1)] For anastomotic lesions, endoscopic disease activity was also found unrelated to prognosis.[2)]

A meta-analysis of 347 cases across 13 studies indicated a tendency for EBD to be technically challenging in the presence of endoscopic disease activity.[3)] A single-center report stated that the presence or absence of ulcers did not influence the success or perforation rates;[4)] however, a single-center report of 273 cases from the US indicated a strong likelihood that repetition of EBD or surgery would be required if endoscopic disease activity is present.[5)]

In a 2016 survey of 126 experts, the proportion of physicians who considered

strictures with active inflammation to also be eligible for EBD was only 35.7%.[6] The 2016 technical review by the European Crohn's and Colitis Organization (ECCO) states that the presence of inflammation or ulcers was not a contraindication for EBD. However, it stated that the absence of ulcers is associated with a favorable prognosis.[7] However, most of the subjects in the reports[8] cited had anastomotic strictures, and only two cases of strictures were *de novo* (unrelated to a surgical anastomosis); hence, the review was not based on sufficient evidence. In Japan, the absence of deep ulcers is often a pre-requisite for performing EBD[9], and the same was also indicated in prospective multi-center collaborative studies based on the Grants from the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare.[10]

Based on the above, the presence of ulcers is not necessarily a contraindication, but the suitability for EBD must still be determined according to individual circumstances. EBD should be avoided in patients with deep ulcers as the risk of perforation is thought to be very high.

References

1. Bettenworth D, Gustavsson A, Atreja A et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017; 23: 133-42.
2. Thienpont C, D'Hoore A, Vermeire S et al. Long-term outcome of endoscopic dilatation in patients with Crohn's disease is not affected by disease activity or medical therapy. *Gut* 2010; 59: 320-4.
3. Hassan C, Zullo A, De Francesco V et al. Systematic review: endoscopic dilatation

in Crohn's disease. *Aliment Pharmacol Ther* 2007; 26: 1457-64.

4. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.
5. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W et al. Outcomes of endoscopic therapy for luminal strictures in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 1575-81.
6. Bettenworth D, Lopez R, Hindryckx P et al. Heterogeneity in endoscopic treatment of Crohn's disease-associated strictures: An international inflammatory bowel disease specialist survey. *J Gastroenterol.* 2016; 51: 939–48.
7. Rieder F, Latella G, Magro F et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis* 2016; 10: 873-85.
8. 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: 689-96.
9. Hirai F, Beppu T, Sou S et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010; 22: 200-4.
10. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.

BQ2: Is it permissible to perform EBD on long strictures?

| Statement: Longer strictures are associated with worse outcomes after EBD treatment. EBD is indicated for strictures with a length of 4–5 cm or less. |
|---|

**Commentary:**

The UK's 2019 guidelines recommend EBD for ileocolonic anastomotic strictures of 4 cm or less[1] and state that EBD is possible for ileal strictures if the endoscope can reach them. This is based on a meta-analysis of 1,163 cases across 24 studies.[2] In a meta-analysis of 167 cases across 5 studies, a difference was detected between the prognosis for strictures of 4 cm or less and those longer than 4 cm. The 2016 consensus of ECCO[3] considered a stricture length of 5 cm as the limit for successful dilation by EBD. A meta-analysis of 3,213 procedures (of which 98.6% were ileal and 62% were anastomotic) for 1,463 cases across 33 studies conducted between 1991 and 2013 found that surgical procedures could be avoided if the strictures were 5 cm or less[4]. In addition, in a 2016 survey of 126 experts, respondents reported that the longest stricture suitable for EBD was 4.5 ± 1.7 cm.[5] Furthermore, according to a consensus of 15 gastroenterologists and radiologists in Europe and the US, based on a systematic review as of July 2017, EBD is indicated for strictures up to 5 cm.[6]

Comparing EBD and surgery, it is estimated that surgery is more beneficial for longer strictures, even though it is associated with a higher rate of complications. When 117 cases of EBD and 258 cases of ileocecal resection were compared, the EBD group had fewer complications but a higher rate of salvage surgery. The same was true even when a comparison was made between the 46 EBD and 40 ileocecal

resection procedures for strictures 5 cm or less.[7] Furthermore, in a study of 39 cases of ileal or ileocecal valve strictures, it has also been shown that the average stricture length was 2.5 (1 to 25) cm in EBD cases and 7.5 (1 to 25) cm in patients requiring surgery[8]

It appears that the longer the stricture, the greater the technical difficulty in performing EBD. However, a Japanese multi-center analysis of 95 cases did not find stricture length as a factor in the success or failure of EBD.[9] Nevertheless, in a cohort study in Israel that included 39 EBD procedures on strictures of 4 cm or greater (of which 4.3% were on strictures 7 cm or more) length, EBD failure was more common among strictures that were 4 cm or longer.[10] Furthermore, in 65 cases at a single center in Japan where EBD was indicated for strictures of 5 cm or less, failures were significantly more common for strictures of 3 cm or longer. One multi-center study in Spain examined 400 EBD procedures (74 ileal, 99 colonic, 227 anastomotic) in 187 cases of IBD; when 174 procedures for strictures of less than 2 cm were compared with 131 procedures for strictures of 2 cm or more, the former were found to sustain the treatment effect. It should be noted that the longest stricture on which EBD was performed in this study was 12 cm.[12]

Furthermore, the longer the stricture, the more difficult it is to avoid surgery. An analysis of 305 cases of EBD performed on small intestinal strictures (including ileocecal valve strictures) at 32 facilities in Japan indicated that strictures of ≥2 cm (90 cases) had a lower surgical avoidance rate than that of strictures less than 2 cm (215 cases); in addition, a stricture of ≥2 cm was identified as an independent risk factor for surgery. However, when successful EBD cases were analyzed, no difference was observed between the two groups in terms of surgery rate or EBD interval.[13] It

was found in the previously-mentioned Israeli cohort study that the time leading to surgery was shorter in cases with strictures ≥ 4 cm in length than those with strictures less than 4 cm.[10] A report of 151 procedures of EBD at a single center in the UK did not identify any significant factors that led to surgery, but strictures >4 cm often required re-dilation.[14]

Generally, EBD is indicated for strictures ≤5 cm in length. In one single-center study of 37 cases in Italy, EBD was performed on strictures with a mean length of 3.4 cm (2–6 cm)[15]. Similarly, in a single-center study of 273 cases in the US, strictures that exceed 5 cm in length were precluded.[16] In Japan, EBD is also often indicated for strictures of ≤5 cm.[17] Furthermore, in a multi-center study in Taiwan (26 cases), the stricture length was 2.3 ± 1.5 cm.[18]

References

1. Lamb CA, Kennedy NA, Raine T et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68(Suppl 3): s1-106.
2. Navaneethan U, Lourdusamy V, Njei B et al. Endoscopic balloon dilation in the management of strictures in Crohn's disease: a systematic review and meta-analysis of non-randomized trials. *Surg Endosc* 2016; 30: 5434–43.
3. Rieder F, Latella G, Magro F et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis* 2016; 10: 873-85.
4. Bettenworth D, Gustavsson A, Atreja A et al. A pooled analysis of efficacy, safety,

and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017; 23: 133-42.

5. Bettenworth D, Lopez R, Hindryckx P et al. Heterogeneity in endoscopic treatment of Crohn's disease-associated strictures: An international inflammatory bowel disease specialist survey. *J Gastroenterol* 2016; 51: 939–48.
6. Rieder F, Bettenworth D, Ma C et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther* 2018; 48: 347-57.
7. Lan N, Stocchi L, Ashburn JH et al. Outcomes of endoscopic balloon dilation vs surgical resection for primary ileocolic strictures in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2018; 16: 1260–7.
8. Mueller T, Rieder B, Bechtner G et al. The response of Crohn's strictures to endoscopic balloon dilation. *Aliment Pharmacol Ther* 2010; 31: 634-9.
9. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
10. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.
11. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. *Dig Endosc* 2014; 26: 545-51.
12. Andújar X, Loras C, González B et al. Efficacy and safety of endoscopic balloon dilation in inflammatory bowel disease: results of the large multicenter study of the ENEIDA registry. *Surg Endosc* 2020; 34: 1112-22.

13. Bamba S, Sakemi R, Fujii T et al. A nationwide, multi-center, retrospective study of symptomatic small bowel stricture in patients with Crohn's disease. *J Gastroenterol*. 2020; 55: 615-26.

14. Ding NS, Yip WM, Choi CH et al. Endoscopic dilatation of Crohn's anastomotic strictures is effective in the long term, and escalation of medical therapy improves outcomes in the biologic era. *J Crohns Colitis* 2016; 10: 1172–8.

15. Scimeca D, Mocciaro F, Cottone M et al. Efficacy and safety of endoscopic balloon dilation of symptomatic intestinal Crohn's disease strictures. *Dig Liver Dis* 2011; 43: 121-5.

16. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W et al. Outcomes of endoscopic therapy for luminal strictures in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 1575-81.

17. 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: 380-6.

18. Chang CW, Tu CH, Chou JW et al. Endoscopic management of strictures in patients with Crohn's disease - A multi-center experience in Taiwan. *J Formos Med Assoc* 2020; 119: 1500-5.

FRQ1: Is it permissible to perform EBD on strictures with abscesses or fistulas?

| Statement: EBD is not indicated for strictures with abscesses or fistulas. |
| --- |

**Commentary:**

In Japan, EBD is only indicated for strictures that lack abscesses or fistulas.[1] A prospective multi-center study based on the Grants from the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare also excluded strictures associated with abscesses or fistulas.[2] Sunada et al. reported that 8 out of 11 cases of strictures with internal fistulas led to surgery; those cases had a significantly worse prognosis than that of strictures without internal fistulas.[3] In an opinion, a fistula within 5 cm of a stricture is a risk factor for procedure-related complications.[4] The 2016 consensus of ECCO considered the existence of abscesses or fistulas to be a contraindication for EBD.[5] Recent review articles also mentioned the absence of abscesses or fistulas as a criterion for the suitability of EBD.[6] [7] However, out of 138 EBD procedures on 64 cases at a single center in Israel, 3 cases with fistulas in the neighborhood of the stricture were successfully treated without perforation.[8] Even in cases complicated with abscesses, EBD may be effective after eliminating the abscess by nil per os and treatment with antibiotics.[9]

References

1. Hirai F, Beppu T, Sou S et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010; 22: 200-4.
2. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.

3. 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: 380-6.
4. Bessissow T, Reinglas J, Aruljothy A et al. Endoscopic management of Crohn's strictures. *World J Gastroenterol* 2018; 24: 1859-67.
5. Rieder F, Latella G, Magro F et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis* 2016; 10: 873-85.
6. Chan WPW, Mourad F, Leong RW. Crohn's disease associated strictures. *J Gastroenterol Hepatol* 2018; 33: 998-1008.
7. Shen B. Interventional IBD: The role of endoscopist in the multidisciplinary team management of IBD. *Inflamm Bowel Dis* 2018; 24: 298-309.
8. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.
9. Ohmiya N, Arakawa D, Nakamura M et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc* 2009; 69: 84-93.

FRQ2: Are there any other kinds of strictures not suitable for EBD?

| Statement: Strongly angulated strictures with adhesions require special attention, as they represent a risk for perforation occurring along and around the strictures. |
|---|

**Commentary:**

Many studies have suggested that strongly angulated strictures represent a contraindication to EBD.[1)–6)] The nationwide prospective study based on the Grants from the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare on the efficacy of EBD considered that strongly angulated strictures and dense adhesions are not indicated for EBD.[7)]

According to reports from overseas, in addition to a failure of endoscopic access to the strictures, there were some cases of failure in passing a balloon catheter through a stricture due to strong angulation at the stricture. [8)] In a Japanese single-center report, sharp angulations, including those in the colon, were excluded from being indicated for treatment with EBD.[9)] One multi-center report from the UK stated that the indications should be determined by considering the stricture location, severity, angulation, and presence/absence of fistulas or abscesses to avoid the procedure-related complications. [10)] In contrast, in a review of 138 cases, angulation did not affect the success rate of EBD or the incidence of complications. However, this review included only 31 EBD procedures on the small intestine.[11)]

Review articles on EBD also considered the presence of sharply angulated strictures as not suitable for EBD.[12)] Guidelines from other countries specify that EBD is indicated for non-angulated strictures and angulated ones are to be avoided.[13)–18)] In addition, non-angulated strictures were considered a predictive factor for successful EBD, while adhesions were considered a risk factor for procedure-related complications.[19)]

Balloons for EBD are generally 5 cm long and become more rigid when dilated. Hence, care should be exercised owing to the possibility of perforation when dilating

strictures with adhesions or strong angulations because of increased pressure load on the areas of the GI tract around the stricture.



References


1. Hirai F, Beppu T, Sou S et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010; 22: 200-4.
2. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. *Dig Endosc* 2014; 26: 545-51.
3. 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: 380-6.
4. Nishida Y, Hosomi S, Yamagami H et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn's disease using double-balloon endoscopy. *Intern Med* 2017; 56: 2245-52.
5. Kanamori A, Sugaya T, Tominaga K et al. Endoscopic balloon dilation for stenotic lesions in Crohn's disease. *Turk J Gastroenterol* 2017; 28: 117-24.
6. Taida T, Nakagawa T, Ohta Y et al. Long-term outcome of endoscopic balloon dilatation for strictures in patients with Crohn's disease. *Digestion* 2018; 98: 26-32.
7. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
8. Hassan C, Zullo A, De Francesco V et al. Systematic review: endoscopic dilatation

in Crohn's disease. *Aliment Pharmacol Ther* 2007; 26: 1457-64.

9. Nomura E, Takagi S, Kikuchi T et al. Efficacy and safety of endoscopic balloon dilation for Crohn's strictures. *Dis Colon Rectum* 2006; 49 (10 Suppl): S59–67.
10. Bhalme M, Sarkar S, Lal S et al. Endoscopic balloon dilatation of Crohn's disease strictures: results from a large United Kingdom series. *Inflamm Bowel Dis* 2014; 20: 265-70.
11. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.
12. Sunada K, Yamamoto H, Yano T et al. Advances in the diagnosis and treatment of small bowel lesions with Crohn's disease using double-balloon endoscopy. *Therap Adv Gastroenterol* 2009; 2: 357–66.
13. Bharadwaj S, Fleshner P, Shen B. Therapeutic armamentarium for stricturing Crohn's disease: medical versus endoscopic versus surgical approaches. *Inflamm Bowel Dis* 2015; 21: 2194-213.
14. Chen M, Shen B. Endoscopic therapy in Crohn's disease: principle, preparation, and technique. *Inflamm Bowel Dis*. 2015; 21: 2222-40.
15. Klag T, Wehkamp J, Goetz M. Endoscopic balloon dilation for Crohn's disease-associated strictures. *Clin Endosc* 2017; 50: 429-36.
16. Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. *Gastroenterology* 2017; 152: 340-50.
17. Shen B. Interventional IBD: The role of endoscopist in the multidisciplinary team management of IBD. *Inflamm Bowel Dis* 2018; 24: 298-309.
18. Chan WPW, Mourad F, Leong RW. Crohn's disease associated strictures. *J*

*Gastroenterol Hepatol* 2018; 33: 998-1008.

19. Bessissow T, Reinglas J, Aruljothy A et al. Endoscopic management of Crohn's strictures. *World J Gastroenterol* 2018; 24: 1859-67.

BQ3: Should a biopsy be performed to rule out malignant strictures?

| Statement: Always consider the possibility of malignancy in intestinal strictures before EBD. Consider histological evaluation with biopsy whenever a dysplastic lesion is suspected at the stricture. |
|---|

**Commentary:**

Crohn's disease can cause malignant neoplasms in the small intestine, and high standardized incidence rates (SIR) of 41.1 (95% CI: 8.5–20)[1)] and 66.67 (18.13–170.68)[2)] of malignant neoplasms in the small intestine have been reported. The SIR of 27.1 (14.9–49.2)[3)] was also high in a meta-analysis of 6 reports between 1989 and 2005. Furthermore, the standardized mortality ratio from Crohn's disease-associated malignant neoplasms in the small intestine is extremely high[4)], at 200 (24.2–722).† The incidence rate of small bowel adenocarcinoma in patients with an eight-year or longer history of Crohn's disease is 0.464 cases per thousand people per year; thus, the long-standing disease may increase the risk of such cancer.[5)] In contrast, a previous report showed that consuming 5-ASAs for two or more years or a history of the partial resection of the small intestine may have a prophylactic effect

against developing small bowel adenocarcinoma.[6] Characteristics of malignant neoplasms include multifocality[7], the presence of the epithelial dysplasia adjacent to carcinoma in a surgical specimen[6], and endoscopic observation of sessile and polypoid dysplastic lesions.[8]

Obstructive symptoms are the most common clinical symptoms of Crohn's disease-associated malignant neoplasms and account for up to 75%[9]. Small bowel malignancy as a comorbidity of Crohn's disease is often revealed only by examining surgical specimens, and it is extremely rare to be diagnosed as a malignant tumor before surgery.[9] Furthermore, reports showing the benefits of screening endoscopy are scant. In a prospective cohort study, the sensitivity for the diagnosis of small bowel adenocarcinoma by endoscopy was just 33%.[10] However, in this study the observation range was approximately 20 cm each for the upper jejunum and the terminal ileum, which is considered insufficient.

While EBD allows patients to avoid surgery, this may worryingly diminish the prophylactic effect against neoplasms and opportunities for early-stage detection that could be provided by small bowel resection. Since EBD enables observation of the distal small intestine, the procedure may allow improvement in the detection rate for neoplastic lesions, including precancerous ones, and the accuracy of endoscopic screening. Therefore, when EBD enables passage through a stricture, it is important to perform further observation to confirm the presence/absence of a neoplastic lesion. Notably, poorly differentiated adenocarcinoma associated with Crohn's disease may develop from the deep mucosal layer, so biopsy results should be carefully considered.[11] Moreover, strictures resistant to dilation[12] may be malignant; therefore, care must be taken. When surgery is required due to perforation during or after EBD, the peritoneal cavity should be explored in detail

to assess the possibility of malignancy in the lesion, and resected accordingly to treat the lesion.

Differentiation of benign and malignant strictures in Crohn's disease is not easy, and hence, during EBD, strictures should be evaluated with detailed endoscopic examination and biopsy considering the possibility of malignant strictures.

(†: There was an error in the original. It has been corrected after confirmation with the author.)

References

1. Jess T, Loftus EV Jr, Velayos FS et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology* 2006; 130: 1039-46.
2. Jess T, Winther KV, Munkholm P et al. Intestinal and extra-intestinal cancer in Crohn′s disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Aliment Pharmacol Ther* 2004; 19: 287-93.
3. Jess T, Gamborg M, Matzen P et al. Increased risk of intestinal cancer in Crohn′s disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005; 100: 2724-9.
4. Yasukawa S, Matsui T, Yano Y et al. Crohn′s disease-specific mortality: a 30-year cohort study at a tertiary referral center in Japan. *J Gastroenterol* 2019; 54: 42-52.
5. Elriz K, Carrat F, Carbonnel F et al. Incidence, presentation, and prognosis of small bowel adenocarcinoma in patients with small bowel Crohn′s disease: a

prospective observational study. *Inflamm Bowel Dis* 2013; 19: 1823-6.

6. Piton G, Cosnes J, Monnet E et al. Risk factors associated with small bowel adenocarcinoma in Crohn′s disease: a case-control study. *Am J Gastroenterol.* 2008; 103: 1730-6.
7. Tang CQY, Teo TZH, Heng GKE et al. Multifocal small-bowel adenocarcinoma mimicking Crohn′s disease. *Gastrointest Endosc* 2019; 90: 691-3.
8. Gu P, Huang B, Rezaie A. An unexpected cause of small bowel obstruction. *Gastroenterology* 2017; 152: e14-5.
9. Dossett LA, White LM, Welch DC et al. Small bowel adenocarcinoma complicating Crohn′s disease: case series and review of the literature. *Am Surg* 2007; 73: 1181-7.
10. Simon M, Cosnes J, Gornet JM et al. Endoscopic detection of small bowel dysplasia and adenocarcinoma in Crohn′s disease: a prospective cohort-study in high-risk patients. *J Crohns Colitis* 2017; 11: 47-52.
11. Liao X, Li G, McBride R et al. Clinicopathological and molecular characterisation of Crohn′s disease-associated small bowel adenocarcinomas. *J Crohns Colitis* 2020; 14: 287-94.
12. Nishida Y, Hosomi S, Yamagami H et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn′s disease using double-balloon endoscopy. *Intern Med* 2017; 56: 2245-52.

CQ1: Is EBD equally safe and effective for anastomotic and *de novo* lesions?

| Recommendation: EBD is almost equally safe and effective for both types of lesions, and we recommend EBD for both. |
|---|
| Modified Delphi scores: median 9, minimum 8, maximum 9. |
| Strength of recommendation: 2. Evidence level: C. |

**Commentary:**

At present, no clinical study has compared the effects of EBD on anastomotic and *de novo* lesions in Crohn's disease as the primary endpoint; however, EBD may have different effects on these two types of lesions because their mechanisms of occurrence also differ.

Until 2010, there were few studies examining the therapeutic efficacy of EBD and clinical course by dilated sites (anastomotic lesion versus *de novo* lesion). Anastomotic lesions for which EBD is indicated are predominantly for small intestine/large intestine anastomoses; few cases were reported where EBD was performed for a small intestine/small intestine anastomosis. Regarding the effects of EBD on *de novo* lesions, data have been reported from Japan[1], whereas there are few studies on *de novo* lesions with a sufficient number of cases in Europe, or the US[2),3)].

From 2010 onward, occasional reports studied EBD's short- and long-term efficacies based on the characteristics of the strictures. At present, most of the studies from Europe and the US focus on small-to-large intestinal anastomotic

lesions. These studies indicate no apparent difference in the effect of EBD on anastomotic versus *de novo* lesions.[4)-6)]

In contrast, since the diagnosis and treatment of small intestinal diseases using balloon endoscopy has expanded mainly in Japan, the short- and long-term effects of EBD for small-to-small (not small-to-large) intestinal anastomotic and *de novo* lesions in Crohn's disease have been reported[7),8)]. In a multicenter prospective study of 95 patients with Crohn's disease who underwent EBD for small intestinal stenosis, Hirai et al. reported no difference in the short-term efficacy of EBD between anastomotic and *de novo* lesions.[9)] Concerning the safety of EBD[6) 9)], many reports also indicated no difference between anastomotic and *de novo* lesions; however, Foster et al. indicated that the complication rate of EBD was higher for side-to-side and side-to-end anastomoses than for end-to-end anastomoses. Therefore, the method of anastomosis is a factor to consider.[10)]

References

1. Ohmiya N, Arakawa D, Nakamura M et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc* 2009; 69: 84-93.
2. Mueller T, Rieder B, Bechtner G et al. The response of Crohn′s strictures to endoscopic balloon dilation. *Aliment Pharmacol Ther* 2010; 31: 634-9.
3. Thienpont C, D'Hoore A, Vermeire S et al. Long-term outcome of endoscopic dilatation in patients with Crohn's disease is not affected by disease activity or medical therapy. *Gut* 2010; 59: 320-4.
4. Morar PS, Faiz O, Warusavitarne J et al. Systematic review with meta-analysis:

endoscopic balloon dilatation for Crohn's disease strictures. *Aliment Pharmacol Ther* 2015; 42: 1137-48.

5. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W et al. Outcomes of endoscopic therapy for luminal strictures in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 1575-81.
6. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.
7. 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: 380-6.
8. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. *Dig Endosc* 2014; 26: 545-51.
9. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
10. Foster EN, Quiros JA, Prindiville TP. Long-term follow-up of the endoscopic treatment of strictures in pediatric and adult patients with inflammatory bowel disease. *J Clin Gastroenterol* 2008; 42: 880-5.

CQ2: Is there a limit to the number of strictures that can be dilated in succession?

Recommendation: We recommend performing dilation without limiting the number of strictures if technically possible.

Modified Delphi scores: median 9, minimum 7, maximum 9.

Strength of recommendation: 2. Evidence level: C.

**Commentary:**

In addition to the number of strictures, the success or failure of EBD for Crohn's disease-associated small intestinal strictures is influenced by factors such as the position of the stricture, presence or absence of active Crohn's disease lesions that contain the stricture, length and shape of the stricture, presence of fistulas, and adhesions in the abdominal cavity.

In a Japanese study of 85 cases of Crohn's disease-associated small intestinal strictures first treated by EBD, the mean number of strictures was 2.4. No significant difference was observed between single and multiple strictures as a factor associated with the need for post-EBD surgery (hazard ratio [HR]=0.70, 95% CI: 0.28–1.75, P=0.45).[1] Furthermore, in a prospective multicenter cohort study in Japan of EBD for small intestinal strictures in patients with Crohn's disease, 48.4% of the 95 cases were single strictures, while 51.6% were multiple strictures (16.8% of cases involved four or more strictures); no significant difference (P=0.97) was reported between single- and multiple-stricture cases with regard to the short-term symptomatic improvement of strictures post-EBD.[2] As for the long-term prognosis post-EBD, a review of 65 cases of Crohn's disease with small intestinal strictures reported no significant difference between single and multiple strictures in the

success rate of EBD (P=0.75). Furthermore, no significant difference was observed comparing single and multiple strictures in terms of the need for repeat EBD dilation post-EBD (P=1.0).[3)]

These findings led to a recently published multicenter study regarding Crohn's disease with small intestinal strictures in 305 cases with symptomatic strictures across 32 facilities in Japan. This study also reported no significant difference, with regard to the number of strictures, between cases where EBD was possible or not (P=0.127). No correlation was found between the number of strictures and need for surgery (HR=1.079, 95% CI: 0.885–1.315, P=0.446) or between the number of strictures and the first post-EBD surgery (HR=0.548, 95% CI: 0.207–1.429, P=0.217).[4)] In addition, one systematic review with 13 studies regarding EBD for small intestinal strictures stated that the number of strictures was not included in the criteria for eligibility for or exclusion from EBD in any of the studies.[5)]

A study from the US comparing 81 single-stricture and 36 multiple-stricture cases found that not only did patients with multiple-strictures need EBD multiple times at shorter intervals and experience nausea and vomiting more often, but they also had a higher rate of surgery post-EBD (66.7%) in comparison to patients with single-strictures (35.8%, P<0.002).[6)] Among cases in the multiple-stricture group, cases with 2–3 strictures were not correlated with post-EBD surgery (HR=15, 95% CI: 0.8–2.8), but the study showed that the post-EBD surgery rate was significantly higher for cases with 4 or more strictures (HR=14.1, 95% CI: 1.6–120.3). Hence, possibly based on this study, the Global Interventional Inflammatory Bowel Disease Group's guidelines recommended EBD as a safe and effective method for patients with three or fewer adjacent strictures.[7)]

Besides $CO_2$ insufflation, in recent years, advancements have been made in the

development of attachments at the end of the endoscope and small-diameter endoscopes. When multiple small intestinal strictures are present in a long segment, the benefits of avoiding surgery with EBD are significant. Among reports published to date, few argued that the rate of procedure-related complications increased as the number of strictures on which EBD is performed increased. If EBD is performed according to eligibility criteria and exclusion criteria, there is little basis for setting a limit on the number of strictures to be dilated in a single session, as long as it is technically possible.

References

1. 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: 380-6.
2. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn′s disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
3. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn′s disease. *Dig Endosc* 2014; 26: 545-51.
4. Bamba S, Sakemi R, Fujii T et al. A nationwide, multi-center, retrospective study of symptomatic small bowel stricture in patients with Crohn′s disease. *J Gastroenterol* 2020; 55: 615-26.
5. Baars JE, Theyventhiran R, Aepli P et al. Double-balloon enteroscopy-assisted

dilatation avoids surgery for small bowel strictures: a systematic review. *World J Gastroenterol* 2017; 23: 8073-81.

6. Lan N, Shen B. Multiple primary Crohn's disease-associated strictures had poor response to endoscopic balloon dilation. *Am J Gastroenterol* 2018; 113: S421–2.

7. Shen B, Kochhar G, Navaneethan U et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol* 2020; 5: 393-405.

CQ3: What is the appropriate dilation diameter in mm?

Recommendation: In terms of safety, the diameter of dilation is to be adjusted according to the diameter of the stricture. In terms of efficacy, we recommend that the final target diameter generally be 12–15 mm.

Modified Delphi scores: median 9, minimum 7, maximum 9.

Strength of recommendation: 2. Evidence level: C.

**Commentary:**

In previous reports, balloon dilators for the small intestine up to 12–15 mm have been used[1], and the maximum dilated diameter was 15 to 20 mm for small intestinal lesions.[2]

Concerning the optimal diameter for dilation, a prospective study by Hirai et al.

reported that symptoms did not improve when an 8–10 mm balloon catheter was used[3]. A dilation of at least 12 mm is recommended to achieve improvement of symptoms. In a retrospective study limited to small intestinal lesions, the rate of avoiding resection improved with dilation of 15 mm or greater in a univariate analysis.[4] Another retrospective study that included both small intestinal and colonic lesions reported improved outcomes with dilation of 12–15 mm or greater.[5,8] In a retrospective study including both small intestinal and colonic lesions using colonoscopy, no significant difference was found in procedure risk between diameters of 14–15 mm and 16–18 mm; however, the group that selected the dilation diameter of 16 to 18 mm had a longer dilation interval after the 4th dilation (mean 240±136.7 days vs. 456±357.3 days, P=0.023).[7]

Although the efficacy of EBD is thought to increase with larger diameters of dilation, an increase in the rate of perforations and other complications remains a concern. Gustavsson et al. reported that in a cohort where 77% were ileocolonic anastomotic lesions, the rate of procedure-related complications was significantly higher in cases where a balloon with a dilation diameter of 25 mm was used.[9] Furthermore, one systematic review concluded that dilation of 15 mm or greater is a risk factor for perforation.[10] However, there have been occasional reports of dilation of less than 15 mm causing perforation as well.[5,8,11,12] In terms of safety, the technique of starting with a small dilation diameter and gradually increasing the diameter has been reported[8,12–16]. For severe strictures, one option might be to start with a dilation diameter of 12 mm or less and gradually increase it. The choice of dilation diameter should be determined after weighing the risks and benefits given the patient's background and condition of the strictures.

In interpreting the analysis results, the following points should be kept in mind.

Almost all reports on EBD for Crohn's disease are single-center studies. Since the number of cases these studies include is limited, small intestinal and colonic lesions were simultaneously analyzed. Many of the reports are retrospective studies that suffer from various biases. For example, since the operator determines the choice of dilation diameter for each procedure, bias due to a correlation between the diameter of the stricture before dilation and the diameter of the balloon-dilator catheter cannot be ruled out. In addition, considering surgery as the outcome, the patient may not opt for surgery even if symptoms did not improve.

References

1. Klag T, Wehkamp J, Goetz M. Endoscopic balloon dilation for Crohn's disease-associated strictures. *Clin Endosc* 2017; 50: 429-36.
2. Hirai F. Current status of endoscopic balloon dilation for Crohn's disease. *Intest Res* 2017; 15: 166-73.
3. Hirai F, Andoh A, Ueno F et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: A nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018; 12: 394-401.
4. Bamba S, Sakemi R, Fujii T et al. A nationwide, multi-center, retrospective study of symptomatic small bowel stricture in patients with Crohn's disease. *J Gastroenterol* 2020; 55: 615-26.
5. Andújar X, Loras C, González B et al. Efficacy and safety of endoscopic balloon dilation in inflammatory bowel disease: results of the large multicenter study of the ENEIDA registry. *Surg Endosc* 2020; 34: 1112-22.

6. Winder O, Fliss-Isakov N, Winder G et al. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. *Medicine (Baltimore)* 2019; 98: e16864.

7. Reutemann BA, Turkeltaub JA, Al-Hawary M et al. Endoscopic balloon dilation size and avoidance of surgery in stricturing Crohn′s disease. *Inflamm Bowel Dis* 2017; 23: 1803-9.

8. Asairinachan A, An V, Daniel ES et al. Endoscopic balloon dilatation of Crohn′s strictures: a safe method to defer surgery in selective cases. *ANZ J Surg* 2017; 87: E240-4.

9. Gustavsson A, Magnuson A, Blomberg B et al. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn′s disease. Aliment Pharmacol Ther 2012; 36: 151-8.

10. Baars JE, Theyventhiran R, Aepli P et al. Double-balloon enteroscopy-assisted dilatation avoids surgery for small bowel strictures: A systematic review. *World J Gastroenterol* 2017; 23: 8073-81.

11. Nishida Y, Hosomi S, Yamagami H et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn′s disease using double-balloon endoscopy. *Intern Med* 2017; 56: 2245-52.

12. 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: 380-6.

13. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W et al. Outcomes

of endoscopic therapy for luminal strictures in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 1575-81.

14. Kanamori A, Sugaya T, Tominaga K et al. Endoscopic balloon dilation for stenotic lesions in Crohn's disease. *Turk J Gastroenterol* 2017; 28: 117-24.

15. Kroner PT, Brahmbhatt BS, Bartel MJ et al. Yield of double-balloon enteroscopy in the diagnosis and treatment of small bowel strictures. *Dig Liver Dis* 2016; 48: 446-8.

16. Ding NS, Yip WM, Choi CH et al. Endoscopic dilatation of Crohn's anastomotic strictures is effective in the long term, and escalation of medical therapy improves outcomes in the biologic era. *J Crohns Colitis* 2016; 10: 1172–8.

FRQ3: Is local administration of corticosteroids or anti-tumor necrosis factor (TNF) alpha antibodies effective to prevent post-EBD recurrence of strictures?

| Statement: The efficacy of local administration of corticosteroids or anti-TNF alpha antibodies to prevent recurrent stenosis is unclear. |
|---|

**Commentary:**

Local injection of corticosteroids is widely used to prevent stricture after endoscopic resection of esophageal cancer and to treat keloids. In 1995, Remboer et

al described the first report of corticosteroid administration for strictures secondary to Crohn's disease after EBD. They administered betamethasone topically to 13 patients with Crohn's disease-associated strictures after 1–2 sessions of EBD and reported that the stenotic symptoms disappeared in all cases.[1] Later, triamcinolone was introduced for dilated strictures; its effect lasts for 3–4 weeks.[2] To administer it, 40 mg of triamcinolone is dissolved in 2–5 mL of saline solution, and 0.5–1.0 mL is applied to each quarter-circumference of the distal end of the stricture or the part where inflammation is most advanced. If the stricture is long, the solution is applied along the stricture at 2 cm intervals.[3] Studies on this FRQ are mostly retrospective observational studies, and there are only two prospective randomized trials reported. One is a single-center prospective randomized study that included 29 children with Crohn's disease. This study confirmed that the group of patients receiving 40 mg/5 mL of triamcinolone locally after EBD had a prolonged interval to stricture recurrence and surgery compared to the placebo group.[4] The other study is a prospective randomized trial which examined anastomotic lesions in 13 cases of ileocecal resection in adult patients with Crohn's disease, and it showed contradictory results to the study described above. The study showed that the group who received 40 mg/5 mL injection of triamcinolone had an increased frequency of needing re-dilation as compared to the placebo group.[5] Meanwhile, in 2007 and 2017 systematic reviews, it was reported that the local administration of corticosteroids does not have an effect on the clinical course of these patients.[6] [7] Therefore, there is no consensus on the efficacy of locally administered corticosteroids after EBD to prevent restenosis. The guidelines from the Global Interventional Inflammatory Bowel Disease Group also recommend "not administering" corticosteroids. However, the evidence level for this recommendation is low.[8]

Although the efficacy of the local administration of anti-TNF alpha antibodies to strictures is reported, the studies are limited to case reports and case series.[9–11)]

References


1. Ramboer C, Verhamme M, Dhondt E et al. Endoscopic treatment of stenosis in recurrent Crohn's disease with balloon dilation combined with local corticosteroid injection. *Gastrointest Endosc* 1995; 42: 252-5.
2. Roques C, Téot L. The use of corticosteroids to treat keloids: a review. *Int J Low Extrem Wounds* 2008; 7: 137-45.
3. Bevan R, Rees CJ, Rutter MD et al. Review of the use of intralesional steroid injections in the management of ileocolonic Crohn's strictures. *Frontline Gastroenterol* 2013; 4: 238-43.
4. Di Nardo G, Oliva S, Passariello M et al. Intralesional steroid injection after endoscopic balloon dilation in pediatric Crohn's disease with stricture: a prospective, randomized, double-blind, controlled trial. *Gastrointest Endosc* 2010; 72: 1201-8.
5. East JE, Brooker JC, Rutter MD et al. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol* 2007; 5: 1065–9.
6. Hassan C, Zullo A, De Francesco V et al. Systematic review: endoscopic dilatation in Crohn's disease. *Aliment Pharmacol Ther* 2007; 26: 1457-64.
7. Bettenworth D, Gustavsson A, Atreja A et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017; 23: 133-42.

8. Shen B, Kochhar G, Navaneethan U et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol* 2020; 5: 393-405.

9. Swaminath A, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. *Inflamm Bowel Dis* 2008; 14: 213-6.

10. Sorrentino D, Avellini C, Beltrami CA et al. Selective effect of infliximab on the inflammatory component of a colonic stricture in Crohn's disease. *Int J Colorectal Dis* 2006; 21: 276–81.

11. Hendel J, Karstensen JG, Vilmann P. Serial intralesional injections of infliximab in small bowel Crohn's strictures are feasible and might lower inflammation. *United European Gastroenterol J* 2014; 2: 406-12.

FRQ4: For how many minutes should the balloon be kept dilated?

| Statement: Generally, dilation is performed for 30 seconds to 2 minutes. |
|---|

**Commentary:**

There is no literature comparing the effects of different dilation duration when EBD is performed for Crohn's disease-associated stricture lesions. Therefore, there is no evidence defining the EBD dilation time for Crohn's disease strictures. Most of the reports, including colonic strictures, indicated a dilation duration of 1–3 minutes[1), 2)]. According to the results of a multi-center questionnaire survey by Bettenworth et al. regarding Crohn's disease-associated strictures for which a colonoscope was used, facilities in Europe used a somewhat long dilation duration of

2 minutes (±1.3 minutes) in comparison to that in North America (1.4 ± 0.95 minutes).[1] **Table 3** shows an overview of the literature specifying the duration of dilation in reports limited to small intestinal strictures. These reports are all from Japan, and the duration used, which ranges from 30 seconds to 2 minutes, was decided based on the operator's clinical experience. In the future, prospective trials will be required to compare the dilation duration used.

Table 3. Overview of dilation duration in endoscopic balloon dilation

| Author | Year | Country | Target | Duration | Reference |
|---|---|---|---|---|---|
| Tsuboi | 2019 | Japan | small intestine | 30 seconds | 3 |
| Takenaka | 2017 | Japan | small intestine | 2 minutes | 4 |
| Sunada | 2016 | Japan | small intestine | 30–60 seconds | 5 |
| Hirai | 2014 | Japan | small intestine | 30–120 seconds | 6 |
| Hirai | 2010 | Japan | small intestine | 1–2 minutes | 7 |
| Ohmiya | 2009 | Japan | small intestine | 1 minute | 8 |

References

1. Bettenworth D, Lopez R, Hindryckx P et al. Heterogeneity in endoscopic treatment of Crohn′s disease-associated strictures: An international inflammatory bowel disease specialist survey. *J Gastroenterol* 2016; 51: 939–48.

2. Navaneethan U, Lourdusamy V, Njei B et al. Endoscopic balloon dilation in the management of strictures in Crohn′s disease: a systematic review and meta-analysis of non-randomized trials. *Surg Endosc* 2016; 30: 5434–43.

3. Tsuboi A, Oka S, Tanaka S et al. Experience with balloon filatation in Crohn′s and non-Crohn′s benign small-bowel strictures: Is there a difference? *Gastroenterol Res Pract* 2019; 2019: 1262595.

4. 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* 2017; 52: 879-88.

5. 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: 380-6.

6. Hirai F, Beppu T, Takatsu N et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn′s disease. Dig Endosc 2014; 26: 545-51.

7. Hirai F, Beppu T, Sou S et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn′

s disease. *Dig Endosc* 2010; 22: 200-4.

8. Ohmiya N, Arakawa D, Nakamura M et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc* 2009; 69: 84-93.

FRQ5: Is the administration of prophylactic antibiotics an effective countermeasure against procedure-related complications?

| Statement: The efficacy of administering prophylactic antibiotics as a countermeasure against procedure-related complications is unclear. |
|---|

**Commentary:**

There are no reports investigating the efficacy of administering prophylactic antibiotics as a countermeasure against the complications of EBD for small intestinal strictures. Antibiotic administration is not widely used after EBD[1)], and is limited to patients with advanced systemic complications, immunocompromised status, or malnutrition that may lead to infection.[2)] The most important precaution to prevent procedure-related complications of EBD is to review the results from each imaging modality and determine for which patients the treatment is appropriate. Given that the occurrence of adverse events that would necessitate the administration of antibiotics cannot be predicted, sufficient evidence is missing to advocate administration before the procedure. However, in actual clinical practice, some centers administer antibiotics before performing EBD because of the possibility of bacterial translocation. Other centers administer antibiotics after EBD to

diminish the risk of infection. The experts' opinions in Japan are divided; thus, a prospective study on the topic is needed.

References

1. Shen B, Kochhar G, Navaneethan U et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol* 2020; 5: 393-405.
2. Chen M, Shen B. Endoscopic therapy in Crohn's disease: principle, preparation, and technique. *Inflamm Bowel Dis* 2015; 21: 2222-40

FRQ6: What would be an indication for other procedures (endoscopic stricturotomy or stenting)?

| Statement: The safety and efficacy of endoscopic treatments other than endoscopic balloon dilation, such as endoscopic stricturotomy or stenting, has not been established. |
|---|

**Commentary:**

Procedures other than EBD that are performed on patients with Crohn's disease-associated small intestinal strictures include endoscopic stricturotomy and stenting. The efficacy of endoscopic stricturotomy has been reported in case reports, a pilot study with a small number of cases[1)], and studies on cases using historical cohorts from a single center.[2)–4)] Since these reports have been limited to strictures at the

anastomosis following resection of the distal ileum or ileocecum and to relatively short strictures (approximately 1–2 cm), and the number of reports and the facilities has also been limited, further studies are necessary regarding the efficacy of endoscopic stricturotomy.

Several reports have described the implementation of stenting; self-expandable metallic stents (SEMSs)[1)–7)], use of a full-covered type lumen apposing metal stent (LAMS) for fistulaplasty[8)], and biodegradable stents.[9) 10)] On LAMS and biodegradable stents, only case reports and pilot studies of a small number of cases are available, and their safety and efficacy are unclear at present. With regard to SEMS, there are reports of the treatment of both colonic strictures and post-ileocecal resection anastomotic lesions.[6) 7) 11)] Further, a report on large-to-small intestinal anastomotic lesions is also available.[12)] In a systematic review[7)] (with 65 cases), one prospective pilot study[11)] (incorporating 11 cases), and two retrospective studies[6) 12)] (incorporating 17 and 21 cases, respectively), the duration of stent placement varied from 1–4 weeks, and some of the reports stated that SEMSs are highly safe and effective[6) 7) 12)], whereas one report also showed a high risk of the stent migration.[11)] Therefore, at present, other than EBD, no other endoscopic treatment can be recommended for the treatment of patients with Crohn's disease-associated small intestinal strictures.

(Note: Colonic and duodenal stents in Japan are used to treat malignant neoplastic strictures; they are not applicable for benign strictures.)

References

1. Moroi R, Shiga H, Kuroha M et al. Endoscopic radial incision and cutting for

Crohn's disease-associated intestinal stricture: a pilot study. *Endosc Int Open* 2020; 8: E81-e6.

2. Lan N, Shen B. Endoscopic stricturotomy versus balloon dilation in the treatment of anastomotic strictures in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 897-907.
3. Lan N, Stocchi L, Delaney CP, et al. Endoscopic stricturotomy versus ileocolonic resection in the treatment of ileocolonic anastomotic strictures in Crohn's disease. *Gastrointest Endosc* 2019; 90: 259-68.
4. Lan N, Hull TL, Shen B. Endoscopic stricturotomy and ileo-colonic resection in patients with primary Crohn's disease-related distal ileum strictures. *Gastroenterol Rep (Oxf)* 2020; 8: 312-8.
5. Small AJ, Young-Fadok TM, Baron TH. Expandable metal stent placement for benign colorectal obstruction: outcomes for 23 cases. *Surg Endosc* 2008; 22: 454-62.
6. Loras C, Pérez-Roldan F, Gornals JB et al. Endoscopic treatment with self-expanding metal stents for Crohn's disease strictures. *Aliment Pharmacol Ther* 2012; 36: 833-9.
7. Loras Alastruey C, Andújar Murcia X, Esteve Comas M. The role of stents in the treatment of Crohn's disease strictures. *Endosc Int Open* 2016; 4: E301-8.
8. Axelrad JE, Lichtiger S, Sethi A. Treatment of Crohn's disease anastomotic stricture with a lumen-apposing metal stent. *Clin Gastroenterol Hepatol* 2018; 16: A25-6.
9. Rejchrt S, Kopacova M, Brozik J et al. Biodegradable stents for the treatment of benign stenoses of the small and large intestines. *Endoscopy* 2011; 43: 911-7.
10. Karstensen JG, Christensen KR, Brynskov J et al. Biodegradable stents for the

treatment of bowel strictures in Crohn's disease: technical results and challenges. *Endosc Int Open* 2016; 4: E296-300.

11. Attar A, Maunoury V, Vahedi K et al. Safety and efficacy of extractible self-expandable metal stents in the treatment of Crohn's disease intestinal strictures: a prospective pilot study. *Inflamm Bowel Dis* 2012; 18: 1849-54.
12. Das R, Singh R, Din S et al. Therapeutic resolution of focal, predominantly anastomotic Crohn's disease strictures using removable stents: outcomes from a single-center case series in the United Kingdom. *Gastrointest Endosc* 2020; 92: 344-52.

FRQ7: After EBD has been performed on a stricture, should prophylactic EBD be performed even if the stricture is asymptomatic?

| Statement: Sufficient evidence on the efficacy of performing prophylactic EBD has not yet been accumulated; this is a question for future research. |
|---|

**Commentary:**

For this FRQ, we define "prophylactic scheduled EBD" as performing EBD at regular intervals to prevent recurrent obstructive symptoms in asymptomatic patients with Crohn's disease-associated strictures.

Matsui et al. reported prophylactic EBD every 2–4 months in outpatients whose strictures were predicted to worsen endoscopically after EBD.[1)] However, if a stricture is asymptomatic, it may remain asymptomatic even without repeat EBD, and the EBD has a risk of complications such as aggravate inflammation, necessitate

or prolong the duration of hospitalization, or cause perforations that require surgical repair; thus, adequate informed consent should be obtained from the patients.

We recommend prophylactic scheduled EBD (1) when the remaining small intestine is short and has a risk for developing short bowel syndrome and (2) for patients who have had recurrent obstructive symptoms due to fibrous strictures not accompanied by inflammation or ulcers. The standard treatment interval is 6 to 12 months, though it should be decided according to the patient's symptoms and pathology.[2] The Global Interventional Inflammatory Bowel Disease Group's guidelines state that since symptoms do not necessarily correlate with the findings of strictures, prophylactic EBD may prevent recurrent obstructive symptoms and allow surveillance for relapse and neoplasm development by advancing deep within the small bowel after EBD.[3] The guidelines also stated that EBD is less effective after development of symptoms or for strictures with prestenotic dilation than for asymptomatic strictures.[3]

References

1. Matsui T, Hatakeyama S, Ikeda K et al. Long-term outcome of endoscopic balloon dilation in obstructive gastroduodenal Crohn's disease. *Endoscopy* 1997; 29: 640-5.
2. Watanabe K, Kawai M, Kamikozuru K et al. Which procedure is preferable: prophylactic scheduled endoscopic or episodic balloon dilation? *Intestine* 2020; 24: 190-6.
3. Shen B, Kochhar G, Navaneethan U et al. Practical guidelines on endoscopic treatment for Crohn's disease strictures: a consensus statement from the Global

Interventional Inflammatory Bowel Disease Group. *Lancet Gastroenterol Hepatol* 2020; 5: 393-405.