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Enteroscopic Balloon Dilation in Small Bowel Stricturing Crohn's Disease: Long-Term Outcomes and Risk Factors for Surgery in a Single-Center Prospective Observational Study

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Keywords: balloon-assisted enteroscopy | biologics | crohn disease | endoscopic balloon dilatation | inflammatory | obstruction | occlusion | small bowel stricture | stenosing | ulcerated

ABSTRACT

Background and Aims: The long-term outcomes of enteroscopic balloon dilation for small bowel strictures in patients with Crohn's disease are not well understood. Although Crohn's strictures can be classified into web-like, ulcerated, and spindle-shaped strictures based on endoscopic findings, the outcomes of enteroscopic balloon dilation according to the shape of Crohn's strictures have not been analyzed. The primary outcome was to evaluate the cumulative surgery-free rate, and the secondary outcome was to evaluate the risk factor for subsequent surgery after enteroscopic balloon dilation.

Methods: This prospective, longitudinal, observational study enrolled patients with Crohn's disease who underwent enteroscopic balloon dilation for small bowel strictures using single-balloon enteroscopy between 2015 and 2023 at Samsung Medical Center, Seoul, Korea.

Results: A total of 150 consecutive patients who underwent 235 enteroscopic balloon dilations were included in this study with a mean follow-up of 42.4 $\pm$ 19.1 months. Thirty-one patients (20.7%) underwent surgery after enteroscopic balloon dilation, and the cumulative 1-, 3-, and 5-year surgery-free rates were 86.7%, 80.4%, and 76.6%, respectively. The cumulative surgery-free rates of enteroscopic balloon dilation for web-like, ulcerated, and spindle-shaped strictures were 96.3%, 91.0%, and 73.3% at 1 year, 96.3%, 84.9%, and 63.0% at 3 years, and 96.3%, 78.3%, and 63.0% at 5 years, respectively ($p = 0.001$). Multivariate Cox regression analysis identified spindle-shaped stricture (vs. web-like stricture: hazard ratio [HR], 13.33; 95% confidence interval [CI], 1.48–120.24, $p = 0.021$), ulcerated stricture (vs. web-like stricture: HR, 8.50; 95% CI, 1.05–69.03, $p = 0.045$), and conventional therapy only (vs. biologic therapy: HR, 2.51; 95% CI, 1.11–5.71; $p = 0.028$) as risk factors for surgery after enteroscopic balloon dilation. The major complication rate of enteroscopic balloon dilations was 2.7% (4/150) on per-patient analysis and 1.7% (4/235) on per-procedure analysis.

Conclusions: Enteroscopic balloon dilation for small bowel strictures in patients with Crohn's disease may be an effective and safe alternative to surgery. Enteroscopic balloon dilation for web-like strictures showed favorable outcomes and biologic therapy following enteroscopic balloon dilation may be helpful to avoid surgery.

Summary

- Summarize the established knowledge on this subject
  - Colonoscopic balloon dilation has been effective for colorectal and ileo-colonic anastomosis strictures in patients with Crohn's disease (CD).
  - Most strictures in patients with CD occur in the small bowel rather than the colon.
  - Recently, balloon-assisted enteroscopy-assisted balloon dilation (enteroscopic balloon dilation, EBD) has become practicable for the treatment of small bowel strictures in patients with CD.
  - Crohn's strictures can be classified into web-like, ulcerated, and spindle-shaped strictures based on endoscopic findings, the outcomes of EBD according to the morphology of Crohn's strictures have not been reported.
- What are the significant and/or new findings of this study?
  - EBD is an effective and safe alternative to surgery for managing small bowel strictures in patients with stricturing CD.
  - The long-term outcome of EBD using balloon-assisted enteroscopy may be dependent on the endoscopic morphologic classification of the stricture, with web-like strictures having a favorable prognosis and spindle-shaped strictures having a poor prognosis.
  - In patients with ulcerated strictures, initiating or switching biologics after EBD may be helpful to avoid surgery.

1 | Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract but particularly the small bowel. One of the most challenging complications of CD is the development of intestinal strictures, which can cause significant morbidity and often require surgical intervention. Although surgery has traditionally been the mainstay of treatment for Crohn's strictures, there has been increasing interest in less invasive alternatives, particularly endoscopic balloon dilation.

Previous studies have reported high success rates and acceptable safety profiles for endoscopic balloon dilation using conventional colonoscopy [1, 2]. The majority of these studies have focused on colonic and ileo-colonic anastomotic strictures in areas accessible by colonoscopy. However, intestinal strictures in patients with CD are commonly found in the small bowel than in the colon [3]. According to the National Cooperative Crohn Disease Study, 10% of patients had at least one colonic stricture, whereas 25% had at least one small bowel stricture, which is often beyond the reach of conventional colonoscopy [4, 5]. Small bowel strictures should be evaluated endoscopically using balloon-assisted enteroscopy (BAE) [6]. BAE-assisted balloon dilation (enteroscopic balloon dilation, EBD) may be a promising alternative to surgery for small bowel strictures that cannot be reached with standard endoscopy [7, 8].

Crohn's strictures can be classified according to their location, length, width, number, and etiology [9–11]. One aspect that has been particularly understudied is the morphology of the stricture and its effect on the outcome of endoscopic balloon dilation. Crohn's strictures can be classified into three main types based on endoscopic findings: web-like, ulcerated, and spindle-shaped [11]. Each of these morphologically classified strictures may represent different stages or severity of the underlying disease process, potentially influencing the success rate of balloon dilation. However, there has been a lack of comprehensive analysis evaluating how these morphologically different strictures affect the long-term outcomes of endoscopic balloon dilation.

To date, EBD with double-balloon and single-balloon enteroscopy for small bowel strictures in patients with CD has shown effective short-term outcomes [12–21]. However, most previous studies had limitations such as small sample sizes, retrospective designs, and lack of long-term outcomes [12–15, 17–23]. Our center previously conducted a retrospective study including 34 patients with CD who underwent EBD [23]. Based on this retrospective study, we established a prospective cohort of patients with CD who underwent EBD for small bowel strictures. Using this prospective cohort, the aim of this prospective, longitudinal, observational study is to evaluate the long-term outcomes of EBD for small bowel strictures and to identify the risk factors for subsequent surgery after EBD.

2 | Materials and Methods

2.1 | Study Population

This study enrolled consecutive patients with CD who underwent EBD for small bowel strictures using single-balloon enteroscopy (SBE) at Samsung Medical Center, Seoul, Korea. The prospective cohort was established with comprehensive data collection of enrolled patients, including demographics, CD-related characteristics (Montreal classification, clinical and laboratory data, medications), enteroscopy-related characteristics (route, insertion depth, procedure time, and SES-CD score), small bowel stricture characteristics (number, etiology, location, width, length, ulceration, pre-stenotic dilation, and stricture morphology), EBD-related factors (balloon diameter, technical success, and complications), and monitoring of clinical course and outcomes. Patients were enrolled between May 2018 and April 2023 with follow-up through April 2024.

Inclusion criteria were as follows: (1) patients diagnosed with CD [13], (2) aged between 18 and 75 years, (3) male or non-pregnant female, (4) with the presence of at least one endoscopically identified small bowel stricture (inability to pass an colonoscope or enteroscope) [24] and (5) undergoing SBE-assisted EBD, and (6) a follow-up period of at least 12 months. Exclusion criteria were as follows: (1) Patients with major comorbidities that could affect SBE (severe hepatic or renal impairment, congestive heart failure, or respiratory failure). Cross-sectional imaging studies, including computed tomography (CT), CT enterography, or magnetic resonance enterography, were performed within 3 months before SBE, and patients were excluded if they had (2) strictures > 4 cm in length, (3) strictures with abscess or fistula, or (4) strictures associated with suspected malignancy.

During SBE, strictures with either deep ulcerations potentially involving the muscular layer or acutely angulated strictures due to adhesion were excluded from EBD because of the risk of complications. In patients with multiple strictures, if the proximal stricture was either beyond the reach of SBE or could not undergo EBD due to an increased risk of complications, but the distal strictures were treated with EBD, these patients were included in the cohort to evaluate long-term outcomes. In addition, patients with coexisting colonic and/or anal strictures requiring EBD were excluded because of the potential risk of symptoms, re-dilation, and surgery being attributed to these colonic and/or anal strictures. The study protocol was approved by the institutional review board of Samsung Medical Center (IRB file number: 2018-09-035).

2.2 | SBE-Assisted EBD

SIF-Q260 (Olympus, Tokyo, Japan) and a disposable hydrophilic-coated silicone splinting tube (ST-SB1, Olympus, Tokyo, Japan) were used for SBE. The procedure was performed either through the mouth (anterograde) or through the anus (retrograde) using the push-and-pull technique. The enteroscope was advanced through the small bowel by alternately inflating and deflating the balloon, and the small bowel was moved toward the endoscopist by folding the small bowel over a splinting tube, similar to pulling a curtain over a pole. Small bowel stricture was defined as a narrowing of the bowel lumen that could not be passed by an enteroscope.

EBD was performed under conscious sedation. The patient's position was adjusted to facilitate visualization of the stricture under fluoroscopy. Stricture width and length, presence of ulceration, and stricture morphology were evaluated by endoscopy and/or fluoroscopy. A 240 cm working length hydrostatic through-the-scope balloon (CRE Pro Single-Use Wireguided Esophageal/Pyloric/Colonic/Biliary Balloon Dilatation Catheters, Boston Scientific Ltd, Marlborough, MA, United States of America) was inserted into the stricture under visual control. The balloon size was selected based on the width of the stricture; inflated outer diameter of 12-13.5-15 mm for stricture width < 5 mm, inflated outer diameter of 15-16.5-18 mm for stricture width 5–10 mm, and inflated outer diameter of 18-19-20 mm for stricture width > 10 mm. If the stricture was tight and the stricture width was pinpoint, a balloon catheter with an inflated outer diameter of 10-11-12 mm was used. Balloon dilation was performed by filling the balloon with contrast medium for 15–60 s with a gradual increase in balloon size. After the final dilation, the enteroscope was attempted to be advanced through the stricture.

2.3 | Endoscopic Morphologic Classification of Small Bowel Strictures

Small bowel strictures were classified into three types based on enteroscopic findings: web-like, ulcerated, and spindle-shaped strictures. A web-like stricture was defined as a very short segmental narrowing caused by a membrane with an interstice and without ulceration (Figure 1A). An ulcerated stricture was defined as a segmental narrowing accompanied by ulceration (Figure 1B). A spindle-shaped stricture was defined as a slender rod-like narrowing with circumferential cicatricial changes (e.g., luminal narrowing, ulcer scars, cobblestoning, pseudo-polyps, and mucosal bridges) located around the stricture, regardless of the presence of ulceration (Figure 1C).

2.4 | Outcomes

In patients with multiple strictures, the stricture with a longer length was considered the index stricture. The per-patient analysis was based on each individual patient with the index stricture, whereas the per-procedure analysis was based on each stricture.

Short-term efficacy was evaluated based on technical and clinical success rates of EBD. Technical success was defined as the enteroscope being able to pass through the stricture immediately after SBE-assisted EBD, as measured by per-procedure analysis. Short-term clinical success was defined as the resolution of abdominal pain and vomiting within 2 weeks after SBE-assisted EBD, as measured by per-person analysis.

Long-term efficacy was assessed by evaluating the 1-, 2-, 3-, and 5-year cumulative rates of surgery-free and re-dilation-free rates after SBE-assisted EBD. The cumulative re-dilation-free rate was evaluated only in patients who underwent endoscopy after EBD. The cumulative surgery-free rate was defined as the proportion of patients who did not require bowel resection for strictures or fistulas, excluding surgery for perianal disease.

The safety of EBD was assessed at the rate of major complications requiring urgent intervention, such as bleeding, perforation, pancreatitis, and fever.

2.5 | Statistical Analysis

Statistical analyses were performed using R (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 10.3.0; GraphPad Software, San Diego, CA, United States of America). Chi-squared test or Fisher's exact test was used to compare frequencies. Continuous variables were expressed as mean $\pm$ standard deviation. Cumulative event-free survival rates of symptom recurrence, re-dilation, and surgery were analyzed using Kaplan–Meier analysis and the log-rank test. A Cox proportional hazards model was used to analyze risk factors for subsequent surgery. Candidate risk factors with $p < 0.1$ in the univariate analyses were included in

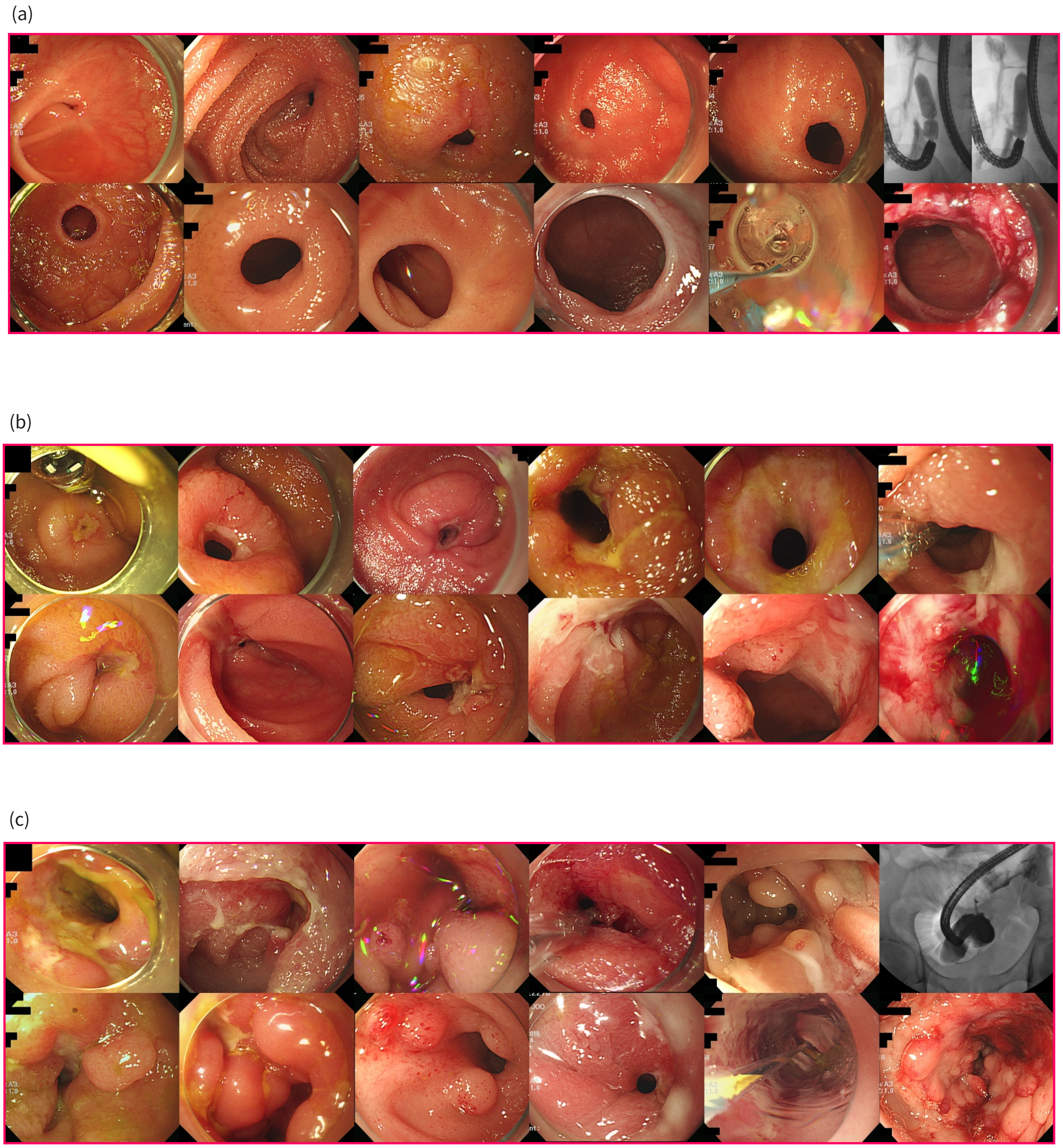

FIGURE 1 | Endoscopic morphologic classification of small bowel strictures in patients with Crohn's disease: (A) web-like stricture, last four images show the process of performing enteroscopic balloon dilation (EBD), including fluoroscopy images, images taken during EBD, and post-dilation images. (B) Ulcerated stricture, and (C) spindle-shaped stricture. The last four images show the process of performing EBD, including fluoroscopy images, images taken during EBD, and post-dilation images.

the multivariate Cox proportional hazards model. The significance level was set at $p < 0.05$ for two-tailed analysis.

3 | Results

3.1 | Clinical Characteristics of the Study Population, Small Bowel Strictures, and SBE-Assisted EBD

A total of 175 patients were considered eligible between January 2018 and May 2023 at Samsung Medical Center, Seoul, Korea. Of these, 3 patients were excluded due to revised diagnoses (chronic enteropathy associated with the SLCO2A1 gene, $n = 2$; intestinal tuberculosis, $n = 1$), 4 patients underwent EBD for anal or colonic strictures, 2 patients were pediatric patients, and 16 patients had less than 1 year, resulting in 150 patients included in the final analysis. Fifty-four patients (36%) had two or more strictures dilated during SBE, with a total of 235 EBDs performed for small bowel strictures (Figure 2).

The clinical characteristics of the study population at the time of EBD are shown in Table 1. The index strictures were classified as web-like in 27 patients (18.0%), ulcerated in 78 patients

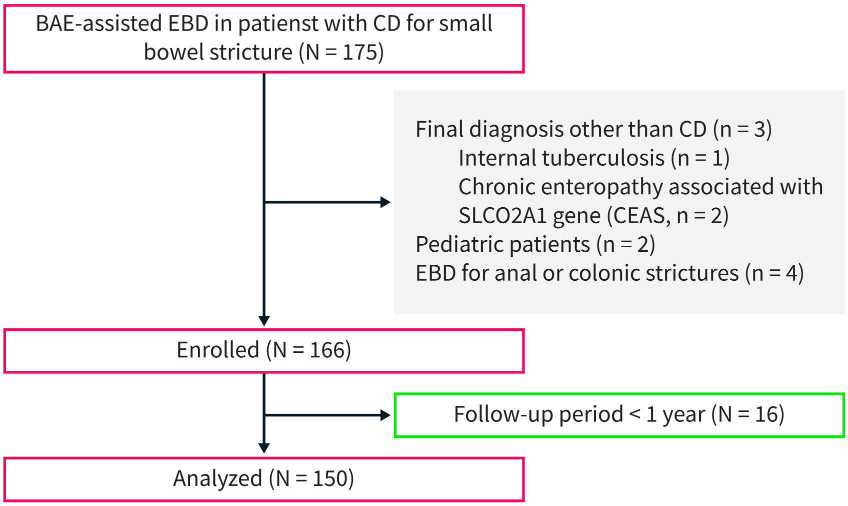

FIGURE 2 | Patient enrollment.

(52.0%), and spindle-shaped in 45 patients (30.0%). Patients with spindle-shaped strictures had longer disease duration and stricture length, higher HBI scores, lower technical success rate, and lower proportion of maximum EBD balloon diameter > 15 mm. The mean follow-up duration was 42.4 ± 19.1 months (range: 12–77 months) with a median of 39.0 months (interquartile range: 28.0–58.0 months).

3.2 | Short-Term Outcome of EBD for Small Bowel Strictures

Of the 235 small bowel strictures treated with SBE-assisted EBD, the enteroscope passed through 185 strictures, resulting in a technical success rate of 78.7%. The success rate was significantly lower in spindle-shaped strictures (40.7%, 22/54) compared with web-like (95.7%, 44/46) and ulcerated strictures (88.1%, 119/135) ($p < 0.001$, Figure 3A). Of the 150 patients, 131 experienced symptom improvement, resulting in a clinical success rate of 87.3% (95% CI, 82.0–92.7). Clinical success was also significantly lower in spindle-shaped strictures (71.1%, 32/45) compared with web-like (96.3%, 26/27) and ulcerated strictures (93.6%, 73/78) ($p = 0.001$, Figure 3B).

3.3 | Long-Term Outcome of EBD for Small Bowel Strictures

After EBD, 31 patients (20.7%) required surgery due to persistent stricture or penetrating complication. Kaplan–Meier analysis estimated the 1-year, 2-year, 3-year, and 5-year cumulative surgery-free survival rates to be 86.7%, 81.4%, 80.4%, and 76.6%, respectively (Figure 4A). Cumulative surgery-free survival rates were evaluated according to the morphological classification of the small bowel stricture. Surgery was required in 1 of 27 patients (3.7%) with web-like strictures, 13 of 78 patients (16.7%) with ulcerated strictures, and 17 of 45 patients (37.8%) with spindle-shaped strictures ($p = 0.001$). Kaplan-Meier analysis estimated the cumulative surgery-free rates for web-like, ulcerated, and spindle-shaped strictures to be 96.3%, 91.0%, and 73.3% at one year; 96.3%, 86.6%, and 63.0% at 2 years; 96.3%, 84.9%, and 63.0% at three years; and 96.3%, 78.3%, and 63.0% at five years, respectively (Figure 4B). Web-like strictures had the most favorable outcomes, whereas spindle-shaped strictures had poor outcomes, with most patients undergoing surgery within 2 years of EBD. Interestingly, the conversion rate to surgery for ulcerated strictures was relatively low in the early follow-up periods, but gradually increased over time.

Of the 102 patients who underwent follow-up SBE after EBD, 48 patients (47.1%) underwent re-dilation with EBD. Kaplan–Meier analysis estimated the 1-year, 2-year, 3-year, and 5-year cumulative re-dilation-free survival rates to be 75.5%, 61.2%, 54.3%, and 47.2%, respectively (Figure 4C). Cumulative re-dilation-free rates were evaluated according to the morphologic classification of the small bowel stricture. Re-dilation was required in 4 of 16 patients (25.0%) with web-like strictures, 30 of 60 patients (50.0%) with ulcerated strictures, and 14 of 26 patients (53.8%) with spindle-shaped strictures ($p = 0.149$). Kaplan-Meier analysis estimated the cumulative re-dilation-free rates for web-like, ulcerated, and spindle-shaped strictures to be 100.0%, 73.3%, and 65.4% at one year; 87.5%, 57.5%, and 53.9% at 2 years; 81.3%, 52.8%, and 46.2% at three years; and 81.3%, 48.8%, and 23.1% at five years, respectively (Figure 4D). Web-like strictures had a lower re-dilation rate, and there was no significant difference in the re-dilation rate between ulcerated and spindle-shaped strictures. Since the aim of this study is to evaluate EBD as an alternative to surgery, the primary outcome was set as the cumulative surgery-free rate rather than the re-dilation-free rate.

3.4 | Risk Factor for Surgery After EBD for Crohn's Small Bowel Strictures

The univariate Cox regression model identified UGI involvement, anastomotic stricture, stricture length ≥ 2 cm, prestenotic dilation, endoscopic morphologic classification, technical success, clinical remission at the time of EBD and step-up therapy with biologics after EBD as potential risk factors for subsequent surgery after EBD in patients with stricturing CD

TABLE 1 | Clinical characteristics of patients and index stricture at the time of enteroscopic balloon dilation (EBD).

			Endoscopic classification of small bowel stricture			
		Overall ($N = 150$)	**Web-like ($n = 27$)**	**Ulcerated ($n = 78$)**	**Spindle-shaped ($n = 45$)**	***p***
Demographics						
Age	≥ 40 years old	54 (36.0%)	8 (29.6%)	27 (34.6%)	19 (42.2%)	0.523
	< 40 years old	96 (64.0%)	19 (70.4%)	51 (65.4%)	26 (57.8%)	
Sex	Female	26 (17.3%)	4 (14.8%)	19 (24.4%)	3 (6.7%)	0.035
	Male	124 (82.7%)	23 (85.2%)	59 (75.6%)	42 (93.3%)	
Smoking	Non/ex-smoker	143 (95.3%)	27 (100.0%)	74 (94.9%)	42 (93.3%)	0.446
	Current smoker	7 (4.7%)	0 (0.0%)	4 (5.1%)	3 (6.7%)	
History of prior surgery	No	107 (71.3%)	19 (70.4%)	57 (73.1%)	31 (68.9%)	0.878
	Yes	43 (28.7%)	8 (29.6%)	21 (26.9%)	14 (31.1%)	
Disease duration	Years, mean ± SD	6.9 ± 6.6	7.4 ± 8.1	5.4 ± 5.7	9.1 ± 6.4	0.008
	≤ 2 years	59 (39.3%)	11 (40.7%)	39 (50.0%)	9 (20.0%)	0.005
	> 2 years	91 (60.7%)	16 (59.3%)	39 (50.0%)	36 (80.0%)	
Montreal classification						
Age at diagnosis	A1 + 2	129 (86.0%)	26 (96.3%)	63 (80.8%)	40 (88.9%)	0.100
	A3	21 (14.0%)	1 (3.7%)	15 (19.2%)	5 (11.1%)	
Location	L1	96 (64.0%)	19 (70.4%)	48 (61.5%)	29 (64.4%)	0.710
	L3	54 (36.0%)	8 (29.6%)	30 (38.5%)	16 (35.6%)	
UGI involvement	(−)	111 (74.0%)	16 (59.3%)	64 (82.1%)	31 (68.9%)	0.043
	(+)	39 (26.0%)	11 (40.7%)	14 (17.9%)	14 (31.1%)	
Behavior	B2	109 (72.7%)	18 (66.7%)	61 (78.2%)	30 (66.7%)	0.285
	B3	41 (27.3%)	9 (33.3%)	17 (21.8%)	15 (33.3%)	
Perianal modifier	(−)	104 (69.3%)	18 (66.7%)	58 (74.4%)	28 (62.2%)	0.352
	(+)	46 (30.7%)	9 (33.3%)	20 (25.6%)	17 (37.8%)	
Clinical and laboratory, and endoscopic findings						
Body weight, kg, mean ± SD		62.9 ± 12.3	62.8 ± 11.6	63.1 ± 13.2	62.6 ± 11.4	0.984
Harvey-bradshaw index (HBI), mean ± SD		3.4 ± 2.2	2.6 ± 2.0	3.3 ± 2.3	3.9 ± 2.1	0.062
Clinical remission	Remission (HBI < 5)	104 (69.3%)	22 (81.5%)	52 (66.7%)	30 (66.7%)	0.319
	Active (HBI ≥ 5)	46 (30.7%)	5 (18.5%)	26 (33.3%)	15 (33.3%)	
Hemoglobin, g/dL, mean ± SD		12.8 ± 2.3	13.3 ± 1.9	12.9 ± 2.4	12.4 ± 2.4	0.229
Albumin, g/dL, mean ± SD		4.2 ± 0.6	4.4 ± 0.4	4.2 ± 0.6	4.0 ± 0.6	0.056
C-reactive protein (CRP), mg/dL, mean ± SD		0.4 ± 0.8	0.3 ± 0.7	0.4 ± 0.6	0.6 ± 1.2	0.291
Biochemical remission	Remission (CRP < 0.5)	112 (74.7%)	23 (85.2%)	58 (74.4%)	31 (68.9%)	0.305
	Active (CRP ≥ 0.5)	38 (25.3%)	4 (14.8%)	20 (25.6%)	14 (31.1%)	
SES-CD	Score, mean ± SD	8.3 ± 3.7	6.1 ± 2.9	8.9 ± 3.0	8.5 ± 4.8	0.003
	Mild activity (≤ 6)	76 (50.7%)	21 (77.8%)	32 (41.0%)	23 (51.1%)	0.004
	Moderate-severe activity (> 6)	74 (49.3%)	6 (22.2%)	46 (59.0%)	22 (48.9%)	
IBD medication prior to EBD						
Immunomodulators use	No	68 (45.3%)	12 (44.4%)	41 (52.6%)	15 (33.3%)	0.118
	Yes	82 (54.7%)	15 (55.6%)	37 (47.4%)	30 (66.7%)	

(Continues)

TABLE 1 | (Continued)

			Endoscopic classification of small bowel stricture			
		Overall (*N* = 150)	**Web-like (*n* = 27)**	**Ulcerated (*n* = 78)**	**Spindle-shaped (*n* = 45)**	***p***
Biologics use	No	81 (54.0%)	13 (48.1%)	49 (62.8%)	19 (42.2%)	0.070
	Yes	69 (46.0%)	14 (51.9%)	29 (37.2%)	26 (57.8%)	
Index stricture characteristics						
Number of strictures	Mean ± SD	1.6 ± 1.2	1.4 ± 1.0	1.6 ± 1.5	1.5 ± 0.7	0.657
	Single	96 (64.0%)	21 (77.8%)	49 (62.8%)	26 (57.8%)	0.220
	Multiple	54 (36.0%)	6 (22.2%)	29 (37.2%)	19 (42.2%)	
Etiology of index stricture	De novo stricture	136 (90.7%)	24 (88.9%)	73 (93.6%)	39 (86.7%)	0.386
	Anastomosis site stricture	14 (9.3%)	3 (11.1%)	5 (6.4%)	6 (13.3%)	
Location of index stricture	Distal ileum	98 (65.3%)	14 (51.9%)	51 (65.4%)	33 (73.3%)	0.179
	Proximal to distal ileum	52 (34.7%)	13 (48.1%)	27 (34.6%)	12 (26.7%)	
Width of index stricture	mm, mean ± SD	5.8 ± 2.4	6.1 ± 2.2	5.9 ± 2.3	5.6 ± 2.6	0.657
	≤ 5 mm	84 (56.0%)	13 (48.1%)	45 (57.7%)	26 (57.8%)	0.662
	> 5 mm	66 (44.0%)	14 (51.9%)	33 (42.3%)	19 (42.2%)	
Length of index stricture	cm, mean ± SD	1.1 ± 0.8	0.4 ± 0.2	0.9 ± 0.4	2.0 ± 0.8	< 0.001
	< 2 cm	122 (81.3%)	27 (100.0%)	76 (97.4%)	19 (42.2%)	< 0.001
	≥ 2 cm	28 (18.7%)	0 (0.0%)	2 (2.6)	26 (57.8%)	
Pre-stenotic dilation	No	70 (46.7%)	13 (48.1%)	41 (52.6%)	16 (35.6%)	0.188
	Yes	80 (53.3%)	14 (51.9%)	37 (47.4%)	29 (64.4%)	
Ulcer at index stricture	None	38 (25.3%)	27 (100.0%)	0 (0.0%)	12 (26.7%)	< 0.001
	Superficial	40 (26.7%)	0 (0.0%)	31 (39.7%)	8 (17.8%)	
	Moderate ~ deep	72 (48.0%)	0 (0.0%)	47 (60.3%)	25 (55.6%)	
Enteroscopic balloon dilation (EBD)-related characteristics						
Technical success of EBD	No	42 (28.0%)	1 (3.7%)	11 (14.1%)	30 (66.7%)	< 0.001
	Yes	108 (72.0%)	26 (96.3%)	67 (85.9%)	15 (33.3%)	
Patients having strictures with EBD not attempted	No	133 (88.7%)	27 (100.0%)	71 (91.0%)	35 (77.8%)	0.011
	Yes	17 (11.3%)	0 (0.0%)	7 (9.0%)	10 (22.2%)	
Maximum EBD balloon diameter	< 15 mm	22 (15.0%)	0 (0.0%)	9 (11.5%)	13 (28.9%)	0.002
	≥ 15 mm	128 (85.0%)	27 (100.0%)	69 (88.5%)	32 (71.1%)	
Medical therapy following EBD						
Post-EBD medical treatment	Conventional therapy only	75 (50.0%)	18 (66.7%)	35 (44.9%)	22 (48.9%)	0.146
	Biologic therapy	75 (50.0%)	9 (33.3%)	43 (55.1%)	23 (51.1%)	

Abbreviations: CRP, C-reactive protein; EBD, enteroscopic balloon dilation; HBI, Harvey-Bradshaw Index; SES-CD, simplified endoscopic activity score for Crohn's disease.

($p < 0.10$). Multivariate Cox regression analysis identified spindle-shaped stricture (vs. web-like stricture: hazard ratio [HR], 13.33; 95% confidence interval [CI], 1.48–120.24, $p = 0.021$), spindle-shaped stricture (vs. web-like stricture: HR, 8.50; 95% CI, 1.05–69.03, $p = 0.045$), and conventional therapy only (vs. biologic therapy: HR, 2.51; 95% CI, 1.11–5.71; $p = 0.028$) as risk factors for surgery after EBD (Table 2).

3.5 | Comparison of Surgery Risk According to Post-EBD Biologic Therapy

In the overall cohort, surgery-free survival showed an increasing trend in patients treated with biologic therapy after EBD compared with those treated with conventional therapy only, but the difference was not statistically significant (log-rank test,

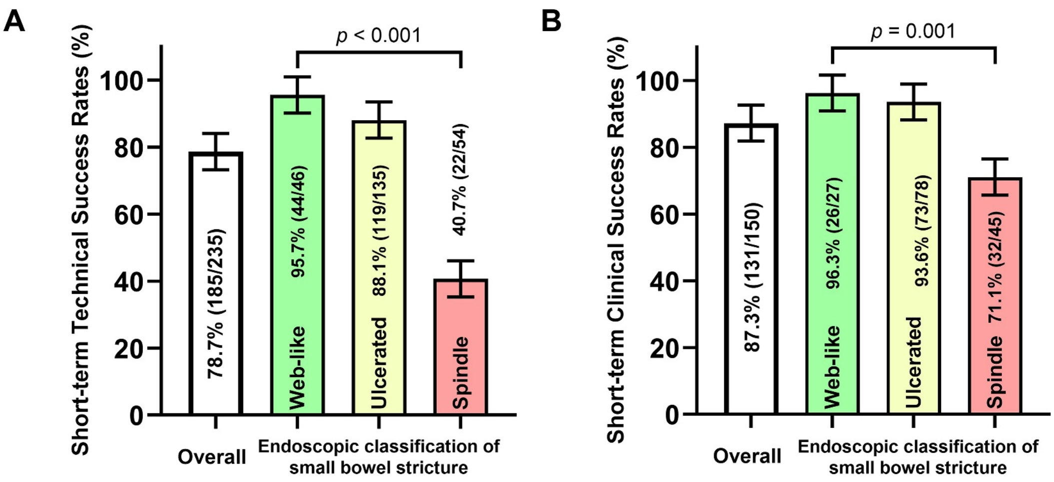

FIGURE 3 | Short-term outcome after enteroscopic balloon dilation (EBD). (A) Short-term technical success rate, (B) Short-term clinical success rate.

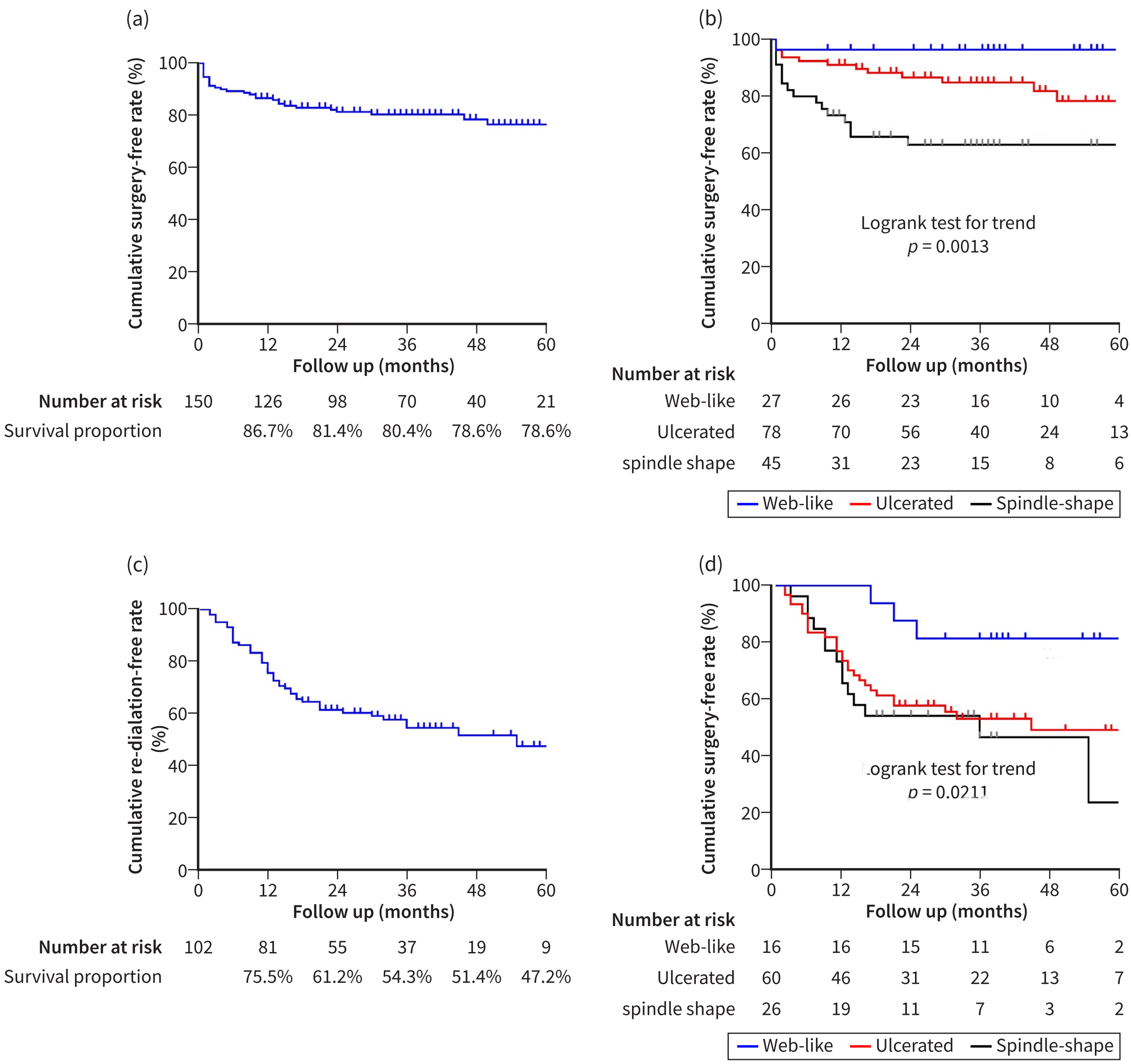

FIGURE 4 | Long-term outcome after enteroscopic balloon dilation (EBD). (A) Cumulative surgery-free survival rate, (B) cumulative surgery-free survival rate according to the endoscopic classification of Crohn's stricture, (C) cumulative re-dilation-free survival rate, (D) cumulative re-dilation-free survival rate according to the endoscopic classification of Crohn's stricture.

TABLE 2 | Univariate and multivariate cox regression analysis to identify the risk factors associated with surgery after enteroscopic balloon dilation (EBD).

		Surgery after EBD		Univariate analysis			Multivariate analysis		
		No ($N = 119$)	Yes ($N = 31$)	HR	95% CI	p	HR	95% CI	p
Age	≥ 40 years old	42 (35.3%)	12 (38.7%)	1	—	0.507			
	< 40 years old	77 (64.7%)	19 (61.3%)	0.78	0.37–1.62				
Sex	Female	22 (18.5%)	4 (12.9%)	1	—	0.513			
	Male	97 (81.5%)	27 (87.1%)	1.42	0.50–4.07				
Smoking	Non/ex-smoker	115 (96.6%)	28 (90.3%)	1	—	0.198			
	Current smoker	4 (3.4%)	3 (9.7%)	2.19	0.66–7.22				
History of prior surgery	No	87 (73.1%)	20 (64.5%)	1	—	0.447			
	Yes	32 (26.9%)	11 (35.5%)	1.34	0.63–2.87				
Disease duration (years)	≤ 2 years	49 (41.2%)	10 (32.3%)	1	—	0.378			
	> 2 years	70 (58.8%)	21 (67.7%)	1.41	0.66–3.01				
Age at diagnosis	A1+2	104 (87.4%)	25 (80.6%)	1	—	0.223			
	A3	15 (12.6%)	6 (19.4%)	1.75	0.71–4.28				
Location	L1	77 (64.7%)	19 (61.3%)	1	—	0.961			
	L3	42 (35.3%)	12 (38.7%)	0.98	0.47–2.06				
UGI involvement	(−)	93 (78.2%)	18 (58.1%)	1	—	0.068	1	—	0.139
	(+)	26 (21.8%)	13 (41.9%)	1.98	0.95–4.10		1.84	0.82–4.12	
Behavior	B2	87 (73.1%)	22 (71.0%)	1	—	0.931			
	B3	32 (26.9%)	9 (29.0%)	0.96	0.43–2.17				
Perianal modifier	(−)	85 (71.4%)	19 (61.3%)	1	—	0.417			
	(+)	34 (28.6%)	12 (38.7%)	1.36	0.65–2.86				
SES-CD	Mild activity (≤ 6)	62 (52.1%)	14 (45.2%)	1	—	0.760			
	Moderate-severe activity (> 6)	57 (47.9%)	17 (54.8%)	1.12	0.55–2.29				
Number of strictures	Single	79 (66.4%)	17 (54.8%)	1	—	0.360			
	Multiple	40 (33.6%)	14 (45.2%)	1.40	0.68–2.89				
Etiology of index stricture	De novo stricture	111 (93.3%)	25 (80.6%)	1	—	0.097	1	—	0.101
	Anastomosis site stricture	8 (6.7%)	6 (19.4%)	2.26	0.86–5.90		2.38	0.84–6.69	
Location of index stricture	Distal ileum	82 (68.9%)	16 (51.6%)	1	—	0.061	1	—	0.131
	Proximal to distal ileum	37 (31.1%)	15 (48.4%)	1.98	0.97–4.06		1.92	0.82–4.47	
Width of index stricture	≤ 5 mm	65 (54.6%)	19 (61.3%)	1	—	0.670			
	> 5 mm	54 (45.4%)	12 (38.7%)	0.85	0.41–1.77				
Length of index stricture	< 2 cm	103 (86.6%)	19 (61.3%)	1	—	0.003	1	—	0.431
	≥ 2 cm	16 (13.4%)	12 (38.7%)	3.12	1.48–6.57		1.52	0.54–4.27	
Pre-stenotic dilation	No	55 (46.2%)	15 (48.4%)	1	—	0.814			
	Yes	64 (53.8%)	16 (51.6%)	0.92	0.45–1.88				

(Continues)

TABLE 2 | (Continued)

		Surgery after EBD		Univariate analysis			Multivariate analysis		
		No (N = 119)	Yes (N = 31)	HR	95% CI	p	HR	95% CI	p
Index stricture shape	Web-like stricture	26 (21.8%)	1 (3.2%)	1	—		1	—	
	Ulcerative stricture	65 (54.6%)	13 (41.9%)	4.68	0.61–35.79	0.137	8.50	1.05–69.03	0.045
	Spindle-shaped stricture	28 (23.5%)	17 (54.8%)	12.14	1.61–91.68	0.016	13.33	1.48–120.24	0.021
Technical success of EBD	No	28 (23.5%)	14 (45.2%)	1	—	0.004	1	—	0.491
	Yes	91 (76.5%)	17 (54.8%)	0.35	0.17–0.72		0.71	0.27–1.87	
Patients having strictures with EBD not attempted	No	107 (89.9%)	26 (83.9%)	1	—	0.234			
	Yes	12 (10.1%)	5 (16.1%)	1.79	0.69–4.69				
Maximum EBD balloon diameter	< 12 mm	12 (10.1%)	5 (16.1%)	1	—				
	12 – 15 mm	25 (21.0%)	6 (19.4%)	0.59	0.18–1.94	0.389			
	> 15 mm	82 (68.9%)	20 (64.5%)	0.55	0.20–1.47	0.231			
Clinical remission at the time of EBD	Remission (HBI < 5)	87 (73.1%)	17 (54.8%)	1	—	0.052	1	—	0.673
	Active (HBI ≥ 5)	32 (26.9%)	14 (45.2%)	2.04	0.99–4.18		1.2	0.52–2.77	
Biochemical remission at the time of EBD	Remission (CRP < 0.5 mg/dL)	89 (74.8%)	23 (74.2%)	1	—	0.828			
	Active (CRP ≥ 0.5 mg/dL)	30 (25.2%)	8 (25.8%)	0.91	0.39–2.12				
Immunomodulators use prior to EBD	No	53 (44.5%)	15 (48.4%)	1	—	0.521			
	Yes	66 (55.5%)	16 (51.6%)	0.79	0.39–1.62				
Biologics use prior to EBD	No	68 (57.1%)	13 (41.9%)	1	—	0.234			
	Yes	51 (42.9%)	18 (58.1%)	1.55	0.75–3.19				
Post-EBD medical treatment	Biologic therapy	63 (52.9%)	12 (38.7%)	1	—	0.077	1	—	0.028
	Conventional therapy only	56 (47.1%)	19 (61.3%)	1.96	0.93–4.11		2.51	1.11–5.71	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; EBD, enteroscopic balloon dilation; HBI, Harvey-Bradshaw Index; HR, hazard ratio; SES-CD, simplified endoscopic activity score for Crohn's disease.

p = 0.0749) (Figure 5A). Interestingly, in the subgroup analysis of patients with ulcerated strictures, those treated with biologic therapy after EBD had a higher surgery-free survival rate than those treated with conventional therapy alone (log-rank test, p = 0.0405) (Figure 5B).

3.6 | Safety

During the study period, 2 patients experienced perforation, 1 patient experienced bleeding, and 1 patient experienced post-procedure fever. Patients with perforation underwent surgery, while patients with bleeding and fever were managed conservatively. The procedure-related complication rate was 2.7% (4/150) on a per-patient analysis and 1.7% (4/235) on a per-procedure analysis.

4 | Discussion

This study is a prospective, longitudinal, observational study designed to evaluate long-term outcomes and risk factors for surgery following EBD for small bowel strictures in patients with CD. EBD was shown to be an effective alternative to surgery with a 5-year cumulative surgery-free rate of 76.6%. In addition, EBD demonstrated a favorable safety profile with a

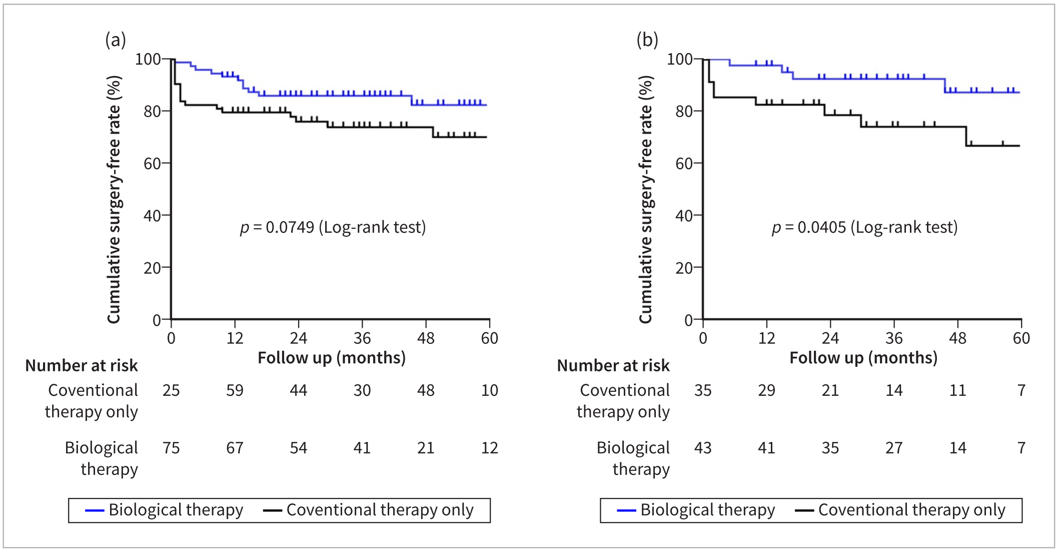

FIGURE 5 | Comparison of surgery risk according to biologic therapy after post-enteroscopic balloon dilation (EBD). (A) Kaplan–Meier curve showing the risk of surgery based on post-EBD biologic therapy in the entire cohort, (B) Kaplan–Meier curve showing the risk of surgery based on post-EBD biologic therapy in patients with ulcerated strictures.

major complication rate of approximately 3%. The long-term outcome of BAE-assisted EBD was dependent on endoscopic morphologic classification and post-EBD biologic therapy. Web-like strictures had a favorable prognosis and spindle-shaped strictures had a poor prognosis. Ulcerated strictures, which accounted for more than half of all strictures, showed an increased risk of surgery over time.

The technical success rate in this study was 78.7%, which is lower than the 90.6% (95% CI, 78.5%–96.2%) estimated in the meta-analysis [25], yet it falls within the previously reported range of 72.0%–100% [14–19, 26, 27]. This may be attributed to our approach of not forcing scope passage after EBD to minimize the risk of complications associated with excessive scope manipulation after successful EBD. Actually, the major complication rate in our study was 2.7%, which is lower than that in the meta-analysis (5.3%) [25]. Perforation during BAE-assisted EBD can occur not only as a direct result of the balloon dilation but also as a result of excessive pressure of the enteroscope shaft applied to EBD-dilated stricture sites caused by deep insertion or forceful manipulation. Based on previous experience, we did not forcefully insert the enteroscope beyond the EBD-dilated stricture if we were concerned about potential complications, and this is believed to be a reason for the low complication rate. Furthermore, the short-term clinical success rate in our study was 87.3%, which is slightly higher than the 82.3% estimated in the meta-analysis [25]. This suggested that the lower technical success rate in our study was unlikely to affect the long-term prognosis.

A pooled meta-analysis of long-term BAE-assisted EBD reported a 2-year surgery rate of 42.9% [25]. Only three retrospective cohort studies, each with more than 50 patients and more than 3 years of follow-up [16, 28, 29], reported 3-year surgery-free rates of 78.1% by Sunada et al. [28], 73% by Hirai et al. [16], and 81.1% with a 5-year rate of 73.5% by Takeda et al. [29] In our prospective study, the 3-year and 5-year surgery-free rates were 80.4% and 76.6%, respectively, similar to these retrospective studies. EBD provides effective long-term outcomes for patients with small bowel stricturing CD.

Web-like strictures of the small bowel are a well-documented complication of chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) [11]. However, web-like strictures are not specific to NSAIDs and can also occur in CD and other inflammatory conditions of the small bowel, as they can develop after repeated superficial ulceration and subsequent fibrosis. When EBD was performed, web-like strictures were easier to dilate than ulcerated and spindle-shaped strictures because the stricture length was shorter and not accompanied by inflammation.

Spindle-shaped strictures are an independent predictor of surgery after EBD of small bowel strictures in CD patients. Surgically resected specimens of spindle-shaped strictures showed that creeping fat had wrapped around the narrowing bowel segment, which explained why EBD was ineffective in spindle-shaped strictures [30]. Creeping fat is characterized by mesenteric fat wrapping around the bowel, which is highly correlated with transmural inflammation, muscular hypertrophy, fibrosis, and stricture formation [31]. Spindle-shaped strictures are often challenging to perform EBD procedures and may not respond effectively, resulting in a low technical success rate of 40.7%. The 1-year surgery-free rate is as low as 73%, indicating a high likelihood of requiring surgery after EBD. The 3-year surgery-free rate further decreased to 63%, indicating that medical treatment after EBD is also likely to be ineffective. Therefore, it may be advisable to consider surgery as spindle-shaped strictures may be expected to respond poorly to endoscopic and biologic therapy.

Ulcerative stricture tended to increase the surgery rate over time. In the patients with ulcerated strictures, the initiation of biologics or switching to other biologics reduced the risk of surgery but not in patients with web-like and spindle-shape strictures (Table S1). Although the benefit of biologics after EBD remains controversial [32], previous studies suggest that biologic therapy, particularly anti-TNF agents, helps maintain mucosal healing and provides both short-term and long-term benefits in preventing restenosis [29, 33]. These findings suggest that the initiation or switching of biologics should be considered in patients with ulcerated strictures.

In this study, a total of 50 patients were initiated on biologic therapy or switched to other biologics after EBD. Interestingly, there were 16 patients on infliximab, adalimumab, and ustekinumab, respectively, and 2 patients on vedolizumab. Excluding vedolizumab due to the small number of patients, the clinical characteristics of patients treated with anti-TNFα (infliximab, adalimumab) and anti-IL23p40 agents (ustekinumab) were compared (Table S2). There was no significant difference in surgery and re-dilation between the anti-TNFα and anti-IL23p40 groups, although surgery and re-dilation were numerically less frequent in patients on ustekinumab. However, the patients with penetrating behavior (B3) were more common in patients treated with anti-TNFα agents (46.9%, 15/32 vs. 12.5%, 2/16, $p = 0.043$).

In the CREOLE study, the 4-year surgery-free rate in CD patients with symptomatic small bowel strictures who were subsequently treated with adalimumab was 50.7%. In our study, 78% of patients received step-up therapy after EBD, and the 4-year surgery-free rate was 78.6% [34]. Although a direct comparison of the 4-year surgery-free rate of the CREOLE study with that of our study is inappropriate, step-up therapy after EBD may lead to better outcomes. In patients with stricturing CD, an EBD-based treatment strategy may be beneficial for long-term outcomes. In addition, this prospective cohort identified clinical and laboratory characteristics at their last visit (Table S3). At 42.4 ± 19.1 months after EBD, the mean body weight of the enrolled patients increased from 62.9 to 66.4 kg, and hemoglobin and albumin levels also increased. Clinical remission was achieved in 133 patients (88.7%) and biochemical remission in 136 patients (90.7%), indicating that EBD can improve the outcome of patients with structuring CD.

This study has limitations. First, this study was conducted in a single center with experienced endoscopists, which may limit the generalizability of the findings. Second, total enteroscopy was not performed, so additional proximal strictures could not be confirmed, and the clinical significance of the observed stricture may be uncertain. However, since small bowel CD mainly affects the distal ileum, BAE probably covered the relevant areas. Third, despite the Kaplan–Meier method, the mean follow-up of 42.4 months and only 23% of the cohort reaching the 5-year follow-up interval limited the proportion of patients contributing to the 3-year and 5-year estimates. Therefore, long-term survival estimates for 3-year and 5-year surgery-free and re-dilation-free survival rates should be interpreted with caution. Future studies with longer follow-up are essential to validate these findings. Fourth, this study enrolled patients treated with EBD; therefore, we could not provide data on patients who underwent surgery directly or were treated only with medication or no treatment instead of EBD.

This prospective longitudinal observational study demonstrates that BAE-assisted EBD is an effective and safe alternative to surgery for the treatment of small bowel strictures in patients with CD. Long-term outcome of EBD was dependent on the endoscopic morphologic classification of small bowel stricture. EBD for web-like strictures showed favorable outcomes. Spindle-shaped strictures significantly increase the risk of subsequent surgery. Current medical treatments for spindle-shaped strictures are ineffective and anti-fibrotic agents should be developed in the near future. In addition, initiating or switching biologics after EBD may reduce the risk of surgery, particularly in patients with ulcerated strictures. Tailored individualized therapeutic strategies may improve the outcomes in patients with stricturing small bowel CD.

Author Contributions

Sung Noh Hong: study concept and design, data acquisition, analysis, and interpretation, and drafting of the manuscript. **Ji Eun Kim, Eun Ran Kim, Dong Kyung Chang:** data acquisition, data interpretation, and study supervision. **Young-Ho Kim:** study concept and design, data interpretation, and study supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed in the current study are not publicly available prior to publication, but are available on reasonable request from the corresponding author (sungnoh.hong@samsung.com).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.