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Safety and efficacy of endoscopic dilation for primary and anastomotic Crohn's disease strictures☆,☆☆

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KEYWORDS
Outcomes;
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Abstract

Background: Literature on endoscopic dilation of Crohn's disease (CD) strictures, especially for primary (non-anastomotic) strictures is limited.
Methods: A historical cohort study was performed on patients who underwent endoscopic stricture dilations for CD in our IBD center. Primary endpoint was the efficacy of first endoscopic dilation in preventing the need for surgery in primary strictures compared to anastomotic strictures. Cox proportional hazards models using robust sandwich covariance matrix estimate were used to evaluate the need for surgery and any further endoscopic intervention.
Results: In our study cohort (mean age 42.2 ± 13.1 years, 57% females, 16.4% current smokers, and median follow-up 1.8 years), 128 patients underwent a total of 430 endoscopic stricture dilations for 169 strictures (88 primary, 81 secondary). Forty-two patients (32.8%) required surgery in the follow-up period, with a mean interval period between first dilation and surgery of 33 months. There was no difference between primary or anastomotic strictures with respect to

Abbreviations: CD, Crohn's disease; CTE, computed tomography enterography; EHR, electronic health record; IBD, inflammatory bowel disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MRE, magnetic resonance enterography; TTS, through the scope.

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the need for surgery (34.1% vs. 29.6%, $p = 0.53$), redilation (59.1% vs. 58%, $p = 0.89$) or total interventions (surgery + redilations, 71.6% vs. 72.8%, $p = 0.86$). Multivariable analysis did not show any significant difference between patients who received and did not receive intralesional steroid injections, biologics or immunomodulators with respect to the need for repeat intervention or surgery.

Conclusion: Efficacy and safety of endoscopic dilation are similar between primary and anastomotic CD strictures. Intralesional steroid injection or use of biologics did not decrease the need for re-intervention or surgery for either primary or anastomotic strictures.

1. Introduction

Strictures in the small bowel and the colon represent one of the most common manifestations of Crohn's disease (CD). It is estimated that up to two-thirds of CD patients undergo surgery at some time for their disease, many of them for strictures.[1] While the pathophysiology of stricture formation is not fully understood, it is believed that a complex interplay among local mesenchymal cells and cytokines including transforming growth factor-beta1 plays an initial role.[2] Various factors that have been proposed to determine the development of strictures include disease location, particularly ileocolonic disease,[3] disease duration and severity,[4] and genetics especially NOD2/CARD15 gene mutations.[5] Until recently, surgical bowel resection has been the mainstay of treatment for symptomatic strictures. However, there is a high rate of recurrence of strictures at the anastomotic site or in the neoterminal ileum after ileocolectomy, often requiring additional surgical interventions. About one-fourth will require second surgery by 4 years, and about one-half by 10–15 years.[6–8] Apart from the risk of mortality related directly to the surgical procedure, these patients are at risk to develop short bowel syndrome, post-operative adhesions and anastomotic strictures contributing to significant lifelong morbidity. Therefore, alternative therapeutic modalities including biological agents, surgical stricturoplasty, and endoscopic dilation of the strictures have been tried.

With the advancement of endoscopic techniques, through the scope (TTS) balloon dilation has started to be widely used for the management of strictures. We have previously shown that endoscopic balloon dilation appears to be safe and effective in treating pouch inlet and outlet strictures in patients with restorative proctocolectomy.[9,10] Many other studies have found stricture dilation for patients with CD to be a safe and effective procedure.[11–13] A recent review suggested that endoscopic dilation appeared to be most effective in short (less than 4 cm) post-surgical anastomotic strictures.[14] The long-term success rate of TTS balloons, especially in the setting of non-anastomotic strictures or primary strictures, has not been well studied. Even the recent American College of Gastroenterology guidelines from 2009 have not laid out firm recommendations for or against endoscopic dilation of primary strictures, given the lack of sufficient data.[1]

In addition to the endoscopic treatment, concurrent medical management has also been tried in different stricture scenarios. However, the data are conflicting. Earlier studies suggested that infliximab was associated with stricture development[15] and its use might be considered as a relative contraindication in CD patients with structuring phenotype. However, recent studies have shown that infliximab may be safe[4] and perhaps effective in the presence of inflammatory strictures.[16] At present, there is a paucity of data supporting the use of intralesional steroid injection in prolonging the time to re-dilation or preventing the need for surgery in CD strictures.[17,18]

The aims of this study were to analyze the long-term outcomes of TTS dilation of Crohn's strictures, particularly to compare the outcomes of TTS dilation of de-novo or primary strictures with anastomotic strictures, to characterize the risk of the procedure, and to study the factors predicting the surgery-free time.

2. Material and methods

2.1. Patients

At our institute, all health care providers use an enterprise electronic health record (EHR) (Epic Systems, Verona, WI) for clinical documentation, order entry and prescriptions. We queried the EHR-derived clinical data repository (Oracle database server, Oracle Corporation, Redwood Shores, California) to identify patients with CD seen in our IBD center. This information was then matched with our billing database and confirmed on manual review of electronic charts.

2.2. Inclusion and exclusion criteria

Inclusion criteria for the study were patients seen in our IBD center and having 1) diagnosis of CD (the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] ICD-9-CM code 555.xx) documented on EHR; 2) presence of strictures on imaging or endoscopy on manual review of patient charts and 3) endoscopic treatment for the stricture between December 1998 and May 2010 documented in our billing database. Patients less than 18 years of age and patients having dilatations for non-Crohn's disease indications were excluded.

2.3. Demographic and clinical variables

Patients' demographic (age, gender, race) and laboratory data were extracted from the EHR using structured query language. Clinical, endoscopic, histology and radiographic data were manually reviewed and coded into the database. Documentation in clinical notes was used to retrieve information about "age at diagnosis", "age at the1st dilation",

"disease duration" (time interval between diagnosis of CD and the first stricture dilation), "type of stricture" (primary versus secondary or anastomotic), "small bowel obstruction", "smoking status" ("never", "current" or "ex-smoker"),"extraintestinal manifestations" (presence of arthralgia or arthropathy, pyoderma gangrenosum, erythema nodosum, IBD-related ocular lesions and primary sclerosing cholangitis) and "date of last follow-up." CD medications were categorized into "aminosalicylates", "immunomodulators" (any use of 6-mercaptopurine, azathioprine or methotrexate), "steroids" (oral or intravenous steroidal agents), "oral budesonide", "antibiotics" (including metronidazole, tinidazole, ciprofloxacin or rifaximin for CD) or "biologics" (any use of infliximab, adalimumab, or certolizumab). Endoscopy reports were reviewed to extract data on "stricture length", "number", "location" (upper gastrointestinal track proximal to ligament of Treitz, jejunum, ileum, colon or anorectal), "balloon size", "scope entry site" (oral, anus, or stoma),"abnormal mucosa on endoscopy" (any inflammation, friability or ulceration), "sedation" (none, conscious sedation or anesthesia [monitored anesthesia care]), "traversable prescope" (traversable before dilation), "traversable postscope" (traversable after dilation), use of "intralesional steroid injection" and "immediate complications" (bleeding, perforation or death). Imaging reports (computed tomography enterography [CTE], magnetic resonance enterography [MRE] or barium studies) were used to determine stricture length when information from endoscopy reports was not available.

2.4. Endoscopic protocol

The practice pattern of our IBD center dictated that all symptomatic patients underwent diagnostic endoscopic evaluation. In addition, surveillance endoscopy was routinely performed in both symptomatic and asymptomatic patients. Outpatient or inpatient endoscopic dilations with flexible, single-channel, video endoscopes (160 and 180-series, Olympus Optical, Tokyo, Japan), and through-the-scope balloons (CRE balloons [10 mm to 20 mm], Boston Scientific Microvasive, Natick, MA) were performed by gastroenterologists specializing in IBD or advanced endoscopy. For endoscopic therapy, balloon size inflated, time of inflation, adjuvant procedure such as intralesional steroid injection was determined based on the location, degree, and length of stricture, at the discretion of the endoscopist. For few patients with long, fibrotic strictures refractory to multiple endoscopic balloon dilatation therapy, needle knife therapy was attempted by one investigator (B.S.). In majority of the cases, sequential dilations with the same balloon up to three sizes were performed and fluoroscopy was not used. For high-grade or angulated strictures not traversable by the endoscope, CRE balloon with a guidewire was used. Passage through the stricture was attempted immediately after the dilation and the passage without resistance was defined as a sign of technical success. Patients were closely monitored for signs of excessive bleeding and abdominal pain during and after the procedure. Patients whose symptoms were not improved by first dilation or those which re-occurred after first dilation were offered the option of repeat endoscopy with balloon dilation or surgery. Patients who chose repeat dilation underwent re-dilation of strictures with goal of re-stretching luminal diameter to 18–20 mm.

2.5. Outcome measurement

Primary outcome was the efficacy of endoscopic dilation in preventing the need for surgery in primary strictures as compared to anastomotic strictures undergoing first dilation. Secondary outcomes were immediate technical success, long-term redilation-free and intervention-free period, and the impact of topical and systemic medical therapy on redilation or surgery rates. Intervention-free period was defined as duration between endoscopic stricture dilation and repeat dilation or surgery. Major complications were defined as perforation, bleeding requiring transfusions or death. Mortality was determined by documentation in the EHR and/or Social Security Death Index (SSDI). Patients were considered to be deceased if either system classified them as dead.

Follow-up began on the day after the first dilation was documented in the EHR and continued until the date of the outcome of interest or censoring. Patients with no observed event were censored on the date of their last encounter in the EHR. For mortality, patients with no observed event were censored on the last clinic encounter or the date of extraction of vital status from the SSDI minus a 6 month lag, whichever came last.

2.6. Statistical analysis

Descriptive statistics were computed for all factors. These included means, standard deviations and percentiles for continuous variables and frequencies and percentages for categorical factors.

Characteristics of primary and anastomotic strictures at time of first dilation were compared using Pearson's chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous factors. Outcomes were analyzed at the patient-level and also by stricture characteristics at the time of first dilation. A time-to-event analysis was performed to assess intervention-free time and factors associated with need of re-interventions. The length of follow-up was defined as the interval between the first dilation to the event of interest (surgery) or last follow-up if the patient remained surgery-free. Cox regression analysis was used to analyze the data. Due to the fact that individual subjects had multiple strictures and the assumption of independence between observations is not met, a hazards marginal model was used to account for the correlation between dilations performed on the same subject. $p < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.2 software (The SAS Institute, Cary, NC) and R version 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

2.7. Ethical considerations

Data was gathered during routine care at the IBD center and no separate attempts were made to contact the patients for the study. The need for informed consent was waived and the study was approved by the Cleveland Clinic Institutional Review Board.

3. Results

3.1. Patient characteristics

Our study cohort consisted of 128 subjects with 169 strictures who underwent 430 endoscopic stricture dilations. Mean age was 42.2 ± 13.1 years, 57% were females, 92% Caucasian and median follow-up time after dilation was 1.8 years (interquartile range, 0.7–2.9 years). Baseline characteristics of the patients are shown in Table 1. Majority of the patients (89.1%) were on medical therapy for CD, with about one-third (34.4%) on 6-mercaptopurine (6 MP)/azathioprine and one-fourth (22.7%) on biologics. 99 patients (77.3%) had one dominant stricture, while 29 (22.7%) had two or more strictures.

3.2. Stricture characteristics at the time of fist dilation

More than half of the strictures (88, 52.1%) were primary strictures, while the remainder 81 (47.9%) were anastomotic (Table 2). The median length of strictures was 2 cm (interquartile range, 1–4 cm) and mean balloon size used was (16.6 ± 3.6 mm). At the time of first dilatation, 58% of primary strictures (51/88) were traversable compared to 51% (41/81) of anastomotic strictures ($p = 0.34$). Abnormal mucosa (inflammation/friability/ulceration) on endoscopy was seen in 96/159 (60.1%) of the strictures. Histology was available for 98 strictures, of which 65 (66.3%) had microscopic inflammation. Intralesional injection with a long acting steroid (triamcinolone) was performed in 44 (26%) of the strictures. There were no significant differences between primary and anastomotic strictures with respect to stricture length, stricture traversability or intralesional steroid injection.

3.3. Technical success and long term efficacy

The technical success (defined as ability to pass a colonoscope through the non-traversable strictures after dilatation) was 83% (63/77) for first dilation and 79.4% (27/34) for second dilation. Forty-two patients (32.8%) underwent surgery in the follow-up period, and mean surgery-free interval was 33 months (primary endpoint). For re-dilations, 58 (58.6%) needed a third dilation. Mean re-dilation-free time (between 2nd and 3rd dilations) was 14 ± 1.5 months. Mean surgery-free time

Table 1 Patient characteristics.

Factor	N = 128
Female	73 (57.0)
Caucasian [a]	115 (92.0)
Age at diagnosis [a]	25.7 ± 11.3
Age at 1st dilation	42.2 ± 13.1
Disease duration (years) [a]	15.8 ± 10.4
Smoking	
Never	65 (50.8)
Current	21 (16.4)
Ex-smoker	42 (32.8)
Medications during follow-up	
Aminosalicylates	52 (40.6)
Immunomodulators	44 (34.4)
Budesonide	49 (38.3)
Steroids	27 (21.1)
Biologics	29 (22.7)
Any CD medications	114 (89.1)
Antibiotic	4 (3.1)
Years from first dilation to last follow-up	2.1 ± 1.9
Number of episodes	2.7 ± 3.3
Number of strictures seen during follow-up	
1	99 (77.3)
2	19 (14.8)
3	8 (6.3)
4	2 (1.6)
Surgery	42 (32.8)
Redilation	75 (58.6)
Any intervention	94 (73.4)
Perforation	3 (2.3)
Bleeding	2 (1.6)
Any complication	4 (3.1)

Data presented as N (%), mean ± SD.
[a] Data not available for all subjects. Race not known for 3 subjects and date of diagnosis unknown for 5.

Table 2 Characteristics of strictures at first dilation.

Factor	All (N = 169)
Stricture type	
Primary	88 (52.1)
Anastomotic	81 (47.9)
Stricture length [a]	2.7 ± 1.9
Location (non-exclusive)	
Upper gastrointestinal track	4 (2.4)
Jejunum	0 (0.0)
Ileum	131 (77.5)
Colon	103 (61.0)
Anal	11 (6.5)
Balloon size [a] (mm)	16.6 ± 3.6
Traversable prescope	92 (54.4)
Scope entry site	
Anus	159 (94.1)
Stoma	4 (2.4)
Pouch	6 (3.6)
Inflammation on endoscopy [a]	96 (60.4)
Inflammation on histology [a]	65 (66.3)
Intralesional steroid injection	44 (26.0)
Sedation	
None	3 (1.8)
Anesthesia	6 (3.6)
Sedation	160 (94.7)
Traversable postscope [a]	154 (91.7)
Redilation needed	99 (58.6)
Surgery	54 (32.0)
Redilation/surgery	122 (72.2)

Data presented as N (%) or mean ± SD.
[a] Data not available for all subjects. Stricture length available for 33, balloon size for 167, inflammation on endoscopy for 159, use of balloon/knife for 167, inflammation on histology for 98, use of traverse postscope for 168 and SBO for 166. Three of the strictures that were dilated were more than 5 cm in length.

was 30.9 ± 1.9 months. Seventy-five patients (58.6%) underwent re-dilation during follow-up, with a median number of repeat dilations of one and mean redilation-free interval of 20 months. In total, 94 patients (73.4%) needed any intervention (surgery or redilation) after the first dilation, with an intervention-free period of 17 months. Outcomes per stricture are detailed in Table 2. Overall, the percentage of strictures that did not require surgery at the end of the first, second, third or fourth year was 77%, 69%, 66%, and 54%, respectively. There was no difference between primary or anastomotic strictures with respect to need for surgery, redilation or total interventions (surgery or redilation) (Table 3 and Fig. 1).

3.4. Complications

Four patients had immediate complications (3 perforations, 1 major bleeding episode), with an overall complication rate of 3.1% per patient and 0.93% per procedure. Two of these patients had anastomotic strictures while two had primary strictures. Three of these four patients presented with an acute abdomen secondary to perforation immediately after the endoscopy. All three needed urgent surgical bowel resection. A fourth patient presented with hematochezia and abdominal pain and was managed conservatively with supportive management and blood transfusions. There was no mortality with either of the complications. All four patients had active disease on biopsy, and underwent intralesional medication injection. Two of these patients had needle-knife stricturoplasties (one with perforation and one with major bleeding episode) in addition to intralesional medication injection. In addition to immediate complications, we looked at unplanned hospitalizations lasting >24 h within 3 days post-procedure for outpatients and unplanned admissions to intensive care units (ICU) within 3 days post-procedure for hospitalized patients. We did not find any further complications accounting for admission or ICU transfer.

Table 3 Differences in dilation outcomes of primary and anastomotic strictures.

Factor	Primary stricture (N = 88)	Anastomotic stricture (N = 81)	*p*-Value
Stricture length (cm) [a]	2.7 ± 2.2	2.7 ± 1.7	0.73
Post dilation scope passing	80 (92.0)	74 (91.4)	0.89
Intralesional steroids	25 (28.4)	19 (23.5)	0.46
Surgery	30 (34.1)	24 (29.6)	0.53
Redilation	52 (59.1)	47 (58.0)	0.89
Redilation and/or surgery	63 (71.6)	59 (72.8)	0.86
Intervention-free months	15.3 (1.9)	18.3 (2.0)	0.26
Repeat dilation-free months	17.9 (2.1)	21.4 (2.2)	0.27
Surgery-free months	28.4 (1.8)	34.4 (1.9)	0.39

Values presented as mean ± SD for length, N (%) for scope passing and intralesional steroid, and mean (SE) for intervention-free periods.
p-Values correspond to Wilcoxon rank sum test for length, chi-square tests for scope passing and intralesional steroid and robust score tests for intervention-free periods.
[a] Stricture length documented for 17 primary and 16 anastomotic strictures.

3.5. Predictors of long-term outcomes

Intralesional steroids were injected in 44 (26.0%) strictures at the time of first dilation. There was no significant association between the use of intralesional steroids and the suggestion of ongoing inflammation during endoscopy (60.5% vs. 60% of those with and without intralesional steroids, respectively; $p = 0.99$) or on histology (64% vs. 67% of those with and without intralesional steroids, respectively; $p = 0.76$). There was no difference in the need of surgery (36% vs. 30%; $p = 0.47$) or number of repeat dilations in strictures that received intralesional steroid versus those that did not receive intralesional steroid (median [P25, P75]: 1 [0, 3] vs., 1 [0, 2]; $p = 0.56$), irrespective of whether the stricture was primary or anastomotic. In addition, age, gender, ethnicity, smoking status, stricture length, location, traversability, size of balloon used and medications did not impact need for surgery or re-intervention in univariate Cox proportional hazards marginal model (see Appendix A, eTables 1 and 2). Multivariable Cox proportional hazards marginal model did not show any significant difference between patients that received and patients that did not receive intralesional steroid, biologics or immunomodulators with respect to the need for surgery or the first repeat intervention. As shown in Table 4, none of the demographics, medication, and procedure or stricture characteristics (including inflammation of the mucosa during endoscopy or histology, balloon size used) could accurately predict the need for surgery in our cohort.

4. Discussion

The primary objective of our study was to evaluate the safety and efficacy of endoscopic balloon dilation of primary strictures in Crohn's disease patients and to compare the outcome with anastomotic strictures. We analyzed outcomes of 128 patients who underwent 430 endoscopic stricture dilations during a median of 1.8 years of follow-up. More than half of our patients had primary strictures, making this the largest series reported on endoscopic dilation of primary strictures. We found that endoscopic dilation was equally safe and effective in the management of primary strictures as in anastomotic strictures with high technical success and low rate of complications (0.93% per procedure, 3.1% per patient). Overall, endoscopic stricture dilation prevented the need for surgery in two-thirds (67.2%) of patients, and delayed the need for surgery by 33 months, though more than one-half of patients required redilation at some course during their follow-up. Re-dilations were found to be as technically successful as the first dilation and had similar efficacy.

So far, most of the literature on endoscopic stricture dilation has focused on post-surgical anastomotic strictures.[14] In 1986, Brower reported one of the first cases of successful endoscopic balloon dilation of a terminal ileal stricture in a CD patient who refused surgery in spite of refractory obstructive symptoms.[19] Since then, many institutions have reported their results of endoscopic balloon dilation, though all studies in adults are retrospective in nature, lack control groups and predominantly include patients with anastomotic strictures. The best evidence on the efficacy and safety comes from a systematic review of 13 studies encompassing a total of 347 Crohn's patients.[14] In this review, Hassan et al. reported a

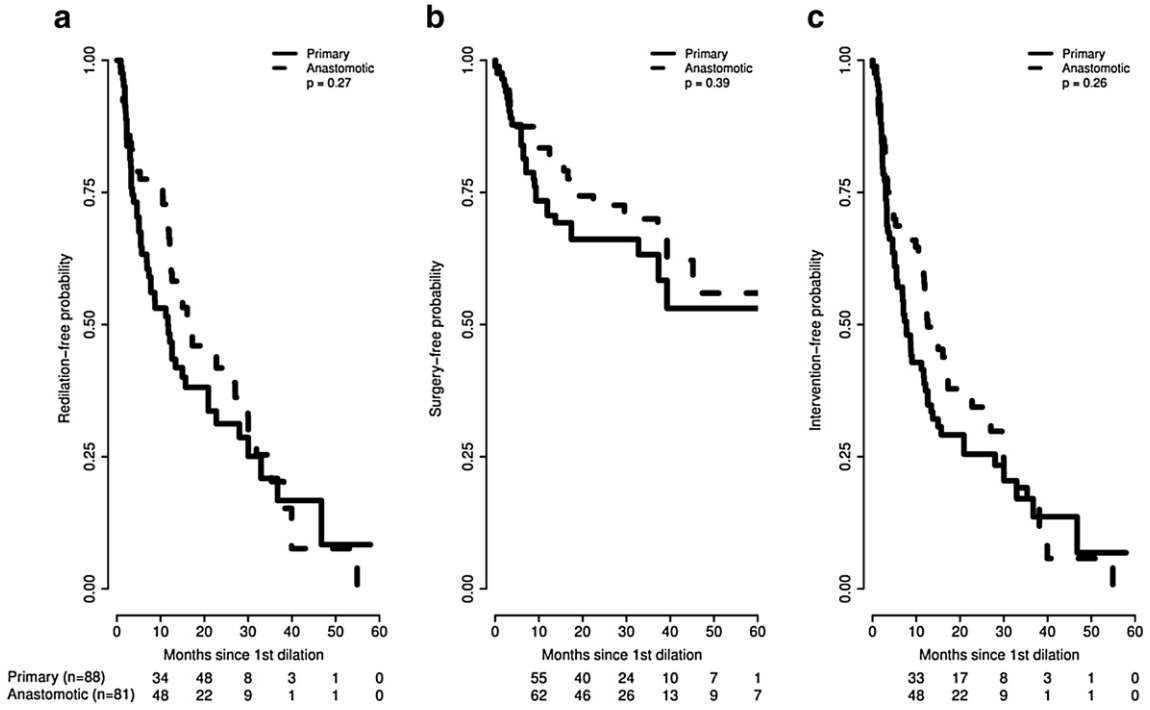

Figure 1 Kaplan–Meir curves for need for surgery, dilation and re-intervention (dilation or surgery) in patients with primary and anastomotic strictures undergoing endoscopic dilation.

technical success of 86%, a major complication rate of 2% and a surgery-free outcome of 58% after a mean follow-up of 33 months. Even though a majority of patients had anastomotic strictures, overall patient characteristics (including demographics, duration of CD), stricture length and location were similar to our study. Recently, Van Assche et al. published their findings on endoscopic stricture dilation based on their experience in 138 Belgian patients undergoing 237 dilations.[20] Again, majority of the patients (84%) had anastomotic strictures. Forty-four percent of patients required no further therapy during the follow-up period, 46% required further dilatation and 24% required surgery. The serious complication rate based on patients treated was approximately 5%. This complication rate is higher than that reported by Hassan et al. or more recently by Mueller et al. and Scimeca et al., and likely reflects a different definition of complication rates used in the study.[12,21–24] Procedures that necessitated prolonged hospitalization were also considered as complications by Van Assche and colleagues.[20]

Table 4 First re-intervention: Multivariable Cox proportional hazards marginal model.

Parameter	HR (95% CI)	*p*-Value
Surgery		
Number of dilations	0.76 (0.59, 0.97)	0.031
Intralesional steroids	1.4 (0.65, 2.9)	0.4
Biologics	1.2 (0.52, 2.6)	0.71
Primary stricture	1.2 (0.66, 2.2)	0.53
Oral steroids	0.64 (0.22, 1.9)	0.42

Cox proportional hazards models using robust sandwich covariance matrix estimate to account for the intracluster dependence.

We also expanded the outcome variables reported in the literature by assessing results of mucosal biopsies and the impact of intralesional steroids, concomitant immunomodulators and biologics on efficacy and safety of endoscopic stricture dilations. Our results are very similar to those reported by Van Assche et al. that neither active mucosal disease at the time of dilatation nor medical therapy afterwards predicts recurrent dilatation or surgery in primary or anastomotic strictures.[20] In addition, 44 (26.0%) of strictures were injected with intralesional steroid during first dilation, but we did not find any beneficial effect of intralesional steroids on the need for redilation, surgery or time to intervention. This is in spite of the fact that majority of strictures had inflammation reported on endoscopy or histologically. The literature on efficacy of intralesional steroid in CD stricture dilation is conflicting, and a recent prospective randomized control trial suggested a trend toward a worse outcome in steroid injection arm.[17] The issue of adjuvant medication use is important since symptom recurrence after endoscopic balloon dilation is common and has been reported in 13%–100% of patients.[20] About two-thirds of patients in our study required repeat dilation with a redilation-free period approaching two years. The quality of life in these patients is likely to be suboptimal due to ongoing or recurrent symptoms. There is a pressing need for medical or endoscopic intervention that can prolong the symptom-free interval after endoscopic dilation.[20–22]

We are just beginning to understand the pathophysiologic underpinnings of stricture formation in CD. While fibrosis in CD strictures is often the end-result of chronic inflammation, there is an increased recognition that anti-inflammatory agents by themselves are insufficient in controlling or reversing advanced fibrosis in CD or other fibrotic diseases such as

pulmonary fibrosis, cirrhosis, systemic sclerosis, and renal and cardiovascular fibrosis.[2] This may be one possible reason that we are not seeing any beneficial effect of intralesional steroid injections or biologics and immunomodulators in preventing redilation or surgery. It will be of interest to see if specific anti-fibrotic agents (currently in experimental stages or used in other diseases) including those that modulate transforming growth factor beta1 (TGF-B1) and/or its signaling pathways can prove as effective adjuvant therapies to endoscopic stricture dilations.[25,26]

There are several potential limitations of our study. First, our study suffers from many pitfalls inherent in retrospective studies. There was no standard protocol for ordering imaging, such as computed tomography enterography (CTE) or magnetic resonance enterography (MRE) prior to each stricture dilation. We also did not have information on certain stricture characteristics (such as angularity or tortuosity) which may have important implications for efficacy and complications. Recently, Mueller et al., in a prospective study of 55 patients, showed that stricture length is the major predictor for surgery, with average length of strictures in patients who required surgery was 7.5 cm compared with 2.5 cm in those patients with terminal ileum/ileocecal valve strictures who did not require surgery.[12] Most of our patients had strictures shorter than 5 cm, therefore we cannot confirm the findings by Mueller et al. Two out of the 15 procedures (13.3%) with needle knife resulted in major complications. Though the numbers failed to reach statistical significance, we feel that the small overall number of complications seen in our study did not have enough power to find statistical difference in complication rate between procedures with and without needle knife. Lastly, our study, like other studies in the past, did not have a control group to compare outcomes of patients undergoing surgery versus endoscopic dilation for primary strictures. In a systematic review of literature comparing surgical stricturoplasty (SP) versus endoscopic balloon dilation, Wibmer and colleagues reported 11% incidence of perioperative complications and 5% incidence of major complications with 24% need for second surgery after a median follow-up of 46 months.[6] In comparison, endoscopic balloon dilation had a lower rate of major complications (3%) at the cost of slightly higher surgical recurrence rate (27.6% after a median follow-up of 21 months). The review did not have any controlled studies directly comparing surgical versus endoscopic treatment and most of endoscopic dilations were done for anastomotic strictures.

So, what can we tell patients to help them make informed decisions regarding surgery vs. endoscopic dilation for CD strictures? Based on our study, we can reassure patients about safety and efficacy of endoscopic dilation even if they have de-novo strictures. More specifically, we can tell them that if their stricture is less than 5 cm in length, accessible by endoscopy and not associated with abscesses or fistulae; we have about 80% chance of successfully dilating the stricture with less than 1% chance per procedure of major complication requiring surgery. They may require a repeat dilation but there is a two-thirds chance that they will not require surgery or delay the need for surgery by about 33 months. If they opt for surgery, they are likely to have about a 5% major complication rate though perhaps a better long term remission, based on available literature. Having surgery does not necessarily prevent the need for future surgeries, as up-to 50% of patients may require repeat surgery in 10 years.[7] The choice for surgery becomes easy if there are longer strictures, location beyond the reach of the endoscope or strictures with associated complications. Without a prospective study comparing quality of life outcomes of post-endoscopic dilation and surgery, we cannot predict future quality of life of patients post-procedure vs. post-surgery.

In summary, our study has shown that endoscopic dilation is as effective and safe for managing primary or de novo strictures as it is for anastomotic strictures. Future efforts should focus on determining quality of life of patients undergoing endoscopic stricture dilation versus surgery for benign CD strictures, and attempt to prolong the intervention-free period by improving technique or concomitant administration of novel anti-fibrotic agents.

Conflict of interest

None of the authors have conflict of interest regarding this paper.

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Acknowledgment

None.

Appendix A

eTable 1 Differences in dilation outcomes of traversable and non-traversable strictures.

Factor	Not traversable pre-dilation (N = 77)	Traversable pre-dilation (N = 92)	*p*-Value
Stricture length*	3.0 [1.8, 4.5]	1.00 [1.00, 2.5]	0.077
Post-dilation traversable*	63 (82.9)	92 (100)	<**0.001**
Surgery	21 (27.3)	33 (35.9)	0.23
Redilation needed	50 (64.9)	49 (53.3)	0.12
Redilation and/or surgery	57 (74.0)	65 (70.7)	0.63
Surgery-free months*	32.1 (1.6)	31.0 (2.1)	0.12

*Data not available for all subjects. Missing values: Stricture length = 136, post-dilation traversable = 1, surgery-free months = 1.
Values presented as median [P25, P75] for length, N (%) for scope passing and intralesional steroid, and median (95% CI) or mean (SE) for intervention-free periods.
p-Values correspond to Wilcoxon rank sum test for length, chi-square tests for scope passing and intralesional steroid and robust score tests for intervention-free periods.

eTable 2 First re-intervention: Univariable Cox proportional hazards marginal model.

Factor	1st redilation		Surgery		1st event	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Male	1.2 (0.78, 1.8)	0.42	1.3 (0.67, 2.5)	0.44	1.06 (0.73, 1.5)	0.74
Caucasian	1.6 (0.74, 3.6)	0.22	0.67 (0.24, 1.9)	0.46	1.5 (0.66, 3.6)	0.32
Smoking: Current vs. never	0.77 (0.47, 1.3)	0.31	0.80 (0.31, 2.1)	0.65	0.75 (0.47, 1.2)	0.22
Smoking: Ex-smoker vs. never	0.97 (0.59, 1.6)	0.91	0.83 (0.39, 1.8)	0.64	0.85 (0.54, 1.4)	0.5
Age at diagnosis	1.00 (0.99, 1.02)	0.68	1.01 (0.98, 1.04)	0.67	1.00 (0.99, 1.02)	0.56
Age at first dilation	0.99 (0.97, 1.00)	0.077	0.99 (0.95, 1.02)	0.52	0.99 (0.98, 1.01)	0.28
Disease duration	0.98 (0.95, 1.00)	**0.044**	0.97 (0.94, 1.01)	0.12	0.98 (0.96, 1.00)	0.1
Aminosalicylates	1.1 (0.75, 1.8)	0.53	0.76 (0.37, 1.6)	0.45	1.10 (0.75, 1.6)	0.63
Immunomodulators	1.2 (0.76, 1.8)	0.48	1.03 (0.52, 2.0)	0.94	1.1 (0.76, 1.7)	0.54
Budesonide	1.08 (0.71, 1.6)	0.71	1.01 (0.51, 2.0)	0.99	1.09 (0.75, 1.6)	0.64
Steroids	1.2 (0.71, 2.0)	0.49	0.61 (0.22, 1.7)	0.35	1.01 (0.62, 1.7)	0.97
Biologics	1.4 (0.88, 2.2)	0.16	1.07 (0.49, 2.4)	0.86	1.2 (0.75, 1.8)	0.48
Antibiotics	1.2 (0.30, 5.0)	0.79	1.7 (0.27, 11.0)	0.57	1.4 (0.31, 5.9)	0.68
Upper	2.1 (1.3, 3.4)	**0.002**	1.9 (0.22, 15.8)	0.57	3.0 (1.8, 4.8)	<**0.001**
Ileum	0.79 (0.45, 1.4)	0.41	0.74 (0.36, 1.5)	0.41	0.79 (0.46, 1.4)	0.4
Colon	0.86 (0.57, 1.3)	0.48	0.94 (0.48, 1.8)	0.85	0.90 (0.62, 1.3)	0.58
Anorectal	0.74 (0.30, 1.8)	0.5	0.83 (0.24, 2.8)	0.76	0.72 (0.31, 1.7)	0.45
Stricture length	0.79 (0.61, 1.02)	0.068	1.3 (0.98, 1.8)	0.073	0.93 (0.72, 1.2)	0.55
Stricture length $\geq$ 3 cm	0.77 (0.32, 1.9)	0.57	4.5 (0.92, 21.8)	0.064	1.1 (0.49, 2.5)	0.81
Stricture length $\geq$ 5 cm	0.20 (0.02, 1.8)	0.15	3.1 (0.67, 13.9)	0.15	0.85 (0.23, 3.1)	0.81
Primary vs. anastomotic stricture	1.3 (0.84, 1.9)	0.26	1.3 (0.70, 2.3)	0.44	1.2 (0.84, 1.8)	0.29
Traversable prescope	0.85 (0.55, 1.3)	0.45	1.6 (0.87, 2.9)	0.13	0.99 (0.67, 1.4)	0.94
Balloon size	1.00 (0.94, 1.06)	0.94	0.98 (0.90, 1.07)	0.64	1.00 (0.95, 1.06)	0.96
Balloon size $\geq$ 18 mm	0.89 (0.58, 1.4)	0.59	0.81 (0.42, 1.6)	0.52	0.98 (0.67, 1.4)	0.92
Inflammation on endoscopy	0.87 (0.56, 1.4)	0.55	1.3 (0.64, 2.6)	0.48	1.03 (0.69, 1.5)	0.89
Inflammation on histology	1.7 (0.91, 3.1)	0.1	1.2 (0.53, 2.9)	0.62	1.7 (0.99, 3.1)	0.056
Intralesional steroid injection	1.3 (0.82, 2.2)	0.24	1.3 (0.61, 2.7)	0.51	1.4 (0.93, 2.2)	0.099
Traversable postscope	0.67 (0.31, 1.5)	0.31	0.94 (0.34, 2.6)	0.91	0.70 (0.35, 1.4)	0.3
Sedation: None vs. anesthesia	3.1 (0.92, 10.2)	0.069	1.6 (0.17, 15.3)	0.67	4.3 (1.9, 9.6)	<**0.001**
Sedation: Sedation vs. anesthesia	3.4 (1.5, 7.7)	**0.003**	2.2 (0.61, 7.9)	0.23	4.1 (1.8, 9.3)	<**0.001**

CI: confidence interval.
Cox proportional hazards models accounting for the intracluster dependence.

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