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Endoscopic Dilatation of Crohn's Anastomotic Strictures is Effective in the Long Term, and Escalation of Medical Therapy Improves Outcomes in the Biologic Era

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Abstract

Background and Aims: To investigate the long-term efficacy of endoscopic dilatation of Crohn's anastomotic strictures and to identify risk and protective factors associated with the need for repeat dilatation or surgery.

Methods: A total of 54 patients who had endoscopic balloon dilatations for anastomotic Crohn's strictures between 2004 and 2009, with follow-up until June 2014, were identified from a single tertiary center. The primary end points were repeat dilatation or surgical resection, and the impact of radiology, medical therapy, and endoscopic data on these outcomes was analysed with Cox proportional hazards analysis.

Results: A total of 151 dilatations were performed on patients with a median age of 52 years [interquartile range (IQR), 46–62 years]. The median duration from the first to the second dilatation was 6 years (IQR, 5–7 years). The median disease duration was 28 years (IQR, 19–32 years). At endoscopy, disease activity was reported in 50/54 (92%) cases, with a median Rutgeerts grading of i2 (range, i0–i4). A median of two (IQR 1–9) dilatations was required, with a time to repeat dilatation of 23 months (IQR 7.2–56.9). Escalation of medical therapy was adopted in 22/54 patients (41% of the study population). On multivariate analysis, only combination therapy (anti-TNFα and immunomodulator) was significantly associated with the (decreased) need for repeated dilatation [hazard ratio (HR) 0.23; 95% CI, 0.07–0.67; $p = 0.01$]. Anastomotic resections were performed in 10 (18%) patients, with a Rutgeerts score of i4 at initial endoscopic balloon dilatation being associated with this outcome (HR 4.55; 95% CI 1.08–19.29; $p = 0.04$) on multivariate analysis.

Conclusion: Endoscopic balloon dilatation of Crohn's anastomotic strictures is safe and effective in the long term. We demonstrate that active disease predicts for future surgery, while escalation of medical therapy may decrease the need for repeat dilatation.

Key Words: Crohn's disease; anastomosis; stricture; medical therapy; surgery

Abbreviations: 5-ASA, 5-aminosalicylic acid; anti-TNF, anti-tumour necrosis factor; AZA, azathioprine; CI, confidence interval; IQR, interquartile range; HR,hazard ratio.

1. Introduction

Crohn's disease results in surgical resection in over 50% of patients within the first 10 years of diagnosis.[1] Within this cohort of patients, 90% will develop disease recurrence at the anastomosis due to ongoing inflammatory activity.[2] Attempts to attenuate this with escalation in medical therapy for high-risk patients have demonstrated improved outcomes in disease activity.[3,4] However, up to 70% of patients with prior surgery will require a further resection.[5]

Assessing recurrence of disease and possible luminal narrowing (using radiology with computer tomography and magnetic resonance imaging) may help to demonstrate pre-stenotic dilatation and transmural activity of disease, as shown by bowel wall thickening and mucosal enhancement in the pre-stenotic lumen.[6,7]

Control of moderate to severe Crohn's disease using combination therapy with immunomodulators and anti-tumour necrosis factor (anti-TNF) medications has been demonstrated to be an effective regimen.[8] In Crohn's disease patients who have undergone ileocolonic resection and anastomosis, the addition of azathioprine (AZA) or anti-TNFα therapy when there are high-risk lesions present at a 6 month colonoscopy is associated with better disease control.[9] Patients who have progressed to stricturing at the anastomosis fall into a high-risk category because it is usually due to disease recurrence at the anastomotic site. However, limited data is available on whether escalation of medical therapy following dilatation of anastomotic strictures may prevent the need for repeat dilatation or surgery. In a recent meta-analysis, short-term success rates of endoscopic balloon dilatation in avoiding surgery are estimated at 78%, with a complication rate of 2%.[10] Long-term outcomes in many studies are only limited to a follow-up period of 3 years with small cohort sizes. Moreover, endoscopic disease, radiologic and serologic markers of disease activity at the time of dilatation, and the effect of alterations in medical therapy on outcome of stricture dilatation are not known. The primary aim of this study was to demonstrate the long-term efficacy and safety of endoscopic balloon dilatation of Crohn's anastomotic strictures in a large referral centre cohort. We also aimed to show the effect of medical therapy and disease activity on long-term clinical outcomes.

2. Methods

Patients were identified via a search of the hospital endoscopy database using the terms 'endoscopic dilatation', 'balloon', 'dilatation', 'CRE', and 'wire'. Manual checks were performed to ensure the inclusion criteria had been met, with *de novo* Crohn's strictures excluded. Dilatations performed between 2004 and 2009 were extracted. A detailed review of the clinical notes provided retrospective data on site of stricture, initial surgery, medical management, and clinical outcomes. Ethics was obtained via Brent REC North West London Hospital R&D Department 08/H0717/24.

2.1. Management protocol

Patients at our institution had endoscopic dilatation performed due to obstructive symptoms, including nausea, vomiting, and abdominal pain. Typically, dilatations were performed via standard colonoscopy or flexible sigmoidoscopy with a 'through-the-scope' balloon (Rigidflex or Controlled Radial Expansion Wire guided Balloon Dilatation CatheterTM, Boston Scientific, Boston, MA, USA), with diameters from 8 mm to 20 mm on inflation and lengths of 30–80 mm. The balloon was filled with water under visual control, and graduated dilatation under direct vision was performed, typically with a 1-min dilatation time at each set diameter; no more than a total of increment of 3 mm was usually dilated at any one sitting. Therapeutic success was defined as the ability to pass the scope through the stricture following dilatation.

A modified Rutgeerts score[9] was graded by a single experienced endoscopist (AH) blinded to the outcome viewing images retrospectively from the initial endoscopy, with activity of disease at the anastomosis site being the most relevant. Therefore, no recurrence was defined as i0 (no lesions) or i1 (≤5 aphthous lesions); recurrence was defined as i2 (>5 aphthous lesions or larger lesions confined to anastomosis), i3 (diffuse ileitis), or i4 (diffuse inflammation with large ulcers at anastomotic site). Histology of the biopsied anastomosis was reviewed from those available, with particular attention to fibrosis and activity of disease to determine the possible underlying cause of the stricture.

Patients had escalation of medical therapy, which was defined as commencement of a thiopurine or anti-TNF within 6 months of the first dilatation, as determined by global physician assessment. Combination therapy was defined as the use of a thiopurine and an anti-TNF drug (Figure 1).

2.2. Outcomes measures

Immediate therapeutic success was defined as the ability to pass the scope through the stricture, with clinical success being defined as improvement of obstructive symptoms. If persistent pain following dilatation occurred, this was assessed clinically and possible imaging with onward surgical management sought. Patients were followed up until one of the primary endpoints were met: (1) resection of the anastomotic stricture, (2) last clinic follow-up, or (3) censor date of June 1, 2014. Long-term efficacy was defined as avoidance of surgical resection or repeat dilatation after the first dilatation. The long-term (>5 years) follow-up data was analysed to assess the impact of endoscopic, histologic, and radiological disease activity, and escalation of medical therapy on repeat dilatation and resection rates.

2.3. Statistics

Descriptive statistics were used to analyse patient demographics. The Chi-squared test was used for differences in proportions of patients experiencing a given outcome. Kaplan–Meier survival analysis with log rank statistics was used to assess event-free survival, and Cox conditional proportional hazards regression analysis was used to assess predictors of recurrence, including endoscopic and biochemical disease activity. All continuous variables were reported with median and interquartile range (IQR) and dichotomized for analysis using the median value as the cut-off. Analysis of long-term outcomes was performed on patients who had a successful initial dilatation and did not suffer from perforation.

3. Results

3.1. Patient characteristics

A total of 54 patients were identified; the median age was 52 years (IQR, 46–62 years) and 21/54 (39%) were male. The median follow-up period was 6 years (IQR, 5–7 years), with a median disease duration of 28 years (IQR, 19–32 years). The patient demographics are listed in Table 1. All dilatations were performed at the anastomosis, with the underlying surgery being ileocaecal resection in 30 (55.5%), right hemicolectomy in 22 (40.7%), and segmental resection in 2 (3.7%). Eighty-seven per cent of patients were on some form of medical therapy at the time of dilatation: 8 (14.8%) on 5-aminosalicylic acid (5-ASA), 33 (61.1%) on thiopurines, and 3 (5.6%) on anti-TNF medication.

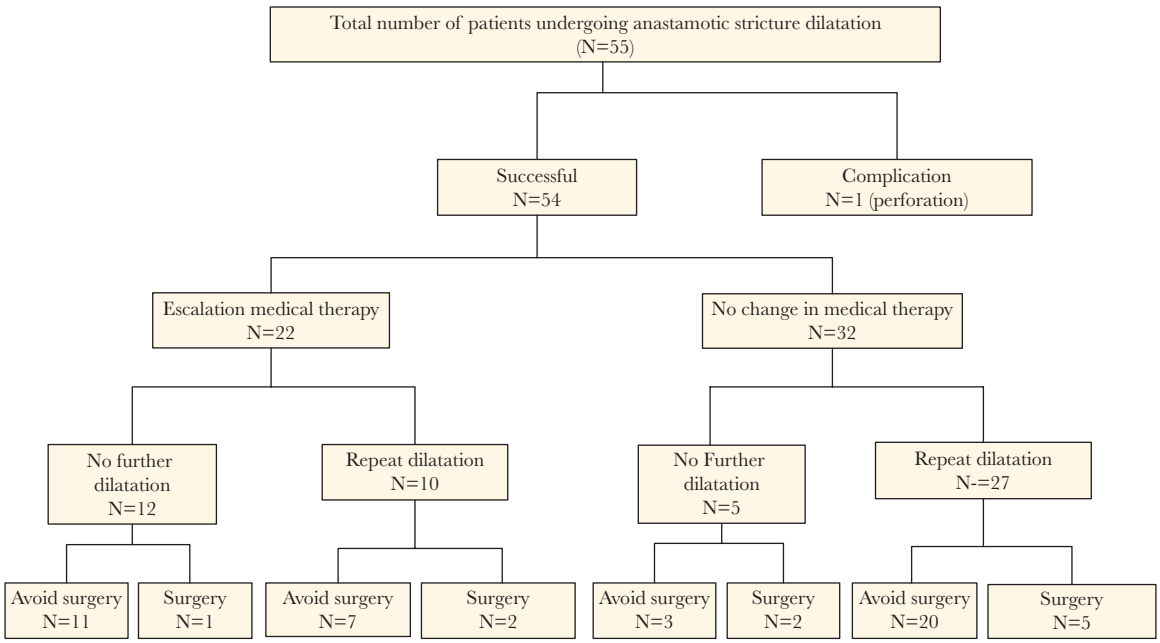

Figure 1: Flowchart with study design.

Table 1. Demographics of patients in cohort.

Demographics	
Number of patients	54
Number of dilatations	151
Gender (M/F)	21/33
Median age (IQR)	53 years (46–62)
Disease duration (IQR)	24 years (17–30)
Median follow-up (IQR)	5.8 years (5.0–8.9)
Original surgery	
Ileocaecal resection	40 (55%)
Right hemicolectomy	22 (40%)
Other segmental resection	1 (2%)
Small bowel resection	1 (2%)
Disease phenotype at diagnosis	
Location of disease	
L1 – terminal ileum	16 (29.6)
L2 – colon	16 (29.6)
L3 – ileocolonic	22 (40.7)
L4 – upper GI	0 (0)
Behaviour of Crohn's disease	
B1 – inflammatory disease	29 (53.7)
B2 – stricturing disease	9 (16.7)
B3 – penetrating disease	16 (29.6)
No. of prior surgeries, *n* (range)	2 (1–4)
Medical therapy at first dilatation	
5-ASA	8 (14.8%)
Immunomodulator	33 (61.1%)
Anti-TNF	3 (5.6%)
Activity of disease (out of 50 graded)	
I0-i1	10/50 (20%)
I0-i2	36/50 (72%)
I3-i4	14/50 (28%)

5-ASA, 5-aminosalicylic acid; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IQR, interquartile range; TNF, tumour necrosis factor.

3.2. Disease characteristics

MRI, CT, or barium follow through was used to assess the stricture in each case: the median length was 20 mm (IQR 10–30 mm), with features of active mucosal inflammation described at the anastomosis in 38/54 (70%) and upstream dilatation in 25/54 (46%). Endoscopic images were used to determine active disease, and assessment with Rutgeerts scoring was possible in 50/54 cases, with a median of i2 (range i1–i4); endoscopic images were not available from four of the index colonoscopies.

3.3. Efficacy of endoscopic dilatation

Repeat dilatation was required in 37/54 (69%) of patients. The median number of dilatations was two (IQR 1–4), with a median time to first repeat dilatation of 23 months (IQR 7.2–56.9). Therapeutic success (ability to pass colonoscope through stricture after dilatation) was achieved in 48/54 (89%) cases, with a median balloon dilatation of 15 mmHg and a clinical success of 98%.

3.4. Effect of clinical and endoscopic factors on repeat dilatation

On univariate analysis, stricture length >40 mm (HR 1.38; 95% CI 1.23–4.51 $p = 0.04$) was associated with a need for repeat dilatation. Other factors such as gender, age, duration of disease, and disease activity (Rutgeerts score ≥i2) at time of first endoscopy did not predict for repeat dilatation (Table 2).

3.5. Effect of medical therapy on repeat dilatation

Following initial endoscopy and dilatation, five (9.2%) patients were on 5-ASA treatment, 43 (79.6%) on an immunomodulator, and 16 (29.6%) on an anti-TNF. There was escalation of medical therapy in 22 patients (40.7%), with combination therapy being used in 12 (22.2%). The use of combination medical therapy (HR 0.26; 95% CI 0.09–0.75; $p = 0.01$) was found to decrease the need for repeat dilatation (Table 2). In further subgroup analysis, anti-TNF therapy was the only medication found to be significantly associated with a decreased risk of repeat dilatation (HR 0.36; 0.16–0.83; $p = 0.02$).

Four variables were chosen due to existing evidence predicting outcomes in Crohn's disease and entered into a multivariate model: duration of disease, stricture length, activity of disease, and combination therapy (see Table 3).[10–12] Combination therapy was

Table 2. Univariate analysis of clinical, radiologic, endoscopic, and medical therapy on outcome of repeat dilatation.

	HR	95% CI	*p*-value
Age >53	0.91	0.48–1.73	0.77
Sex (M)	1.66	0.87–3.17	0.12
Duration of disease >24*	1.08	0.56–2.08	0.82
Radiologic			
Length >40 mm*	**1.38**	**1.23–4.51**	**0.04**
Mucosal enhancement	2.05	0.93–4.52	0.08
Upstream dilatation	1.54	0.80–2.96	0.19
Medical therapy			
Before initial dilatation			
Steroids	0.93	0.33–2.64	0.89
Immunomodulator	1.14	0.57–2.26	0.71
5-ASA	1.88	0.66–5.33	0.24
Anti-TNF	1.67	0.40–7.13	0.48
<6 months after initial dilatation			
Immunomodulator	0.68	0.32–1.45	0.32
5-ASA	1.11	0.39–3.15	0.45
Anti-TNF	**0.36**	**0.16–0.83**	**0.02**
Combination therapy*#	**0.26**	**0.09–0.75**	**0.01**
Endoscopic factors			
Size of balloon:			
<15 mm	ref		
≥15 mm	1.49	0.58–3.83	0.41
Modified Rutgeerts score			
i3–i4*	1.46	0.66–3.21	0.35
i4	1.05	0.45–2.42	0.92

*Variables included in the final multivariate model. #anti-TNF therapy and immunomodulators. 5-ASA, 5-aminosalicylic acid; CI, confidence interval; HR, hazard ratio; TNF, tumour necrosis factor.

Table 3. Multivariate analysis – repeat dilatation outcomes.

	HR	95% CI	*p*-value
Length >40 mm	1.40	0.40–4.80	0.61
Combination therapy	0.227	0.07–0.67	0.01
Duration of disease >24 years	1.10	0.54–2.26	0.79
Rutgeerts score >i3	1.31	0.59–2.94	0.51

* CI, confidence interval; HR, hazard ratio.

significantly associated with a reduced need for repeat dilatation (HR, 0.23; 95% CI, 0.07–0.67; $p = 0.01$) (see Figure 2). The remaining 32/54 (59.3%), who did not have escalation in medical therapy, received a repeat dilatation prior to any changes in medications, with a time to repeat dilatation of 19 months (IQR 5.75–46.58).

Of the patients who had repeat dilatation, longer duration of disease (>24 years) was associated with a shorter time to second dilatation ($p = 0.048$).

3.6. Effect of clinical, radiologic, endoscopic factors, and medical therapy on surgery

After initial dilatation, 10 (18%) patients progressed to surgical resection of the anastomotic stricture due to worsening or recurrence of symptoms. The median time to progression to surgery was 2.4 years (1.8–3.9). On univariate analysis, the factor that predicted for surgery was Rutgeerts i4 (HR, 3.33; 95% CI, 1.27–8.74; $p = 0.03$) (see Table 4).

On multivariate analysis (see Table 5), using variables with $p < 0.1$ on univariate analysis (anti-TNF therapy, Rutgeerts i4, upstream dilatation, stricture >40 mm), Rutgeerts i4 was correlated with increased likelihood of surgery (HR, 4.55; 95% CI 1.08–19.29; $p = 0.04$).

3.7. Radiology and correlation with endoscopic disease activity

All images were reviewed, with length of stricture, underlying mucosal enhancement, or suspected signs of chronicity noted on intestinal imaging modalities. Radiological findings did not significantly correlate with active disease as observed at time of endoscopy, with an R value of –0.11 and kappa of –0.04; $p = 0.57$.

3.8. Complication

There was one perforation, identified within 24 h of the procedure, in which the patient had worsening abdominal pain and confirmatory cross-sectional imaging. This resulted in a resection of the anastomosis and a temporary ileostomy, which was reversed 12 months later.

4. Discussion

Post-operative anastomotic stricturing in Crohn's disease can be treated effectively with repeated balloon dilatation in the long term, as demonstrated by our long-term data. Our data shows that escalation of medical therapy to include an anti-TNF following the initial dilatation may decrease the need for repeat dilatation. Stricture length >40 mm was shown on univariate analysis to be a significant predictor for further dilatation. Severe disease (graded as Rutgeerts i4 disease) at the time of the initial endoscopy increased the risk of repeat surgery. This data suggests that the presence of inflammatory disease at the site of an anastomotic stricture may indicate that escalation of medical therapy to at least an anti-TNF, or more effectively combination therapy, may prevent the need for repeat intervention.

After bowel resection for Crohn's disease, the anastomosis is the most common location of recurrence.[9] Disease progression results in luminal narrowing and stricturing disease.[13] Avoidance of further resection is possible with the use of balloon dilatation.[14] As far as we are aware, this patient cohort represents the longest follow-up period in the biologic era (in which use of anti-TNF therapy has become routine, in a scheduled fashion, and which has the likelihood of concomitant immunomodulator therapy). No association between activity of disease at the time of initial endoscopy and future outcomes had been identified; however, our study showed that disease activity was associated with future surgical resection.

Our data demonstrated that longer disease duration was associated with a shorter time to repeat dilatation. This may be due to the underlying pathology being a fibrotic, post-surgical stricture, with healing occurring in a defined pattern, with the possibility of progression to luminal narrowing, despite escalation of medical therapy.[9]

We demonstrate that combination therapy with an immunomodulator and anti-TNF may decrease the need for repeat dilatation and improve long-term outcomes in conjunction with endoscopic dilatation. Van Assche et al.[15] found no significant predictors of re-intervention in terms of C-reactive protein or endoscopic activity, nor was there any influence due to concomitant medications. Patients receiving anti-TNF in the Van Assche study may also have had more severe disease, as demonstrated by the rate of repeat dilatation being high (13.8% per patient-year).[15] Furthermore, the patients on anti-TNF therapy in their study had the shortest follow-up period out of all medications prescribed

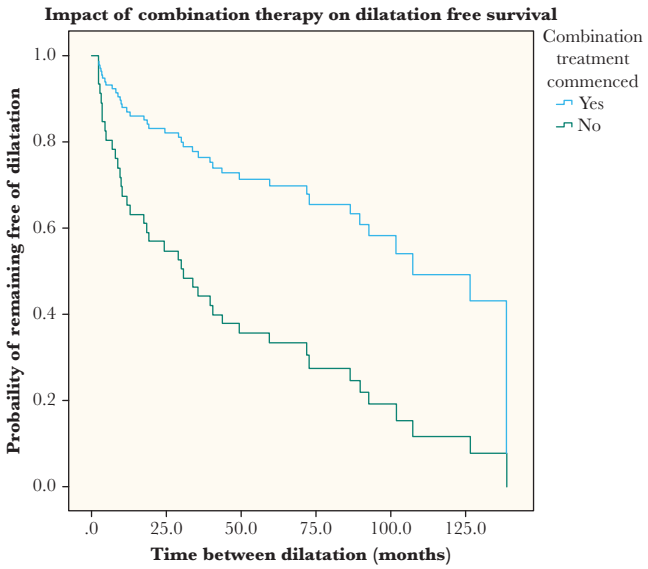

Figure 2. Impact of combination therapy on dilatation-free survival.

Table 4. Univariate analysis of clinical, radiologic, endoscopic, and medical therapy on outcome of surgical resection.

	HR	95% CI	*p*-value
Age >53	0.90	0.238–3.429	0.88
Sex (M)	2.14	0.57–8.03	0.26
Duration of disease >24 years	6.00	0.74–48.61	0.12
Radiologic			
Length >40 mm*	1.19	0.15–9.60	0.09
Mucosal enhancement	4.80	0.59–39.12	0.14
Upstream dilatation*	1.76	1.12–2.76	0.08
Medical therapy			
Post			
Immunomodulator	2.00	0.25–16.01	0.52
5-ASA	1.13	0.35–1.25	0.57
Anti-TNF*	0.167	0.021–1.362	0.09
Combination therapy	0.25	0.03–2.02	0.19
Endoscopic activity			
i3–i4	2.93	1.32–6.50	0.28
i4*	**3.33**	**1.27–8.74**	**0.03**

*Multivariate analysis was performed on these factors. 5-ASA, 5-aminosalicylic acid; CI, confidence interval; HR, hazard ratio; TNF, tumour necrosis factor.

Table 5. Multivariate analysis – surgical outcomes.

	HR	95% CI	*p*-value
Upstream dilatation	1.27	0.29–5.52	0.75
Stricture >40 mm	2.17	0.43–10.90	0.35
Anti-TNF	1.83	0.34–9.82	0.48
Rutgeerts score >i3	4.55	1.08–19.29	0.04

CI, confidence interval; HR, hazard ratio; TNF, tumour necrosis factor.

(2.8 years). This may not be enough to demonstrate the longer-term effects of anti-TNFs on strictures post-dilatation. We found no significant difference in follow-up time between those who had escalation in medical therapy versus those who had no change to medical therapy.

Furthermore, severity of disease activity at initial endoscopy (Rutgeerts i4) was found to predict a greater risk of future surgery with our standardized grading of disease activity. In this cohort of patients, our data would suggest that, where active inflammation is present, escalation of therapy to include at least anti-TNF therapy is necessary to augment the natural history of Crohn's disease and improve clinical outcomes.

Nanda et al.,[16] in a smaller cohort of 31 patients with a shorter follow-up period (median of 46 months), demonstrated that 21% avoided further dilatation or surgery, with a median time to repeat dilatation of 13.8 months. Again, in this study no difference was noted between those who needed repeat dilatation and those who did not when placed on immunomodulators or anti-TNF therapy. Eight per cent of patients had anti-TNF therapy prior to initial dilatation, which increased to 45% following dilatation in their cohort; this concurs with the proportions who were escalated in our study.

A systematic review by Hassan et al.[10] of 13 studies reported a similar technical success rate of 86% and a long-term efficacy of 58%, with a major complication rate of 2% overall. It also stated that a stricture length <40 mm was associated with a surgery-free outcome. Similarly, a stricture length < 40 mm was associated with a decreased risk of re-dilatation in our cohort on univariate analysis.

The only previous published study that reported a significant difference in terms of medical therapy was by Honzawa et al. in a small cohort of 25 patients.[17] Their data showed that patients who were commenced on immunomodulator therapy prior to initial dilatation had fewer repeat dilatations than those commenced post-dilatation (1.6 vs 4.8 $p = 0.04$); however, the intervals between dilatations were not significantly different.

The data surrounding the use of anti-TNF therapy for stricturing in Crohn's disease has differed widely. Initial studies suggested that anti-TNF worsened stricturing because the inflammatory component was replaced by fibrosis, with luminal narrowing.[18] Van Assche et al. [14] also reported that those treated with anti-TNF had higher rates of surgery. However, more recent data from ileal strictures shows that the progression to surgery is the same.[12] The successful treatment of symptomatic strictures with anti-TNF therapy

in several studies means that the inflammatory component can heal without stricturing.[19,20]

Endoscopic dilatation techniques differ between the previous published studies, and the reported immediate success rates vary between 73% and 100%. In our study we showed an excellent 53/54(98%) immediate success rate, without need for repeat dilatation in 17/54 (31%) or surgery in 82% of patients after a first dilatation.

There was a significant difference in the need for repeat dilatation between patients receiving escalation of medical therapy to combination treatment and those having no change to their medical therapy (45% vs 84%, respectively). The higher rates of clinical success may also be due to patients receiving dietetic support with a low-residue diet following the procedure.

Our study has some limitations. Due to its retrospective nature, similar to previous studies, it lacks a control group (of patients going direct to surgery), and patients were escalated as part of medical therapy, as determined by the clinician. The degree of luminal narrowing caused by inflammation versus fibrosis was unknown, and escalation of medical treatment would have been biased toward those having active inflammatory disease. Therefore, patients with active disease were likely selected to escalate to combination therapy with anti-TNFs and immunosuppressives, which may explain the positive effect on surgery- and re-dilatation–free survival. A further limitation was that Rutgeerts scoring was graded from endoscopic images, which would have precluded accurate grading in those in whom the scope could not be passed through the stricture (11%). Two out of three patients underwent surgery after initial dilatation, without escalation in medical therapy. After removing these patients, (HR 0.34; 95% CI 0.13–0.87, $p = 0.024$), combination therapy was still significant.

In a recent European Crohn's and Colitis Organisation statement on the topic, it was concluded that endoscopic balloon dilatation was safe and effective at avoiding surgery in patients with anastomotic stricture.[21] Infliximab injected locally with dilatation had significantly better outcomes. with avoidance of surgery in all 12 patients versus 3 out of 11 in the group that had dilatation alone.[22] The true benefit of these types of novel endoscopic treatments is still unknown, and further data is needed.

5. Conclusion

In summary, the long-term data from our cohort demonstrates that Crohn's anastomotic strictures can be successfully managed with endoscopic balloon dilatation and may not need further surgery. Escalation of medical therapy in those with active inflammatory disease at the site of the anastomosis (to include combination therapy with a thiopurine and anti-TNF) appears to reduce the need for repeat dilatation and surgery. Moreover, severe active inflammation (Rutgeerts) at the anastomosis may predict the need for further surgery; thus, escalating medical therapy early in this group could possibly alter the outcome in the long term.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Disclosures

Nik Ding: Abbvie Advisory board; Falk Advisory Board.

Author Contributions

Analysis and interpretation of data: NSD, YWM, CHC, STG, AHu, AHa. Drafting of the manuscript: NSD, CHC. Critical revision of the manuscript for important intellectual content: NSD, YWM, CHC, STG, NA, AHu, AHa. Statistical analysis: NSD, YWM, CHC, AHu. Administrative: NSD, STG, NA, AH, AHa. Technical: NSD, BS, NA, AH, AHa. Study supervision: BS, STG, NA, AH, AHa.

The manuscript, including related data, figures and tables has not been previously published, and the manuscript is not under consideration elsewhere.

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