



## Alimentary Tract

# Predictors of early recurrence after strictureplasty for Crohn's disease of the small bowel during the years of biologics<sup>☆</sup>



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## ABSTRACT

**Background:** The identification of patients prone to early recurrence of Crohn's disease at the site of a strictureplasty is fundamental in the clinical practice.

**Aims:** Aim of the study is to detect the risk factors for early reoperation for recurrence after primary strictureplasty.

**Methods:** From 2000, patients undergoing a primary strictureplasty and a subsequent reoperation for recurrence of Crohn's disease at the site of a strictureplasty were included. Univariate and multivariable linear regression models were performed to analyse the relationship between the time to recurrence and independent variables.

**Results:** Fifty-nine patients were included. Median time to recurrence was 4.5 years (0.7–12.6). At the multivariate linear regression, early relapse was significantly associated with use of biologics before primary surgery ( $-2.69$ ,  $p < 0.0001$ ) and location of disease in the ileum ( $-1.61$ ,  $p 0.017$ ). The use of biologics after surgery was similar between groups (40.7 vs 37.5%,  $p 0.79$ ).

**Conclusions:** The location of Crohn's disease in the ileum and the use of biologics before surgery are strong predictors of early site-specific recurrence after strictureplasty. In this group of patients, a tailored follow-up and aggressive postoperative treatment should be considered.

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## 1. Introduction

Crohn's disease is characterized by the tendency to recur despite radical surgery. Over a quarter of patients require a reoperation within five years, and the proportion of symptomatic relapses increases over time [1]. The risk of developing short bowel syndrome is a serious concern among physicians and patients dealing with such a complex disease. Therefore, several bowel sparing techniques were developed in the past years. Strictureplasties have been proven to be effective and safe, and authors from recognized referral centres analyzed the long-term outcomes of the procedure and identified the variables correlated with recurrence [2–7].

However, the analysis of the timing of recurrence of disease at the site of the strictureplasty has not been addressed in details. In particular, little is known about the risk factors associated with an early relapse.

Moreover, the majority of the aforementioned studies included patients who had surgery before the introduction of anti-TNF (tumor necrosis factor) drugs, and whether the pre- or postoperative use of biologics might influence the timing of recurrence after bowel-sparing surgery is still unclear.

The aim of the present study is to analyse patients' characteristics, use of biologics, location of disease and long-term outcomes in order to identify the factors related with an early relapse of Crohn's disease on the site of a strictureplasty.

## 2. Materials and methods

Patients who underwent a strictureplasty for CD of the small bowel and ileocecal valve in our tertiary centre were retrospectively identified. Patients who experienced a surgical recurrence

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(defined as a relapse of CD at the site of a strictureplasty requiring a reoperation) were included in the study. As the aim of the study was to investigate the specific outcomes of the strictureplasty, the onset of disease at any other site was not censored as a recurrence.

Only patients who had both operations (primary strictureplasty and reoperation for recurrence) in our centre were included. Such limitation was necessary in order to reduce the bias of the different definitions of surgical technique, extension of disease and location of the strictures among centres. All patients were treated by the same multidisciplinary team; therefore, the indications to biological therapy and surgical treatment were homogeneous among patients.

According to the introduction of biologics in our clinical practice (late 90's), only patients who had the primary strictureplasty after 2000 were included in the study, thereby assuring that all had access to anti-TNF medication both before and after surgery. Exclusion criteria were colonic, stomach and duodenum strictureplasty, and lack of significant surgical details and follow-up.

Patient's characteristics, duration of disease, comorbidities, medical and surgical history were recorded. Strictureplasties were divided into conventional (Heineke-Mikulicz and Finney) and non-conventional (side-to-side isoperistaltic, disease-to-disease free, and other modifications) techniques.

The location of Crohn's disease was defined as jejunum, ileum and terminal ileum, according to the description in the operative notes. No existing classification was used, as none of them actually distinguishes the three segments of small bowel, and this was found to be a limitation in our practice. Terminal ileum was defined as the last 50 cm of the small bowel and included the ileocecal valve. The jejunum and ileum are usually macroscopically discernible, as the jejunum tends to present with a thicker wall, longer vasa recta and less arterial arcades. The location and extension of the strictures were reported in details in the operative notes, as well as the specifics of the strictureplasty (number, length of the stricture, technique) and/or the resection. Any lack of these variables was considered an exclusion criterion.

Perioperative complications were defined according to the Clavien–Dindo classification [8].

Complications, need of reoperation, use of biologics and changes of smoking habits during the follow-up after surgery were recorded.

Time to recurrence was dichotomized using the median value as a cut-off, in order to arbitrarily create two groups of patients according to the timing of relapse (EARLY and LATE recurrence).

### 2.1. Statistical analysis

Variables were presented as median (range) or number (%). Comparison of categorical variables was analyzed with Chi-square or Fisher's exact test as appropriate, and Wilcoxon rank sum test was used for quantitative and ordinal variables.

Univariate and multivariable linear regression models were performed to study the relationship between the time to recurrence and some independent variables.

To evaluate the best model fit, adjusted R-squared, Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were calculated and reported. The results of the linear regression were reported as coefficient (95% Confidence Interval). In the univariate linear regression of "time to recurrence" (in years) by independent variables, the coefficient summarizes the change in "time to recurrence" per unit increase of the independent variables, as well as in the multivariate linear regression, after adjusting for simultaneous linear change in independent variables.

The Kaplan–Meier curves were reported to graphically analyse the recurrence; the log-rank test was performed to compare the

**Table 1**

Demographic and disease characteristics at the time of the primary strictureplasty surgery of patients who experienced a site-specific recurrence of Crohn's disease, and timing and pattern of the recurrence. Variables are expressed as number (%) or median (range).

	N or median	% or range
Primary surgery		
Total number of patients	59	
Male gender	38	65.5%
Age	42	22–72
Body mass index	20.8	14.9–29.4
Duration of disease (years)	9.2	0.3–29.2
Biologics before surgery	18	30.5%
Smoking before surgery	21	35.6%
Previous surgery for Crohn's disease	23	39%
Location of disease		
Terminal ileum	44	74.6%
Ileum	24	40.7%
Jejunum	19	32.2%
Associated resection	32	54.2%
Location of associated resection		
Terminal ileum	20	33.9%
Ileum	12	20.3%
Jejunum	5	8.5%
Location of strictureplasty		
Terminal ileum	31	52.5%
Ileum	34	57.6%
Jejunum	14	23.7%
Conventional strictureplasty	47	79.6%
Nonconventional strictureplasty	25	42.3%
Number of strictureplasty/patient	2	1–16
Pattern of recurrence over the follow-up		
Median follow-up time (months)	126.8	15.1–209.2
Median time to recurrence (years)	4.5	0.7–12.6
Recurrence of conventional strictureplasty	44	93.6%
Recurrence of nonconventional strictureplasty	19	76%
Biologics between strictureplasty and recurrence	23	39%
Smoking between strictureplasty and recurrence	17	28.8%

recurrence-free rate over the follow-up between subgroups (use of biologics, location of strictureplasty).

A p value <0.05 was considered significant. Statistical analyses were performed using Stata/SE 14.1 for Windows (StataCorp LLC, College Station, TX, USA).

The study was approved by the local Ethical Committee.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Alma Mater Studiorum University of Bologna.

### 3. Results

Since 2000, 2453 surgical procedures for Crohn's disease were performed in our centre. Of these, 311 procedures containing at least one strictureplasty were identified. Among these patients, the analysis of long-term outcomes revealed a site-specific recurrence rate of 3.2% at 3 years, 12.1% at 5 years, and 23.2% at 10 years.

After the application of the exclusion criteria, 59 patients (65.5% male) were included in the study, as they underwent a reoperation for a recurrence of CD on a strictureplasty previously performed in our centre. A total of 217 strictureplasties were performed during the primary surgery (median number of strictureplasties per patient: 2, range 1–16). Demographic and disease characteristics at the primary surgery are summarized in Table 1.

Biologic therapy was administered before the primary strictureplasty in 30.5% of patients. The use of anti-TNF drugs was not homogeneously distributed along the study period: between 2000 and 2006 only 7.1% of patients received biologics before the primary surgery, compared to 51.6% of those who had surgery from 2007 to 2014. On the opposite, a similar rate of postoperative use

**Table 2**

Comparison of demographics, disease characteristics and operative variables patients who experienced an EARLY (<4.5 years) or LATE ( $\geq 4.5$  years) recurrence of Crohn's disease at a strictureplasty site. ASA: American Society of Anesthesiologists. Variables are expressed as number (%) or median (range). p Value <0.05 was considered significant.

	Early	Late	p Value
Number of patients	27	32	
Length of follow-up (months)	91.3 (39–184)	139.6 (15–209)	0.012
Time to recurrence	2.7 (0.7–4.4)	6.45 (4.5–12.6)	0.0001
Age	39 (26–63)	44.5 (22–72)	0.22
Male gender	17 (63%)	21 (65.6%)	0.70
Body mass index	21 (16.7–25.6)	20.7 (14.9–29.4)	0.54
Duration of disease (years)	5.3 (0.3–22.4)	10.3 (0.3–29.2)	0.13
Extraintestinal manifestations	4 (14.8%)	5 (15.6%)	0.93
Previous abdominal surgery	8 (29.6%)	7 (21.9%)	0.49
ASA score 3	6 (22.2%)	3 (9.4%)	0.17
Biologics before surgery	14 (51.8%)	4 (12.5%)	0.0011
Smoking before surgery	9 (33.3%)	12 (37.5%)	0.74
Previous surgery for Crohn's disease	11 (40.7%)	12 (37.5%)	0.79
Biologics between strictureplasty and recurrence	11 (40.7%)	12 (37.5%)	0.79
Smoking between strictureplasty and recurrence	7 (25.9%)	10 (31.3%)	0.65
Location of disease			
Terminal ileum	20 (74.1%)	24 (75%)	0.93
Ileum	22 (81.4%)	13 (40.6%)	0.0011
Jejunum	8 (29.6%)	11 (34.4%)	0.69
Location of strictureplasty			
Terminal ileum	11 (40.7%)	20 (62.5%)	0.095
Ileum	22 (81.4%)	12 (37.5%)	0.0005
Jejunum	6 (22.2%)	8 (25%)	0.80
Type of strictureplasty			
Conventional strictureplasty	23 (85.2%)	24 (75%)	0.33
Nonconventional strictureplasty	11 (40.7%)	14 (43.7%)	0.81
Number of strictureplasties/patient	3 (1–16)	2 (1–14)	0.030
Associated resection	19 (70.3%)	13 (40.6%)	0.021
Location of associated resection			
Terminal ileum	11 (40.7%)	9 (28.1%)	0.30
Ileum	9 (33.3%)	3 (9.4%)	0.021
Jejunum	0	5 (15.6%)	0.010

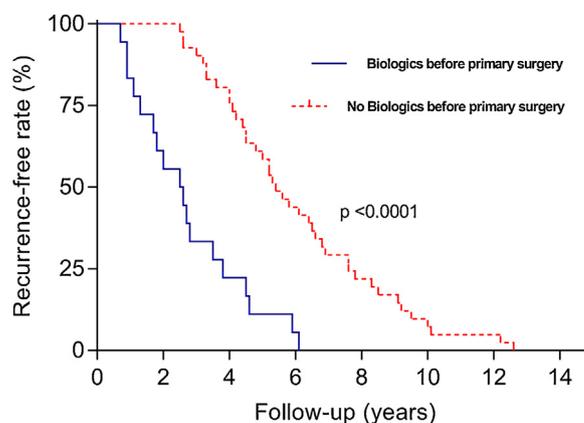
of biologics (between the first strictureplasty and the recurrence) was observed in the two surgery periods (39.2% vs. 38.7%).

The analysis of the location of disease (terminal ileum, ileum and jejunum) showed that 42 patients (71.2%) had Crohn's disease located at a single tract, while 14 (23.7%) and 3 (5.1%) presented with active disease at two or all three locations. In particular, the terminal ileum was the most common site of disease (74.6% of patients), followed by the ileum (40.7%) and the jejunum (32.2%).

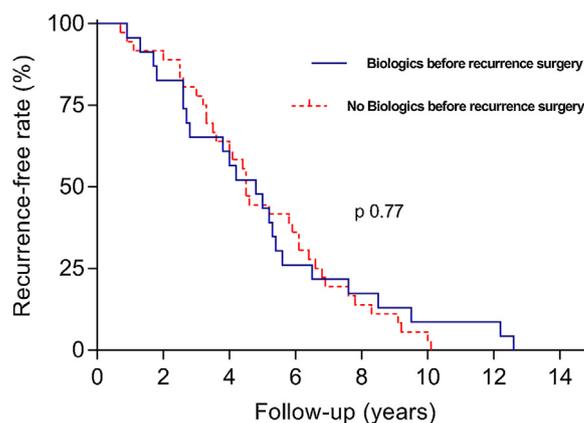
The majority of patients (54.2%) required a resection associated with the strictureplasty.

The median follow-up time was 126.8 months (15.1–209.2) and the median time to recurrence was 4.5 years (0.7–12.6).

Two groups of patients (EARLY and LATE) were arbitrarily created according to the time of relapse (< or  $\geq$  than the median time of recurrence). The comparison between groups showed similar age, gender, rate of previous surgery for Crohn's disease and extraintestinal manifestations. The median duration of disease before primary surgery was almost twice as long in LATE group (10.3 vs. 5.3 years), although the difference was not statistically significant. (Table 2) The rate of biologics before primary surgery was significantly higher in EARLY group (51.8 vs. 12.5%, p 0.0011). On the contrary, the use of anti-TNF drugs after the primary surgery did not correlate with the time to recurrence (40.7% and 37.5% in EARLY and LATE group).



**Fig. 1.** Comparison of the site-specific recurrence-free rate after strictureplasty of the small bowel by the use of anti-TNF alpha drugs before primary surgery.



**Fig. 2.** Comparison of the site-specific recurrence-free rate after strictureplasty of the small bowel by the use of anti-TNF alpha drugs between primary surgery and recurrence.

The Kaplan–Meier curves graphically reported the comparison of the recurrence rate according to the use of biologics before (Fig. 1) and after (Fig. 2) the primary operation, and confirmed that biological therapy before the original strictureplasty surgery was strongly associated with early relapse ( $p < 0.0001$ ).

The site of disease was strongly associated with the timing of recurrence. In particular, 81.4% of patients in the EARLY group had a location of Crohn's in the ileum (compared to 40.6% LATE cases, p 0.0011), treated by strictureplasty (81.4% vs. 37.5%, p 0.0005) and/or resection (33.3% vs. 9.4%, p 0.021).

The results of the univariate and multivariate linear regression are reported in Table 3.

At the univariate regression, preoperative use of biologics (coefficient  $-3.3$ ,  $p < 0.0001$ ), associated resections (coefficient  $-1.9$ ,  $p 0.007$ ) and location of the strictureplasty in the ileum (coefficient  $-2.65$ ,  $p < 0.0001$ ) were significantly associated with a shorter time to recurrence. At the multivariate regression, only biologics ( $-2.69$ ,  $p < 0.0001$ ) and location at the ileum ( $-1.61$ ,  $p 0.017$ ) maintained a significant relationship with an early relapse. Adjusted R-squared (0.40), Akaike's information criterion (262.3) and Bayesian information criterion (270.6) confirmed the validity of the model fit.

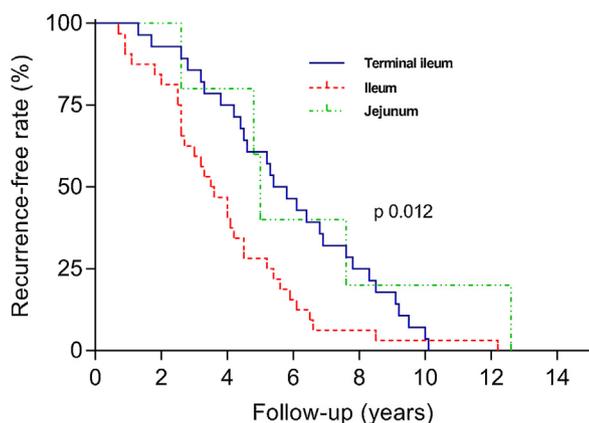
Fig. 3 shows the rate of surgical recurrence over the follow-up according to the location of the strictureplasties.

The recurrence-free rate at 4 years was 80% (at 8 years 20%), 75% (at 8 years 25%) and 40.6% (at 8 years 6.2%) if the location of the recurrence was located respectively in the jejunum, terminal ileum and ileum (p 0.012).

**Table 3**

Univariate and multivariate linear regression: relationship between independent variables and time to recurrence (years). At the multivariate, only variables significantly associated at the univariate analysis were included. CI: confidence interval. p Value <0.05 was considered significant. Akaike's information criterion: 262.3. Bayesian information criterion: 270.6. Adjusted R-squared: 0.40.

Variable	Coefficient	95% CI	p Value
Univariate linear regression			
Duration of disease	0.012	−0.09, 0.11	0.81
Biologics before surgery	−3.30	−4.6, −1.96	<0.0001
Biologics after surgery	0.05	−1.45, 1.55	0.94
Smoking after surgery	0.14	−1.47, 1.76	0.86
Associated resection at surgery	−1.92	−3.30, −0.53	0.007
Location of strictureplasty			
Terminal ileum	1.15	−0.28, 2.59	0.11
Ileum	−2.65	−3.96, −1.34	<0.0001
Jejunum	0.42	−1.29, 2.14	0.62
Conventional strictureplasty	−1.17	−2.97, 0.62	0.19
Nonconventional strictureplasty	0.27	−1.21, 1.75	0.72
Number of strictureplasties	−0.14	−0.33, 0.05	0.16
Multivariate linear regression			
Biologics before surgery	−2.69	−3.96, −1.41	<0.0001
Associated resection at surgery	−0.78	−2.05, 0.48	0.22
Location of strictureplasty: ileum	−1.61	−2.93, −0.30	0.017



**Fig. 3.** Comparison of the site-specific recurrence-free rate after strictureplasty of the small bowel by location of the strictureplasties affected by recurrence.

#### 4. Discussion

Strictureplasties are widely accepted as a safe and effective alternative to bowel resection for the treatment of Crohn's disease of the small bowel and ileocecal valve. The most recent ECCO (European Crohn's and Colitis Organisation) guidelines state that "strictureplasty and intestinal resection are reasonable options for short strictures" and that, in particular, "short small bowel strictures are best treated with the Heineke-Mikulicz technique, and longer strictures with Finney-like procedures or isoperistaltic strictureplasty" (EL4) [9]. Few single-centre studies and the two most recent meta-analyses reported acceptable outcomes and rates of recurrence that were at least comparable with those observed after resection [5,6,10–12].

Strictureplasties have their limitations. The indication is limited to a subpopulation of Crohn's patients; in particular, whereas fistulae, abscesses and perforation are present, or in severely debilitated patients, resection has to be preferred. In the other cases, bowel sparing surgery should be considered, in order to reduce the risk of short bowel syndrome in the future.

Among the different studies, the time to recurrence ranges between few months and many years. Few risk factors for relapse have been identified. Sampietro et al., in their prospective study reporting the long-term outcomes after conservative surgery for

Crohn's disease of the small bowel, identified age at diagnosis, disease location (by the Vienna classification), stricturing disease, and increased bowel wall thickening at the 12 month postoperative ultrasound as significant risk factors for recurrence. Interestingly, the authors found that patients affected by a more proximal disease were more prone to develop a recurrence [7].

Crohn's disease is an incurable condition. Surgery treats the complications, but a relapse is somewhat expected in these usually young patients. The disease has its own course regardless of the surgical technique, and patients undergoing a strictureplasty will require a reoperation more likely due to the onset of disease at another site of the alimentary tract. The site-specific recurrence is much less common. Our study indirectly supports this conclusions. The median time to (a site-specific) recurrence is 4.5 years (the median follow-up time is over 10 years). However, some patients reported a recurrence as early as few months after the primary operation. In other cases, a relapse was diagnosed after over 12 years of indolence. It is not clear which patients, among those who eventually will experience a recurrence of the disease, are at higher risk of an early relapse.

The variables associated with a shorter disease-free time after strictureplasty have not been properly investigated. Whether the time to recurrence depends exclusively on the disease characteristics or the surgical technique has a role, is not known. Similarly, the impact of biologics on the long-term outcomes after surgery is still unclear.

The identification of those patients who are prone to develop early relapse after strictureplasty could help the clinician to tailor the surgical plan (planning a resection instead of strictureplasty, for instance) and the postoperative follow-up. In such view, the analysis of the site-specific recurrence is of primary importance, in order to highlight variations between different techniques and/or location of disease.

The effects of anti-TNF Alfa drugs on the progression of Crohn's disease are still debated. Initial reports found decreased hospitalization and number of procedures after the introduction of Infliximab therapy [13,14]. On the contrary, more recent population studies showed increased rates of hospital admission and a similar proportion of surgery for symptomatic disease [15,16]. The effect of biologics on the timing of recurrence is still unknown [17].

To our knowledge, this is the first study assessing the long-term outcomes of strictureplasty in the era of biologics. The study period was carefully selected in order to include only patients who could have had access to biologics before and after surgery, in order to reduce the bias associated with a non-homogeneous population. As the biologics were introduced in the clinical practice in the late 90's, only patients having surgery from 2000 were included.

A higher proportion of patients affected by an EARLY recurrence underwent biological therapy before surgery (51.8 vs. 12.5%, p 0.0011). The association between preoperative use of biologics and timing of recurrence was also confirmed at the multivariate linear regression. This likely reflects the presence of a more aggressive disease (requiring a stronger treatment) before the primary surgery. In this sense, a trend towards an earlier relapse should be expected in this group of patients.

On the opposite, the use of anti-TNF Alfa after surgery did not seem to affect the timing of relapse, as shown in Fig. 2. The retrospective nature of the study did not allow to analyse the indication and timing of biologics after surgery. There is evidence that early disease is more responsive to medical therapy than late or recurrent one [18,19]. Moreover, some authors proved that a pre-emptive rather than late treatment with Infliximab after surgery was associated with a lower rate of reoperations [20,21].

Despite the initial evidence that postoperative relapse of Crohn's disease could be reduced or delayed by an early employment of bio-

logics, the PREVENT study showed that Infliximab was not superior to placebo in preventing recurrence of Crohn's disease after surgery [22]. The use of biologics before primary surgery was found to be a significant risk factor of recurrence also in this randomized trial.

The PREVENT study included only patients undergoing ileocecal resections for Crohn's disease of the terminal ileum. Such limitation, although necessary to provide a homogeneous study group, does not reflect the complexity of patients undergoing surgery for Crohn's disease.

In our study, the terminal ileum location was associated with a LATE presentation of relapse (62.5 vs. 40.7%,  $p$  0.095). Taking into account all the limits of the present study, it could be argued that a disease located in the terminal ileum tends to develop in a more indolent way. This might partially explain why the PREVENT study did not show any effect of the biologics on the clinical recurrence.

On the opposite, strictureplasties of the ileum are more likely affected by an EARLY relapse (81.4 vs. 37.5%,  $p$  0.0005 at the univariate comparison,  $-1.61$ ,  $p$  0.017 at the multivariate linear regression).

Other authors showed that the site of disease could be associated with different behaviors of presentation of Crohn's disease [23,24]. Sampietro et al. showed that a more proximal location was associated with a higher risk of recurrence [7]. However, the authors reported the location of disease using the Vienna classification, which arranges the disease located more proximally than the terminal ileum in the same group. Our study shows that the current classifications lack of site-specificity, in particular regarding the L4 group (any location proximal to terminal ileum) [25]; according to our results, the jejunum and the ileum locations are associated with totally different outcomes, especially regarding the time to recurrence. As shown in Fig. 3, in our study population (therefore including only patients who experience a relapse), the recurrence occurred twice as faster when located in the ileum. This evidence is so far limited to patients undergoing a strictureplasty, but it's possible that a similar behavior could be found in all patients affected by CD, regardless of the surgical technique.

Should this trend be confirmed within a larger population, the existing classifications should be discussed in order to report the exact location of the disease in the small bowel.

The univariate comparison between groups showed that the duration of Crohn's disease before primary surgery was almost twice as long in the LATE group (10.3 vs. 5.3 years,  $p$  0.13), possibly suggesting that a more indolent disease is likely to maintain the same behavior also postoperatively. A similar finding was shown by Dietz et al. [2]. However, the univariate and multivariate linear regression did not confirm the initial evidence of a possible impact of the disease duration on the postoperative outcomes.

The limits of the present study are the retrospective nature and the lack of details about the indication to anti-TNF Alfa drugs. However, the rigorous inclusion criteria reduced the bias associated with the population case-mix.

The relationship between the specific location of disease in the small bowel and the behavior of disease after surgery will need to be investigated in larger, and possibly prospective, series of Crohn's patients undergoing any surgical procedure.

At the moment, there is no clear evidence that biologics might retard the postoperative recurrence of Crohn's disease. Large, randomized studies failed to show any efficacy of Infliximab in preventing recurrence of the disease after ileocecal resection [22]. However, as previously highlighted, the observation was limited to a specific subgroup of patients undergoing only ileocecal resection. Moreover, other biologic drugs have been developed, and their effectiveness has still to be evaluated. Crohn's disease is a complex entity, associated with a variety of phenotypes and behaviors which depend on several characteristics, including, for instance, the location of disease. These different presentations seem to be asso-

ciated with different outcomes after medical or surgical treatment, and most of the variables associated with such heterogeneity of response are still to be identified.

Nevertheless, in the meanwhile, biologic therapy remains the most effective therapy for Crohn's disease and should be considered as a first line of treatment, especially in those patients at a higher risk of early recurrence after conservative surgery for Crohn's disease.

## 5. Conclusions

Taking into consideration the greater risk of early relapse, patients who had a strictureplasty of the ileum should undergo a more careful follow-up. Given the unclear role of biologics in preventing postoperative recurrence of disease, a tailored, preemptive medical treatment immediately after surgery might also be considered in this subgroup of patients.

## Conflict of interest

None declared.

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