



## Updating predictors of endoscopic recurrence after ileocolic resection for Crohn disease

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### ABSTRACT

**Background/Aims:** Identifying predictors of endoscopic recurrence (ER) has become very important to guide the decision of postoperative strategy. This study aimed to determine the rate of endoscopic recurrence until 12 months after ileocolic resection for Crohn disease (CD) in a cohort and identify its possible predictors.

**Materials and Methods:** We conducted a retrospective single-center study that included patients with CD who underwent ileocolic resection between 2003 and 2014. ER was defined according to the Rutgeerts' score, defined as i2, i3, or i4 at ileocolonoscopy that was performed 6-12 months after surgery. The patients were classified into two groups according to the Rutgeerts' score: non-ER (Rutgeerts' i0/i1) and ER (Rutgeerts'  $\geq$ i2). Multivariate logistic regression analysis was performed, including significant variables on univariable analysis, to identify ER predictors.

**Results:** Forty-two patients were included. The mean period of the first postoperative colonoscopy was 9 months, and ER was observed in 25 patients (59.5%). The perianal disease and shorter duration of CD were the only ER predictors ( $p=0.024$ ; OR, 8.36; 95% CI, 1.329-52.642 and  $p=0.039$ ; OR, 0.965; 95% CI, 0.933-0.998, respectively).

**Conclusion:** Endoscopic recurrence affects almost two-thirds of patients with CD after ileocolic resection, with perianal involvement and a shorter duration of disease being significant risk factors. These factors may indicate a more aggressive disease associated with rapid progression and support the need of intensive early treatment to improve patients' outcomes.

**Keywords:** Crohn disease, endoscopy, surgery

### INTRODUCTION

Crohn disease (CD) is characterized for periods of exacerbation that alternate with periods of remission (1). Even with the great advances on CD pathogenesis and available therapeutic options, most of the patients require an intestinal surgery during their lifetime (1,2).

Endoscopic recurrence (ER) is defined as the reappearance of lesions after complete surgical resection. New lesions can recur in the anastomotic region within weeks to months of surgery, and after ileal resection, nearly 80% of the patients have new lesions in the neo-terminal ileum within 1 year after resection (3,4).

Endoscopic recurrence is determined by the presence of inflammation and ulceration and is categorized according to the Rutgeerts' score (3). There is a gap between clinical recurrence and ER, and the severity of endoscopic lesions post-surgery predict clinical relapse (3). Once clinical relapse interferes with the patient's quality of life, it is essential to stratify the risk for post-surgery relapse (5). Therefore, an ileocolonoscopy evaluation within the first year after resection may be useful for stratifying patients at a high risk for clinical recurrence (3).

This study aimed to determine the rate of ER and to determine ER predictors in patients with CD at 6-12 months after surgery.

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**MATERIALS AND METHODS**

We reviewed and analyzed the medical records of a cohort at a single center who underwent ileocolic resection for CD between January 2003 and December 2014. All data were collected from the general electronic data system of the Hospital da Senhora da Oliveira, Guimarães, Portugal.

Patients with incomplete surgical resection and positive margins on the surgical specimen; who were scheduled for a follow-up period of < 1 year; who had previous history of stricture-plasty, bowel or colonic resection, and perianal surgery; and who did not undergo colonoscopy within 1 year after surgery were excluded. The median time to the first ileocolonoscopy after surgery was determined.

Patients were classified into two groups according to the Rutgeerts' score (3): non-ER (Rutgeerts i0/i1) and ER (Rutgeerts ≥i2). The potential risk factors for ER (≥i2) were analyzed and divided into four groups: factors related to the patient, disease, surgery, and pharmacological treatment.

Regarding the indication for surgery, patients were divided into two groups (6). Perforating indication was defined as acute free perforation, subacute perforation with an abscess, and chronic perforation fistula formation. Non-perforating indication was defined as intestinal obstruction, medical intractability, hemorrhage, and toxic dilation (6).

This study was conducted according to principles of the World Medical Association Declaration of Helsinki. Anonymous clinical data were obtained after each patient agreed to the procedure by providing written informed consent.

**Statistical Analysis**

Statistical analyses were performed using Statistical Package for Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA). A multivariate logistic regression analysis was performed that included only factors that were significant on univariable analysis to identify factors associated with ER. Thus, p values of <0.05 were considered to be statistically significant.

**RESULTS**

Seventy patients of our center underwent ileocolic resection. Complete medical records were obtained from 58 patients; however, only 42 patients met our inclusion criteria. Of these, 50% were females and had a mean age of 29.2 years [interquartile range (IQR), 21-34.8 years] at CD diagnosis.

The first colonoscopy on follow-up was performed at an average of 9 months (IQR, 6-12 months) after surgery, and an overall ER was observed in 59.5% of patients (25 of 42); of those, 52% of patients (13 of 25) had severe ER (≥i3) (Table 1).

Clinical observations and demographics of these patients and their medical therapy were comparable between the ER and

**Table 1.** Rutgeerts' score

Rutgeerts	N (%)
i0	14 (33.3)
i1	3 (7.1)
i2	12 (28.6)
i3	8 (19)
i4	5 (11.9)

**Table 2.** Factors related to the patient and to medical therapy

Variable	ER	Non-ER	p
<b>Gender</b>			0.346
Female	11	10	
Male	14	7	
<b>Family history of IBD</b>	2	0	0.506
<b>Age at surgery</b> (years) (mean±SD)	30.3±10.9	35.3±10.2	0.141
<b>Smoking</b>			1
Never smoked	16	9	
Current smoker	8	5	0.331
Ex-smoker	1	3	
<b>Preoperative medications</b>			
Corticosteroids	13	6	0.353
Mesalamine	12	6	0.414
Azathioprine	11	8	1
Anti-TNF drugs	4	2	1
<b>Postoperative medications</b>			
Mesalamine	12	10	0.491
Azathioprine	19	12	0.733
Anti-TNF drugs	6	5	0.733
<b>Start time of mesalamine after surgery</b> (days) (mean±SD)	22.3±31.7	11.4±18.1	0.350
<b>Start time of AZT after surgery</b> (days) (mean±SD)	38.7±28.9	76.3±68.9	0.083
<b>Start time of anti-TNF drugs after surgery</b> (days) (mean±SD)	49.8±36.7	44.4±17.2	0.769

AZT: azathioprine; ER: endoscopic recurrence; IBD: inflammatory bowel disease; SD: standard deviation; TNF: tumor necrosis factor

non-ER groups (Table 2). None of these factors were associated with ER. The median age of the patients at the time of resection was 32.3 years (IQR, 23-41.3 years).

At the time of surgery, 25 patients (59.5%) had never smoked, 13 (31%) were current smokers, and 4 (9.5%) were ex-smokers.

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**Table 3.** Disease related factors

	ER	Non-ER	p
<b>Age at diagnosis</b>			
A2	19	14	0.716
A3	6	3	
<b>Disease location</b>			
L1	10	5	0.482
L3	15	12	
<b>Disease behavior</b>			
B2	8	5	0.859
B3	12	17	
<b>Perianal disease</b>			
	13	2	0.008
<b>Disease Duration</b> (months) (mean±SD)			
	13.9±17.7	59.2±70.4	0.019
<b>ERS</b> (mm/hour) (mean±SD)			
	18.8±14.7	15.1±14.3	0.423
<b>CRP</b> (mg/L) (mean±SD)			
	8.8±16.5	7.2±13.1	0.727

CRP: C reactive protein; ER: endoscopic recurrence; ERS: erythrocyte sedimentation rate; SD: standard deviation

**Table 4.** Surgery-related factors

	ER	Non-ER	p
<b>Timing of surgery</b>			
Elective	14	10	0.856
Urgent	11	7	
<b>Indication</b>			
Perforating	17	11	0.824
Non-perforating	8	6	
<b>Surgical procedure</b>			
Open	23	16	1
Laparoscopic	2	1	
<b>Type of anastomosis</b>			
Side to side	24	16	1
End to side	1	1	
<b>Postoperative complications</b>			
Intra-abdominal abscess	1	2	0.556
Anastomotic dehiscence	2	1	1
<b>Extension of the specimen</b> (cm) (mean±SD)			
	37.7±16.1	36.2±25.2	0.813
<b>Granulomas in surgical specimen wall</b>			
	12	7	0.663
<b>Granulomas in mesenteric lymph nodes</b>			
	2	4	0.202

ER: endoscopic recurrence; SD: standard deviation

Only 2 patients (4.8%) had a family history of inflammatory bowel disease.

The choice to initiate prophylactic therapy after surgery with azathioprine, anti-TNF drugs, or both in combination were based on the penetrating phenotype and other aggressive disease factors, such as perianal disease and age <40 years at diagnosis in 83.3% of patients (35 of 42).

After surgery, 31 patients took azathioprine; of these, 19 had ER (p=0.733). Eleven patients took anti-tumor necrosis factor (anti-TNF) drugs after surgery; of these, 6 had ER (p=0.733). Disease-related factors were compared between the two groups, as shown in Table 3. The median duration between CD diagnosis and surgery was 32 months (range, 0-254 months).

According to the Montreal classification, the majority of our patients were A2 (78.6%). Regarding the disease location, 35.7% exhibited disease in the ileum (L1), 64.3% in the ileocolic, and none with only colon involvement. Patients mainly presented with penetrating behavior (L3) (69%), and 31% had stricturing disease (L2). None of the patients concomitantly presented with upper gastrointestinal tract involvement.

Of the 15 patients with perianal disease, 13 had ER on follow-up (p=0.008). There was a higher incidence of ER in patients with a shorter duration of disease (13.9 vs. 59.2 months, with ER and non-ER, respectively, p=0.019). Table 4 shows surgery-related factors that were compared between the two groups.

Patients underwent ileocolic resection for strictures (33.3%), abscess and fistula (52.4%), and free perforation (14.3%). Among the 28 patients with perforating indications, 17 had ER; eight of the 14 patients with non-perforating indications had ER, without significant statistical difference between the two groups (p=0.824).

An urgent operation was performed in 18 patients (42.9%).

The mean length of the intestine resected was 37.1±20 cm, none with a large intestinal resection. We found no association with regard to the intestine length resected and ER (p=0.813).

The presence of wall granulomas was noted in 19 patients (45.2%), 12 in ER patients, and 7 in patients without ER (p=0.663). The granulomas of mesenteric lymph nodes were identified in 6 (14.3%) patients: 2 with ER and 4 without ER (p=0.202).

In the multivariate analysis, the perianal disease and shorter duration of CD remained the only ER predictors (p=0.024; OR, 8.36; 95% CI, 1.329-52.642 and p=0.039; OR, 0.965; 95% CI, 0.933-0.998, respectively).

## DISCUSSION

Crohn disease surgery is not curative because the disease often recurs in the remaining bowel (3). According to the European Crohn's and Colitis Organisation consensus, the following factors have been shown to predict early postoperative recurrence in the majority of studies: smoking, prior intestinal surgery, penetrating disease behavior, perianal involvement, and extended small bowel resection (>100 cm) (7).

Although they are, by consensus, risk factors for postoperative recurrence, there are a disparity of results between several studies that may be explained by the ambiguous definition of disease recurrence and the type and number of predictors factors included. In fact, according to the literature, the recurrence rate varies as per the criteria used for diagnosis: clinical, endoscopic, radiological, or surgical.

The term recurrence refers to the appearance of lesions after surgery, which is evaluated using imaging methods (as ultrasound, computed tomography, or magnetic resonance imaging) or using endoscopy (7). Currently, ileocolonoscopy is the first-line method for diagnosing postoperative ER and is recommended to be performed during the first year after surgery (7).

Our analysis evaluated ER after and between 6-12 months of surgery according to the Rutgeerts' score and compared the risk factors between groups with ER and without ER. After ileocolic resection, we observed an ER of 59.5% after a mean of 9 months.

There was no statistical difference regarding sex and age at surgery between the groups with ER and without ER. Actually, sex has not been proven to be a risk factor for ER (7,8). Additionally, there is conflicting evidence regarding the effect of age on the risk for ER; therefore, it is not a definite risk factor for ER (7,9,10).

Although we did not find a statistically significant difference in ER between the groups of smokers and nonsmokers probably because we had few smoker patients, most studies showed that it is a modifiable patient-related independent predictor (10-13).

As per the Montreal classification, none of the parameters showed a statistical difference relative to ER. Although in this study, the behavior of the disease according to the Montreal classification has not been shown to be a predictor of ER, the majority of our patients had a penetrating phenotype, and this has been consistently known to be a risk factor for an aggressive disease course and a predictor of ER in the literature (14-16).

In this study, the presence of perianal disease increased the risk for ER. It is well known that patients with a perianal disease are a subgroup of patients with a more severe disease, which has been associated to an increased risk for ER (2,17).

A shorter duration of CD in the ER group was found, with a statistical difference from the non-ER group, and has been established as a risk factor in our study. However, there is conflicting data regarding the association of the disease duration with the risk for ER (9). Several studies have shown the association between ER and the duration of the disease. Pogglioli et al. (18) found a higher incidence of ER in patients with disease duration of <6 years compared with patients with a duration of CD of >6 years. In contrast, Lautenbach et al. (19) found an association between the longer duration of disease and surgery.

The majority of patients had a perforating indication for surgery. We found no significant difference in ER between perforating and non-perforating indications. The role of surgical indication in CD recurrence remains controversial, with some studies suggesting that perforating CD results in a higher recurrence rate compared with non-perforating CD, whereas other studies have not shown a difference in recurrence (6,20-22).

In our series, there was no association between the extension of the surgical resection specimen and ER maybe because we did not have any case of extensive resection. Several studies have demonstrated that recurrence is higher after a long length resection of the diseased bowel (2). However, other studies have not shown this association (23).

There are contradictory reports about granulomas in the resection specimen on recurrence (16,24-26). In a recent report, the presence of granulomas in the mesenteric lymph nodes was found to be an independent risk factor for ER (27).

Several medications, such as mesalamine or antibiotics, have been advocated for the prevention of postoperative disease recurrence (28,29). However, the marginal role of mesalamine for preventing ER is currently known and with regard to metronidazole, loss of efficacy beyond 12 months and side effects precludes its use in the prevention of ER (7,29,30).

Thiopurines have been shown to reduce endoscopic and clinical recurrence postoperatively (31). Recent reports suggest that anti-TNF drugs, infliximab, and adalimumab can delay and reduce postoperative recurrence (32,33).

Statistically, postoperative medication (thiopurines or anti-TNF drugs) did not affect the rate of ER. This might be due to the fact that only 11 patients (26.2%) had not taken thiopurines and only 11 patients (26.2%) have been treated with anti-TNF drugs post-surgery. However, we can raise the hypothesis that the high number of our patients who maintained thiopurines post-surgery can decrease the ER rate because our rate of ER (59.5%) is lower than the Rutgeerts reports (3,4).

The optimal monitoring and prophylaxis strategy for postoperative recurrence has not been established. Some authors recommend prophylaxis with thiopurines, soon after surgery,

in high-risk patients (34). De Cruz et al. (35) recently reported that treatment, according to recurrence risk, and adjusting it on the basis of ileocolonoscopy findings at 6 months after surgery is better than conventional drug therapy alone for preventing postoperative CD recurrence.

There are several limitations to our study because it is a retrospective study design that reviews medical records and the number of included patients in each group may preclude a significant *p* value.

Nevertheless, our study revealed that almost two-thirds of CD patients had ER. Most of these had a severe ER ( $\geq 3$ ), with important implications for prognosis, with perianal involvement, and a shorter duration of disease, being significant risk factors. Therefore, identification of patients at high risk for ER allows a targeted approach of these patients, benefiting from increased monitoring and therapeutic prophylaxis and hoping for a better prognosis for these patients.

Further studies designed to analyze the impact of immediate prophylaxis after surgery in identified high-risk patients is warranted to find the best practice for these patients.

**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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