



Early post-operative endoscopic recurrence in Crohn's disease patients: Data from an Italian Group for the study of inflammatory bowel disease (IG-IBD) study on a large prospective multicenter cohort



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KEYWORDS

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Abstract

Introduction: The incidence of endoscopic recurrence (ER) in Crohn's disease following curative resection is up to 75% at 1 year. Endoscopy is the most sensitive method to detect the earliest mucosal changes and the severe ER at 1 year seems to predict a clinical relapse.

Methods: The aim of this prospective study was to evaluate the incidence of early ER 6 months after curative resection. Secondary outcome was to evaluate the role of 5-aminosalicylic acid (5-ASA) in the prevention of ER at 6 months. A total of 170 patients were included in the study. They were carried-out from the evaluation of the appearance of ER during a trial performed to assess the role of azathioprine vs. 5-ASA as early treatment of severe ER. All the patients started 5-ASA treatment 2 weeks after surgery.

Results: Six months after surgery ER was observed in 105 patients (62%). The endoscopic score was reported as severe in 78.1% of them (82 out of 105). At univariable analysis only ileo-colonic disease influenced the final outcome associating to a lower risk of severe ER ($p = 0.04$; OR 0.52, 95% CI 0.277–0.974).

Conclusion: In this prospective Italian multicenter IG-IBD study a great proportion of ER occur within 6 months from ileo-colonic resection, with a significant rate of severe ER. Furthermore this study confirms the marginal role of 5-ASA in the prevention of ER. This suggests that post-surgical endoscopic evaluation should be performed at 6 months instead of 1 year to allow an adequate early treatment.

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1. Introduction

More than 70% of patients with Crohn's disease (CD) require surgery at least once during the course of their disease.¹ The recurrence of CD after a curative ileo-colonic resection is one of the most important issues in the management of inflammatory bowel disease (IBD) and frequently leads to repeated surgical procedures. Endoscopy has proved to be the most sensitive method to detect post-surgical endoscopic recurrence (ER). Many endoscopic studies have shown that Crohn's lesions developed in the neoterminal ileo or in the ileo-colonic anastomosis within the first year after surgery.^{2–4} Rutgeerts et al. demonstrated in a prospective endoscopic cohort study that the post operative clinical course of CD is predicted by the severity of endoscopic lesions of disease during the first year after resection. Patients with none or mild lesions (Rutgeerts' score i0 and i1) seem to have a favorable post operative clinical course. In contrast, patients with severe endoscopic lesions (Rutgeerts' score \geq i2) seem to have a high risk of developing early symptoms and complications.² In the Rutgeerts' study the reported incidence of ER following curative resection was 73% at 1 year. Eighty-three percent of ER was severe suggesting an adequate timing of colonoscopy in order to consider a possible aggressive medical treatment. Over the last decade the prevention and management of post-operative ER have been modified by immunosuppressive and biologic treatments considering the evidence of their role in prevention of endoscopic and clinical recurrence.^{5–12} In order to identify earlier the patients at risk of severe ER, we performed a prospective Italian IG-IBD multicenter study evaluating at 6 months the endoscopic recurrence in CD patients who underwent a curative ileo-colonic resection. The aim of this study was to select a group of patients that could benefit from a more precocious therapy.

2. Materials and methods

2.1. Patients characteristics

From April 2005 to June 2010, 252 consecutive CD patients who had been treated by a first or second curative resection of the terminal ileum and part of the right colon were included in the study. Patients were enrolled from 11 Italian referral centers for IBD [Internal Medicine, Villa Sofia-Cervello Hospital, Palermo; Department of Gastroenterology, IRCCS, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (FG); Department of Gastroenterology, Federico II University, Naples; Gastroenterology unit, San Camillo Forlanini, Rome; Department of Gastroenterology, San Filippo Neri Hospital, Rome; Department of Internal Medicine, Policlinico Sant'Orsola Malpighi, Bologna; Department of Gastroenterology, Policlinico Umberto I Hospital, Rome; Department of Gastroenterology, Tor Vergata University, Rome; Department of Gastroenterology, Palermo University, Palermo; Department of Gastroenterology, Messina University, Messina; and Department of Gastroenterology, Padua University, Padua]. This prospective cohort was carried-out from the evaluation of the appearance of ER during a trial performed to assess the role of azathioprine (AZA) vs. 5-aminosalicylic acid (5-ASA) as early treatment of severe ER. The study was approved by the local institutional review board (IRB) and registered with the Eudract number of 2006-001315-30. In the current paper we analyzed data on early ER of patients enrolled in the trial. All the patients started 2.4 g daily of 5-ASA 2 weeks^{5,13} after surgery, according to the study protocol, until endoscopy. Patients who underwent conservative surgery (strictureplasty), patients operated on for Crohn's colitis without ileitis and patients in whom lesions were not removed, were excluded. Patients with active perianal CD were also excluded. Eighty-two patients did not undergo

colonoscopy at 6 months: 39 according to the exclusion criteria, 30 refused and 13 were lost during the follow-up. The remaining patients were enrolled in this study after signing an informed consent. The length of ileo-colonic resection depended on the presence and extension of the ileo-colonic disease constructing the anastomosis in a macroscopically uninvolved tract of ileum and colon. Surgery was performed by skilled IBD surgeons in each referral center.

ER recurrence was evaluated according with Rutgeerts' score considering the appearance of endoscopic lesions in the neoterminal ileum and/or in the anastomotic line, at the mesenteric and antimesenteric border. Data were collected in an electronic database for the final analysis.

2.2. Outcomes

The main outcome of this study was to evaluate the rate of ER 6 months after surgery.

Secondary outcome was to evaluate the role of 5-ASA in the prevention of ER at 6 months.

2.3. Statistical analysis

Data were analyzed using the software package SPSS 15 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as means \pm SD or range when appropriate. Categorical variables were summarized as frequency and percentage. Significant differences were calculated using a χ^2 test for categorical variables. Demographic and disease variables were related to the main outcome (endoscopic recurrence) using univariable analysis (Mantel–Cox model). We considered the following variables: sex, age at diagnosis, smoking habit, disease duration, history of surgery, site of disease, history of immunosuppressants, history of fistulas and extraintestinal manifestations.

Differences were considered significant for p -value < 0.05 . We planned to carry out a multivariable analysis if we obtained a p -value < 0.05 at univariable analysis.

3. Results

A total of 170 patients (99 males [58%]), with a mean age at diagnosis of 32.7 ± 12.7 years, were evaluated in the final analysis and all the characteristics of the patients are summarized in Table 1. At 6 months from the resective surgery the cumulative postoperative ER was observed in 105 patients. As showed in Table 2, 65 patients (38.2%) had no lesions at the follow-up colonoscopy, 23 (13.5%) had a score of i1, 17 (9.1%) had a score of i2, 23 (13.5%) had a score of i3, and 42 (24.8%) had a score of i4. Finally the endoscopic score was reported as severe or very severe in 78.1% (82 out of 105). At univariable analysis only ileo-colonic disease influenced the final outcome associating to a lower risk of severe ER ($p = 0.04$; OR 0.52, 95% CI 0.277–0.974) as showed in Table 3.

The overall ER rate ($\geq i1$) was 61.7% (105 out of 170) despite the treatment with 5-ASA.

Table 1 Baseline characteristics of study population (N = 170).

	N (%)
Male/female	99 (58)/71 (42)
Mean age at diagnosis (years) \pm SD	32.7 \pm 12.7
Median disease duration (months), range	36 (1–429)
Smoking habit	
• Current smokers	55 (32.4)
• Non-smokers	83 (48.8)
• Ex-smokers	33 (18.8)
Luminal disease location	
• Ileocolitis	90 (52.9)
• Ileitis	80 (47.1)
Previous abdominal surgery	30 (17.6)
Fistulizing disease	36 (21.2)
Extraintestinal manifestations	25 (14.7)
History of immunosuppressants	43 (25.3)
Type of anastomosis	
• Latero-lateral	108 (63.5)
• Termino-lateral	42 (24.7)
• Termino-terminal	20 (11.8)

4. Discussion

In this prospective Italian IG-IBD multicenter study the ER at 6 months, in patients operated-on for ileal or ileo-colonic CD, was high with a significant rate of severe ER. ER was observed at 6 months in 61.7% (105 out of 170) of the patients and 78.1% of these (82 out of 105) had severe ER (Rutgeerts' score $\geq i2$). In our study ER according to Rutgeerts' score was: i0 in 38.2% of the patients, i1 in 13.5%, i2 in 10%, i3 in 13.5%, and i4 in 24.8%. At univariable analysis ileo-colonic disease was associated to a lower risk of severe ER at 6 months.

Rutgeerts et al., in 1990, showed endoscopic recurrent lesions in 73% (65 out of 89) of CD patients 1 year after curative ileo-colonic resection.² Of these, 83% (54 out of 65) had a severe ER. In a previous study by the same author³ recurrent disease was endoscopically confined to the neoterminal ileum and the anastomosis in 72% of the patients (21 out of 29). Eighty-one percent of these patients (17 out of 21) presented a severe ER within 1 year after the curative resection. Rutgeerts et al. described as severe lesions the presence of: "numerous ulcers" (9 patients),

Table 2 Endoscopic recurrence at 6 months according to Rutgeerts' score.

	N/170 (%)
Endoscopic recurrence	
• 0	65 (38.2)
• i1	23 (13.5)
• i2	17 (10)
• i3	23 (13.5)
• i4	42 (24.8)
Severe endoscopic recurrence ($\geq i2$)	82 (48.2)

Table 3 Univariable analysis for endoscopic recurrence at 6 months.

	p-Value	OR (95% CI)
Sex	p = 0.74	0.90 (0.484–1.682)
Age at diagnosis	p = 0.72	1.01 (0.980–1.030)
Smoking habit	p = 0.22	1.51 (0.772–2.983)
Disease duration	p = 0.26	1.01 (0.980–1.001)
Previous surgery	p = 0.86	1.07 (0.473–2.441)
Site of disease (ileo-colonic vs. ileal)	p = 0.04	0.52 (0.277–0.974)
Previous immunosuppressants	p = 0.87	1.06 (0.518–2.185)
Fistulizing disease	p = 0.28	0.66 (0.312–1.411)
Extraintestinal manifestation	p = 0.73	1.19 (0.427–3.347)

neoterminal ileum “studded with ulcers” (3 patients), and “nodules and large ulcers” (5 patients).

The overall percentage of ER in this prospective multicenter Italian study is quite lower than Rutgeerts' findings (61.7% vs. 73 and 72%) but in our study this recurrence rate was observed at 6 months after the curative resection compared to 1 year in the Rutgeerts' studies. Nevertheless the interesting findings of this IG-IBD study is the high rate of severe ER (78.1%), comparable to Rutgeerts' studies,^{2,3} but observed already at 6 months after the curative resection.

In a recent trial by Reinisch et al.,¹⁴ that evaluated the role of AZA in the prevention of post-operative ER compared to 5-ASA, the enrolled CD patients had been operated on between 6 and 26 months before the endoscopy with a reported median of 13.5 and 12.5 months in the AZA and 5-ASA arm respectively. The authors reported at baseline the following ER Rutgeerts' score: i2 in 29 patients (37%), i3 in 14 (18%), and i4 in 35 (45%). However the timing of ER for each group of patients was not reported and the number of the evaluated patients was lower than in our study (78 vs. 170).

Among all the patients with ER (\geq i1) the rate of “very severe ER” (i3 and i4) in our study was similar to that reported in Rutgeerts' series: 2 62% (65 out of 105) vs. 60% (39 out of 65). In the Reinisch's study¹⁴ 49 out of 78 patients (63%) were reported to have very severe ER (i3 and i4) and the remaining 29 patients presented a Rutgeerts' score of i2. Patients with mild ER (i1) were not included in the study so it is not possible to calculate the correct rate of very severe ER with respect to all patients with ER.

In the management of CD, the prevention and the treatment of ER, particularly severe recurrence, represent an important issue in the treatment of the disease.^{15,16} In the prospective endoscopic cohort by Rutgeerts et al. the clinical course of CD after surgery was predicted by the severity of endoscopic lesions during the first year after resection. The patients with ER more than i1 in the neoterminal ileum had a higher risk of early symptoms and complications.²

Over the last decade a lot of papers have been published on the prevention and the treatment of ER^{5,15,16} especially in patients with risk factors for disabling disease course after surgery: fistulizing disease, site of disease (ileal vs. colonic), smoking, young age, previous resection, extent of lesions and type of anastomosis.^{15,16} This is an important issue and

we consider it important to know that the majority of severe and very severe ER appeared early after surgery (at 6 months) as observed in our study.

Among risk factors for ER data from the literature are mixed and no consistent relationship between disease location and rate of ER has been shown. However disease involving the proximal small bowel is considered to represent a high risk clinical situation.¹⁷ The univariable analysis of our study showed that only ileo-colonic disease influenced the final outcome associating to a lower risk of severe ER (p = 0.04; OR 0.52, 95% CI 0.277–0.974).

Regarding the second outcome of this study we confirmed the weak role of 5-ASA in the prevention of early ER. Severe ER rate (\geq i2) in patients undergoing colonoscopy was 47% (77 out of 163) despite the treatment with 5-ASA at the dosage of 2.4 g daily. A meta-analysis by Renna et al's.¹⁸ on prevention of post-operative recurrence showed that in the placebo arms severe ER rate (\geq i2) ranged between 43% and 59% at 3 month colonoscopy and 63% at 6 month colonoscopy. In the Florent et al's. trial the ER rate in 5-ASA arm was 50% at 12 weeks.¹⁹ Other studies evaluated the efficacy of 5-ASA in the prevention of post-surgical endoscopic recurrence but with heterogeneous outcomes, results, and follow-up length, not comparable with our findings. In two studies the recurrence was defined as both endoscopic and/or radiological recurrence.^{20,21} In the first study²⁰ the 12-month rate of severe recurrence was 24% in the 5-ASA group. In the second study²¹ the endoscopic and radiological rate of recurrence was significantly decreased in the 5-ASA treated patients, compared with patients treated with placebo, with a risk ratio from Cox regression of 0.654 (90% CI, 0.47–0.91; p = 0.016). Lochs et al.²² reported data at 6 weeks and 18 months with severe recurrence rates of 30 and 66% respectively. In the Hanauer et al.'s trial²³ the 24-month recurrence rate was 48%. A trial comparing two different dosages of 5-ASA (2.4 vs. 4 g daily) reported 12-month severe endoscopic recurrence of 37% in lower dosage group and 27% in the higher dosage group.²⁴ In a Cochrane meta-analysis⁵ the risk for any ER was not significantly reduced with 5-ASA but the risk of very severe ER resulted significantly lower with an NNT of 8 (risk ratio 0.5). Nevertheless there was significant heterogeneity in the timing of endoscopic evaluation of disease recurrence. The authors concluded that 5-ASA plays a modest benefit in the prevention of ER. Our result is similar to the placebo rate at 3 months and to the 5-ASA rate at 6 months confirming a marginal role of 5-ASA in the prevention of severe ER.

In conclusion this prospective Italian multicenter IG-IBD study showed, in a large cohort, that a great proportion of ER occur within 6 months from resection in CD and that most of these are very severe with a Rutgeerts' score \geq i3. Furthermore this study confirms the marginal role of 5-ASA in the prevention of ER. Considering the available medical treatments for severe ER with immunosuppressive and biological drugs^{15,16} we consider that colonoscopy should be performed at 6 months after curative resection instead of the generic “within the first year after surgery” reported in the current European guidelines.¹⁶ We retain that performing a colonoscopy 1 year after surgery increases the risk of already finding a complicated recurrence of the disease.

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