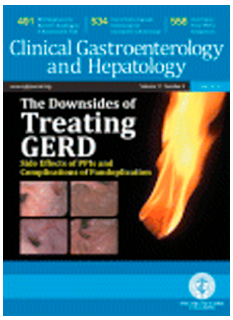
Journal Pre-proof



Rates of Post-operative Recurrence of Crohn's Disease and Effects of Immunosuppressive and Biologic Therapies

Pauline Rivière, Séverine Vermeire, Marie Irles-Depe, Gert Van Assche, Paul Rutgeerts, Quentin Denost, Albert Wolthuis, Andre D'Hoore, David Laharie, Marc Ferrante

PII: S1542-3565(20)30441-9
DOI: https://doi.org/10.1016/j.cgh.2020.03.064
Reference: YJCGH 57110

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 22 March 2020

Please cite this article as: Rivière P, Vermeire S, Irles-Depe M, Van Assche G, Rutgeerts P, Denost Q, Wolthuis A, D'Hoore A, Laharie D, Ferrante M, Rates of Post-operative Recurrence of Crohn's Disease and Effects of Immunosuppressive and Biologic Therapies, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.03.064.

Rates of Post-operative Recurrence of Crohn's Disease and Effects of Immunosuppressive and Biologic Therapies

Pauline Rivière[1,2], Séverine Vermeire[2], Marie Irles-Depe[1], Gert Van Assche[2], Paul Rutgeerts[2], Quentin Denost[4], Albert Wolthuis[3], Andre D'Hoore[3], David Laharie[1], Marc Ferrante[2].

1. Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium.
2. Department of Hepatogastroenterology and Digestive Oncology, Haut-Lévêque Hospital, CHU de Bordeaux, Bordeaux, France.
3. Department of Abdominal Surgery, University Hospitals Leuven, KU Leuven, Leuven, Belgium.
4. Department of Abdominal Surgery, Haut-Lévêque Hospital, CHU de Bordeaux, Bordeaux, France.

Short title: Crohn's disease postoperative recurrence

Corresponding author: M Ferrante.

Department of Gastroenterology and Hepatology

University Hospitals Leuven / KU Leuven

Herestraat 49

B3000 Leuven

Belgium

Tel: +32 16 34 42 25

Fax: +32 16 34 44 19

Email: marc.ferrante@uzleuven.be

Funding: none.

Conflict of interest:

Pauline Rivière has no conflicts of interests. Séverine Vermeire has received grant support from AbbVie, MSD, Pfizer and Takeda; received speaker fees from AbbVie, MSD, Takeda, Ferring, Dr. Falk Pharma, Hospira, Pfizer Inc and Tillots; and served as a consultant for AbbVie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer Inc, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Marie Irles-Depe has no conflicts of interest. Gert Van Assche received financial support for research from Abbvie, MSD; lecture fees from Janssen, Takeda, Ferring, MSD, Abbvie; and consultancy fees from Abbvie, MSD, Takeda. Paul Rutgeerts received consultant or advisory boards or lectures fees from Johnson & Johnson; MSD; UCB; AbbVie; Takeda; Genentech; Bristol-Myers Squibb; Tillotts Pharma; Parexel; Quintiles; Robarts; Amgen/Medimmune/AstraZeneca. Quentin

Denost, Albert Wolthuis and Andre D'Hoore have no conflicts of interest. David Laharie has received board or lectures fees from Abbvie, Celgene, Ferring, Janssen, MSD, Novartis, Pfizer, Roche and Takeda. Marc Ferrante received financial support for research from Janssen Biologics, Pfizer and Takeda; lecture fees from Abbvie, Amgen, Biogen, Boehringer-Ingelheim, Chiesi, Falk, Ferring, Janssen, Lamepro, Mitsubishi Tanabe, MSD, Pfizer, Takeda, Tramedico, Tillotts, Zeria; consultancy fees from Abbvie, Boehringer-Ingelheim, Celltrion, Ferring, Janssen, Lilly, Mitsubishi Tanabe, MSD, Pfizer, Takeda.

Author contributions:

Pauline Rivière performed research and statistical analysis, interpreted data and drafted the manuscript. Séverine Vermeire, Gert Van Assche, Paul Rutgeerts, David Laharie and Marc Ferrante designed the study, interpreted data and critically revised the manuscript. Marie Irles-Depe, Anthony de Buck van Overstraeten, Quentin Denost, Albert Wolthuis and Andre D'Hoore performed data collection. All authors approved the final version of the manuscript.

Acknowledgements:

Séverine Vermeire and Marc Ferrante are senior clinical investigators of the Research Foundation – Flanders (FWO).

Abbreviations:

Anti-TNF: anti-tumor necrosis factor; CD: Crohn's disease; CI: confidence interval; CRP: C-reactive protein; HR: hazard rations; IQR: interquartile range; mRS: modified Rutgeerts' score; POR: postoperative recurrence; RS: Rutgeerts' score; 95% CI: 95% confidence interval

Word count: abstract 341 words (after editing by science editor), main text 3275 words.

Abstract

Background & Aims: The Rutgeerts' scoring system is used to evaluate patients with Crohn's disease (CD) following ileocolic resection, based on endoscopic findings at the anastomosis and in the neoterminal ileum. We investigated rates of clinical and surgical recurrence of CD after surgery and effect of therapy modification based on post-operative endoscopic findings.

Methods: We collected data from 365 adults with CD (20% with Rutgeerts' score i0, 10% with score i1, 49% with score i2, 12% with score i3, 9% with score i4) who underwent ileocolonoscopy within 12 months of ileocolic resection with anastomosis from 2000 through 2013 at 2 centers in Belgium and France. Patients were followed for 3 y or more after the ileocolonoscopy. Clinical post-operative recurrence (POR) was defined as occurrence of CD symptoms along with biologic, radiologic, and/or endoscopic features of disease activity; modified surgical POR was defined as either an endoscopic or surgical intervention.

Results: After a median follow-up time of 88 months, 48% of patients had clinical POR and 26% had modified surgical POR. Rates of survival without clinical POR or a modified surgical POR were lower in patients with Rutgeerts' scores of i2, i3, or i4 compared to patients with scores of i0 or i1 ($P<.001$ and $P=.02$). New immunosuppressant or biological therapy was initiated following endoscopy in 129/254 patients (51%) with Rutgeerts' score of i2, i3, or i4 vs 7/111 patients (6%) with scores of i0 or i1 (odds ratio for new therapy, 14.9; 95% CI, 7.1–36.8; $P<.001$). A modest decrease in risk of clinical POR was observed for patients with Rutgeerts scores of i3 or i4 after initiation of immunosuppressive or biological therapy based on endoscopic findings (Breslow $P=.03$), but this was not observed for patients with scores of i2 (Breslow $P=.46$).

Conclusions: Use of immunosuppressants and tumor necrosis factor antagonists to treat patients with an asymptomatic endoscopic post-operative recurrence of CD did not reduce long-term risk of clinical recurrence in patients with Rutgeerts' scores of i2, but it had a small effect in patients with scores of i3 or i4.

Key words: IBD, inflammatory bowel diseases, prognostic factor, TNF

Introduction

Involvement of the terminal ileum is frequent in patients with Crohn's disease (CD) and surgery may be required when lesions become refractory to medical therapy or evolve to either stenotic or penetrating disease (1)(2). Surgical rates have dropped since the 1960s due to improvement of medical therapy (3). However, in more recent cohorts, 1 out of 3 patients with CD still undergo an intestinal resection (4) and the need for a second surgery remains stable (5). The majority of patients experience endoscopic CD recurrence within the year following surgery, classically located at the anastomosis and/or in the neoterminal ileum (6). It has been shown that endoscopic lesions often precede clinical symptoms and that aphthous ulcers are markers for early recurrence (7)(8).

Rutgeerts *et al.* developed a postoperative recurrence (POR) endoscopic score to predict clinical postoperative recurrence risk based on early endoscopic findings at the anastomosis and in the neoterminal ileum (7). Five categories of the Rutgeerts' score (RS) were defined in the seminal publication (7): i0: no lesions in the distal ileum; i1: less than 5 aphthous lesions in the distal ileum; i2: 5 or more aphthous lesions with normal mucosa in-between, or skip areas of larger lesions or lesions limited to the ileo-colonic anastomosis; i3: more than 5 aphthous lesions with diffusely inflamed mucosa in between; i4: large ulcers with diffuse mucosal inflammation in between or nodules or stenosis in the distal ileum (Supplementary Table 1).

The Rutgeerts' score is now widely used to guide post-operative management (9). However, few data showing that endoscopy-driven postoperative management improves long-term disease outcome are available so far, especially in the biologic era. Regarding current guidelines for managing the CD postoperative setting, patients classified i0-i1 do not have to change treatment while those having a diffuse ileitis (i3-i4) need treatment escalation (2)(10)(11)(12). The management of patients having an i2 endoscopic POR, that was

heterogeneous in the index cohort, remains a matter of debate. A modified Rutgeerts' score was proposed to divide the i2 category between lesions confined to the ileo-colonic anastomosis (i2a), and more than 5 aphthous ulcers in the ileum with normal mucosa-in-between (i2b) (13)(14). However, recent data published by our group and Bayart *et al.* showed no difference in terms of clinical postoperative recurrence nor surgical postoperative recurrence between patients with Rutgeerts' scores of i2a and i2b (15)(16). Therefore, more data are required for managing asymptomatic patients with Rutgeerts' scores of i2.

The present study aimed at evaluating CD clinical and surgical POR rates in a post-anti-TNF cohort as well as the impact of therapy modification based on postoperative endoscopic findings.

Methods

Study population

This retrospective study was conducted in two academic centers, Leuven University Hospitals (Belgium) and Bordeaux University Hospitals (France) (15). Consecutive CD adults undergoing an ileocolic resection with ileocolic anastomosis between 2000 and 2013 were included. Patients were identified from two institutional databases prospectively maintained by the departments of abdominal surgery in Leuven and pathology in Bordeaux. Inclusion criteria were the following: adult patients having a CD diagnosed on usual criteria (17), surgery removing all ileocolic diseased segments, ileocolic anastomosis reachable by colonoscopy, ileocolonoscopy performed in the year following index surgery (or restoration of the fecal stream in case of a temporary ileostomy) and follow-up duration more than 3 years after the index endoscopy.

Patients' characteristics

Disease location and phenotype, previous ileocolic resections, and active penetrating disease at surgery were obtained from the patient's electronic medical file. Introduction of an immediate postoperative preventive therapy was evaluated. At time of postoperative endoscopy, presence of diarrhea or abdominal pain, modified Rutgeerts' score, C-reactive protein (CRP), hemoglobin and albumin values, and CD treatment modifications according to endoscopic findings were retrieved. Smoking status was evaluated at time of postoperative endoscopy, as "never smoked", "former smoker" and "current smoker".

Exposure to CD therapy before surgery was categorized as follows: patients having received thiopurines or methotrexate at any time before surgery without any biological therapy were considered as previously exposed to conventional immunosuppressant; if they had been treated by anti-tumor necrosis factor (anti-TNF) therapy or another biological therapy at any

time before surgery, with or without immunosuppressant, they were considered as previously exposed to biologicals. Immediate postoperative preventive therapy was defined as thiopurines, methotrexate or anti-TNF or any other biological therapy initiated immediately after surgery, in order to prevent POR.

Outcomes measures

One investigator (P Rivière), trained and blinded for the patient's outcomes, revised endoscopic reports for each patient to attribute the Rutgeerts' score and the modified Rutgeerts' score based on description of the lesions on endoscopic report and the available images. Pictures and/or videos were available for the majority of the procedures. Because the Rutgeerts' score was not systematically used before 2008, it was not possible to evaluate the disagreement between the original scoring and the reevaluation. The Rutgeerts' score and modified Rutgeerts' score were defined as described in the literature (7)(14) (Supplementary Table 1).

Clinical POR was defined as the occurrence of CD related symptoms associated to objective signs of disease activity, i.e. CRP > 5 mg/l and/or endoscopic recurrence ≥ i2 and/or radiologic evidence of neoterminal ileitis. When the recurrence was not localized at the surgery site (e.g. perianal disease, colitis, jejunitis), patients were censored (considered as lost to follow-up at date of recurrence). Endoscopic dilatation was defined as balloon insufflation at the ileocolic anastomosis during an ileo-colonoscopy when a non-passable stenosis was present and the patient had mentioned obstructive symptoms before endoscopy. Surgical POR was defined as a new surgery including resection or stricturoplasty of the ileocolic anastomosis. Modified surgical POR was defined as the occurrence of either endoscopic dilatation or new surgery. Therapy modification after endoscopy was defined as immunosuppressant or anti-TNF introduction within 6 weeks of the post-operative

ileocolonoscopy based on the time necessary to start a new therapy in the 2 centers whatever the duration use of the treatment.

Statistical analyses

Continuous data were expressed as median (interquartile range [IQR]) and compared using a Mann Whitney U-test. Categorical variables were expressed as frequencies and compared using a chi-square test. Kaplan-Meier curves were plotted for time from postoperative endoscopy to clinical POR and surgical POR and were compared with Log rank statistics. Univariable Cox regression following the Breslow method was conducted for eligible predictive factors of cPOR and new surgery. Analyses for clinical POR risk and predictors were restricted to patients not experiencing already a clinical POR prior to the postoperative endoscopy. For analysis of surgical POR all patients were included, even if they developed clinical POR prior to the postoperative endoscopy. Results are presented as hazard ratio (HR) with 95% confidence intervals (95% CI). Variables with p-value below 0.20 in univariate regression were included in a full model of multivariable Cox regression. Manual stepwise elimination was performed to find the best suitable model of factors predicting clinical, surgical POR and endoscopic dilatation during follow-up.

Two-sided statistical tests were used for all analyses. A p-value <0.05 was considered as significant. Statistical analyses were performed using R version 3.5.1 (R Development Core Team, Vienna, Austria).

Results

Study population

Nine hundred and seven patients underwent an ileocolic resection from 2000 to 2013, 716 in the University Hospitals Leuven, and 191 in Bordeaux University Hospitals. After exclusion of patients postoperatively followed-up in another center (n=185), without ileocolonoscopy within the year after surgery (n=247) and without 3 years of follow-up (n=110), the analysis was performed on the remaining 365 patients (Figure 1).

Baseline characteristics of the 365 patients analyzed are presented in Table 1. To summarize, 210 (58%) were women, median (IQR) age at surgery was 37 (26-49) years and median duration of the disease was 9.8 (3.0-17.9) years. Active penetrating disease was the main surgical indication, in 172 (47%) patients; 97 (27%) underwent prior surgical ileocolic resections. Regarding treatments given before surgery, 202 (55%) patients have been exposed to at least one immunosuppressant, including 135 (37%) who received also an anti-TNF agent, and 18 (5%) patients to an anti-TNF alone. Immediate preventive treatment by thiopurines, methotrexate or anti-TNF therapy had been initiated after surgery in 74/365 (20%) patients. Patients receiving a preventive therapy did not differ from the remainder of the cohort in terms of previous surgery (p=0.81), penetrating phenotype (p=0.08) and smoking status (p=0.30). The presence of at least one of these risk factors was associated with the use of prophylactic therapy: 60/265 (23%) patients with at least one risk factor started a prophylactic therapy vs. 10/100 (10%) with no risk factor (p=0.04).

Outcome at postoperative endoscopy and during follow-up

Median time between resection surgery or closure of ileostomy and postoperative ileocolonoscopy was 6.2 (5.4-7.8) months. Seventy-four patients (20%) had an i0 Rutgeerts' score, 37 (10%) i1, 180 (49%) i2 from whom 91/180 i2a and 89/180 i2b, 42 (12%) i3 and 32

(9%) i4. Endoscopic findings are displayed in Table 2. Patients having received a preventive therapy by immunosuppressant or anti-TNF after surgery scored significantly more often i0 or i1 than patients without preventive therapy (41% *vs.* 28%, p=0.02).

After a median follow-up of 88 (67-118) months from endoscopy, clinical POR, endoscopic dilatation and new surgery were observed in 176 (48%), 54 (15%) and 41 (11%) of patients, respectively. Clinical POR was confirmed by endoscopic or radiologic neoterminal ileitis in 168/176 (95%) patients and CRP elevation in 8/176 (5%) patients.

Outcomes according to the modified Rutgeerts' score

During follow-up, clinical POR occurred in 21/74 (28%) of patients with RS of i0, 13/37 (35%) with RS of i1, 88/180 (49%) with RS of i2, 27/42 (64%) with RS of i3 and 27/32 (84%) with RS of i4, respectively. During follow-up, surgical POR occurred in 3/74 (4%) of patients with RS of i0, 4/37 (11%) with RS of i1, 19/180 (11%) with RS of i2, 7/42 (17%) with RS of i3 and 8/32 (25%) with RS of i4 patients, respectively. Endoscopic dilatation was performed in 9/74 (28%) of patients with RS of i0, 3/37 (8%) with RS of i1, 29/180 (16%) with RS of i2, 6/42 (14%) with RS of i3 and 7/32 (22%) with RS of i4 patients. Kaplan-Meier curves from endoscopy to clinical POR and to surgical POR according to RS at the first endoscopy are displayed in Figure 2a and 2b respectively. Clinical POR- and surgical POR-free survival rates were lower in patients with RS of i2-i3-i4 compared to patients with scores of i0 or i1 ($p<0.001$ and $p=0.02$, respectively). These results were not modified by exclusion of the patients receiving a preventive treatment after surgery.

Predictive factors for cPOR and sPOR are described in Supplementary Materials section.

Impact of treatment escalation guided by endoscopic findings

A new CD treatment was initiated following endoscopy in 129/254 (51%) patients with RS of i2-i4 *vs.* 7/111 (6%) with RS of i0-i1 patients (Odds Ratio OR 14.9 [95% CI 7.1-36.8], $p<0.001$). Based on endoscopic findings, among the patients with RS of i2 an anti-TNF

therapy was started in 22/180 (12%) patents and an immunosuppressant in 23/180 (13%). Among the patients with RS of i3-i4, an anti-TNF therapy was started in 26/74 (35%) and an immunosuppressant in 21/74 (28%). A significant increase in terms of biologicals prescription for patients with a RS $\geq$ i2 was observed after 2009 (8/104 (8%) *vs.* 40/150 (27%), p<0.01) whereas no difference was observed for immunosuppressant introduction before and after 2009 (p=0.84).

Among patients with RS of i2, no difference was observed in terms of clinical POR if an immunosuppressant or an anti-TNF therapy was initiated after postoperative endoscopy (p=0.55). At 3 years, patients with RS of i2 started with an anti-TNF after endoscopy had a 71.4% clinical POR-free survival rate, compared to 81.0% in patients starting an immunosuppressant and 71.7% in patients with no CD therapy. These results were not modified when separating the i2a and i2b subgroups (p=0.66 and p=0.71, respectively). Kaplan-Meier curve from endoscopy to clinical POR for patients with RS of i2 according to endoscopy-guided therapy modification is presented in Figure 3a. Similarly, no difference was observed in terms of surgical POR-free survival rate according to endoscopy-guided therapy modification in patients with RS of i2 (p=0.18).

Among the patients with RS of i3-i4, initiation of an anti-TNF therapy or an immunosuppressant was associated with lower clinical POR rates (p=0.03) (Figure 3b). At 3 years, patients with i3-i4 started with an anti-TNF after endoscopy had a 55.6% clinical POR-free survival rate, compared to 78.6% in patients starting an immunosuppressant and 28.6% in patients with no CD therapy. No benefit was observed on surgical POR rates (p=0.48).

For both i2 and i3-i4 groups, these results were not modified by exclusion of patients treated by preventive treatment after surgery.

Discussion

In our large retrospective study having a long follow-up duration, despite substantial progress in medical therapy and the implementation of endoscopy-driven introduction of medical therapy in the postoperative setting, clinical recurrence-free survival rates were close to those observed in the index description by Rutgeerts *et al.* in the 1990s (7). This surprising result challenges the benefit of endoscopy-guided therapy modification. In patients with an i2 Rutgeerts' score, no effect on forthcoming clinical POR or need for a new surgery was observed when an immunosuppressant or a biological treatment was started after the postoperative endoscopy. Treatment modification in the patients with RS of i3-i4 seemed to improve the clinical postoperative recurrence-free survival. In the i3-i4 population, outcomes were better for patients receiving an immunosuppressant compared to a new anti-TNF therapy, probably reflecting the more complicated previous medical history of patients who had to initiate anti-TNF therapy. No effect was observed in terms of surgical recurrence risk.

The modest impact of an endoscopy-guided therapy of POR in our study is consistent with findings from randomized controlled trials and epidemiological data. The POCER study compared clinical features-based management to 6 month-endoscopy based management, with step-up treatment by azathioprine or adalimumab. At 18 months, clinical recurrence rates were not different between the two groups. Moreover, only 38% of patients who received azathioprine or adalimumab for endoscopic recurrence ≥ i2 at 6 months in the active care group patients were in endoscopic remission 1 year later (10). A randomized trial from the International Organization for Study of Inflammatory Bowel Diseases in patients at higher risk of postoperative CD recurrence found no difference in terms of endoscopic remission at 2 years between systematic azathioprine therapy after surgery and initiation based on ileocolonoscopy findings at week 26 or 52 (18). Recent data from the Swedish nationwide cohort study showed that need for a second abdominal surgery in Crohn's disease has not

decreased in the last 30 years (5). One explanation could be the treatment refractoriness of the CD postoperative setting. In our cohort, 42% of patients had been exposed to biologicals before surgery and anti-TNF exposure before surgery was an independent predictor of clinical POR.

The benefit of immediate prophylactic therapy after surgery remains a matter of debate. In the PREVENT trial, infliximab or placebo was started immediately after the surgery. Infliximab did not better than placebo to prevent clinical recurrence at 18 months after the surgery, although endoscopic recurrence rate was significantly lower in patients treated by infliximab (19). Infliximab seemed to be more effective to prevent the development of i3-i4 lesions (7.5% in the infliximab group *vs.* 32% in the placebo group) than i2 lesions (25.9% in the infliximab group *vs.* 29.3% in the placebo group) (19). In the APPRECIA trial, comparing immediate preventive therapy by adalimumab *versus* azathioprine, no difference was observed in terms of clinical or endoscopic recurrence rate at 1 year (20). In our cohort, patients receiving an immediate prophylactic therapy by immunosuppressant or biologic therapy had less severe endoscopic recurrence at the first endoscopy and the prophylactic therapy was protective against clinical POR during follow-up in multivariate analysis.

The major limitation of our study is its retrospective setting. Inter-observer reproducibility of the RS has been shown to be suboptimal, especially for the i2 subscore (21). Each endoscopy was revised for the study. However, this classification was retrospective and based on endoscopic reports and pictures generated by several investigators without standardization. In this retrospective setting, assessment of clinical POR could have been biased. Ileocolonoscopy was not performed routinely in all operated patients, mostly in the early years of the cohort (2000-2007), partly because small bowel barium transit was used more than endoscopy in one center (Leuven). Some patients were excluded because of shorter follow-up duration, possibly because of absence of CD recurrence. These two factors could

have led to a selection bias of more severe patients. Endoscopic dilatation of anastomotic stricture was performed based on the operator's perspective of patient's symptoms. After stratification by POR endoscopic score and therapy, the small number of patients limited the accuracy of the analysis. Two centers were involved in this work and management could have been heterogeneous. However, no difference was observed between the two centers when comparing patients' profiles, preventive therapy or treatment modifications (data not shown). Management of POR changed over time and patients received more anti-TNF for endoscopic POR after 2009 introducing a potential heterogeneity in the population.

In conclusion, clinical and surgical POR rates remain high despite the impact of preventive therapy on endoscopic lesions and the endoscopy-guided therapy modifications. In asymptomatic patients with RS of i2, initiation of a CD therapy based on endoscopic findings does not change POR risk in the long-term follow-up. Despite significant advances in medical therapies available, clinical POR rates of patients with RS of i3 and i4 remain high thirty years after the first publication of a postoperative recurrence cohort in CD (22). These retrospective data suggest that watchful waiting could be an option for patients with RS of i2, while intensification of therapy should be considered in patients with RS of i3-i4. For both groups, disease activity should be closely monitored by ileocolonoscopy at 6-12 months or surrogate markers, such as fecal calprotectin (23), to assess lesions stability in patients with RS of i2 and treatment efficacy in patients with RS of i3-i4. Prospective studies are needed to evaluate this strategy.

Legend to Figures

Figure 1: Flow chart demonstrating the selection of patients.

Figure 2: Outcomes after ileocolic resection stratified by Rutgeerts' score at postoperative endoscopy. a. Kaplan-Meier curves plotted from endoscopy to clinical postoperative recurrence, defined as symptoms suggestive of Crohn's disease recurrence associated to objective criteria of disease activity (C-reactive protein > 5 mg/l and/or Rutgeerts' score ≥ i2 and/or radiologic terminal ileitis). **b.** Kaplan-Meier curves plotted from endoscopy to surgical postoperative recurrence defined as new resection of the ileo-colonic anastomosis.

Figure 3: Clinical postoperative recurrence-free survival rates according to endoscopy-guided therapy modification. a: Patients with an i2 Rutgeerts' score at postoperative endoscopy; b: Patients with an i3-i4 Rutgeerts' score at postoperative endoscopy. Kaplan-Meier curves plotted from endoscopy to clinical recurrence, defined as symptoms suggestive of Crohn's disease recurrence associated to objective criteria of disease activity (CRP > 5 mg/l and/or Rutgeerts' score ≥ i2 and/or radiologic terminal ileitis). Analysis restricted to patients not experiencing already clinical recurrence at postoperative endoscopy. Immunosuppressant: methotrexate or azathioprine.

References

1. Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre J-P. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. Gut. 2005 Feb;54(2):237–41.

2. Bemelman WA, Warusavitarne J, Sampietro GM, Serclova Z, Zmora O, Luglio G, et al. ECCO-ESCP Consensus on Surgery for Crohn's Disease. J Crohns Colitis [Internet]. 2017 May 11 [cited 2019 Mar 4]; Available from: https://academic.oup.com/ecco-jcc/article-lookup/doi/10.1093/ecco-jcc/jjx061

3. Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease--based on results from a regional patient group from the county of Copenhagen. Gut. 1985 Feb;26(2):146–50.

4. Zhulina Y, Udumyan R, Tysk C, Montgomery S, Halfvarson J. The changing face of Crohn's disease: a population-based study of the natural history of Crohn's disease in Örebro, Sweden 1963-2005. Scand J Gastroenterol. 2016 Mar;51(3):304–13.

5. Kalman D, Nordenvall C, Hallqvist Everhov A, Ludvigsson JF, Sachs MC, Ekbom A, et al. OP016 Need for primary abdominal surgery, but not repeated surgery, has decreased: a nationwide study of temporal trends in Crohn surgery in Sweden 1990–2014. J Crohns Colitis. 2018 Jan 16;12(supplement_1):S011–2.

6. D'Haens GR, Gasparaitis AE, Hanauer SB. Duration of recurrent ileitis after ileocolonic resection correlates with presurgical extent of Crohn's disease. Gut. 1995 May 1;36(5):715–7.

7. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990 Oct;99(4):956–63.

8. Olaison G, Smedh K, Sjödahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. Gut. 1992 Jan 3;33(3):331–5.

9. Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011 Jun;17(6):1415–22.

10. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet Lond Engl. 2015 Apr 11;385(9976):1406–17.

11. Nguyen GC, Loftus EV, Hirano I, Falck–Ytter Y, Singh S, Sultan S, et al. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. Gastroenterology. 2017 Jan;152(1):271–5.

12. Domènech E, López-Sanromán A, Nos P, Vera M, Chaparro M, Esteve M, et al. Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the monitoring, prevention and treatment of post-operative recurrence in Crohn's disease. Gastroenterol Hepatol Engl Ed. 2017 Aug 1;40(7):472–83.

13. Domènech E, Mañosa M, Bernal I, Garcia-Planella E, Cabré E, Piñol M, et al. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: results of a prospective, observational, long-term follow-up study. Inflamm Bowel Dis. 2008 Apr;14(4):508–13.

14. Gecse K, Lowenberg M, Bossuyt P, Rutgeerts PJ, Vermeire S, Stitt L, et al. Sa1198 Agreement Among Experts in the Endoscopic Evaluation of Postoperative Recurrence in Crohn's Disease Using the Rutgeerts Score. Gastroenterology. 2014 May 1;146(5):S-227.

15. Rivière P, Vermeire S, Irles-Depe M, van Assche G, Rutgeerts P, de Buck van Overstraeten A, et al. No Change in Determining Crohn's Disease Recurrence or Need for Endoscopic or Surgical Intervention With Modification of the Rutgeerts Scoring System. Clin Gastroenterol Hepatol [Internet]. 2018 Oct [cited 2019 Feb 7]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1542356518310796

16. Bayart P, Duveau N, Nachury M, Zerbib P, Gerard R, Branche J, et al. Ileal or Anastomotic Location of Lesions Does Not Impact Rate of Postoperative Recurrence in Crohn's Disease Patients Classified i2 on the Rutgeerts Score. Dig Dis Sci. 2016 Oct;61(10):2986–92.

17. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017 Jan;11(1):3–25.

18. Ferrante M, Papamichael K, Duricova D, D'Haens G, Vermeire S, Archavlis E, et al. Systematic versus Endoscopy-driven Treatment with Azathioprine to Prevent Postoperative Ileal Crohn's Disease Recurrence. J Crohns Colitis. 2015 Aug;9(8):617–24.

19. Regueiro M, Feagan BG, Zou B, Johanns J, Blank MA, Chevrier M, et al. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. Gastroenterology. 2016 Jun 1;150(7):1568–78.

20. López-Sanromán A, Vera-Mendoza I, Domènech E, Taxonera C, Vega Ruiz V, Marín-Jiménez I, et al. Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial. J Crohns Colitis [Internet]. [cited 2017 Jun 5]; Available from: https://academic.oup.com/ecco-jcc/article-abstract/doi/10.1093/ecco-jcc/jjx051/3574893/Adalimumab-vs-Azathioprine-in-the-Prevention-of

21. Marteau P, Laharie D, Colombel J-F, Martin L, Coevoet H, Allez M, et al. Interobserver Variation Study of the Rutgeerts Score to Assess Endoscopic Recurrence after Surgery for Crohn's Disease. J Crohns Colitis. 2016 Sep;10(9):1001–5.

22. Rivière P, Ferrante M. Management of Postoperative Crohn's Disease: Missing Pieces of the Puzzle. J Crohns Colitis. 2017 Oct 27;11(11):1291–2.

23. Garcia-Planella E, Mañosa M, Cabré E, Marín L, Gordillo J, Zabana Y, et al. Fecal Calprotectin Levels Are Closely Correlated with the Absence of Relevant Mucosal Lesions in

Postoperative Crohn's Disease: Inflamm Bowel Dis. 2016 Dec;22(12):2879–85.

Table 1: Characteristics of the study population

	n = 365
Women, n (%)	210 (58)
Median age at surgery (IQR), years	37 (26-49)
Median disease duration at surgery (IQR), years	9.8 (3.0-17.9)
Median time to post-operative endoscopy (IQR), months	6.2 (5.4-7.8)
Median follow-up duration after endoscopy (IQR), months	77.8 (50.4-114.3)
Disease location:	
Ileal/ileocolic, n (%)	210(58) /154 (42)
Preoperative disease behavior:	
Inflammatory/stricturing/penetrating, n (%)	11(3)/155(43)/198(54)
Active penetrating disease at surgery, n (%)	172 (47)
Preoperative exposure to an immunosuppressant only, n (%)	67 (18)
Preoperative exposure to an anti-TNF agent (+/- immunosuppressant), n (%)	153 (42)
Prior ileocolic resection, n (%)	97 (27)
Temporary ileostomy after surgery, n (%)	48 (13)
Immediate preventive therapy after surgery [a], n (%)	74 (20)
- Thiopurines	51 (14)
- Methotrexate	4 (1)*
- Anti-TNF	20 (5)
Smoking status at post-operative endoscopy [b], n (%)	
- Never smoked	174 (45)
- Former smoker	61 (17)
- Active smoker	116 (32)

[a]: thiopurines or methotrexate or anti-TNF therapy started after surgery, before post-operative endoscopy

[b]: smoking status was missing for 14 patients

*one patient received methotrexate + anti-TNF therapy

IQR: interquartile range; CD: Crohn's disease.

Table 2: Endoscopic characteristics of the study population

	n = 365
Rutgeerts' score at post-operative endoscopy, n (%)	
- i0	74 (20)
- i1	37 (10)
- i2	180 (49)
- i3	42 (12)
- i4	32 (9)
Median C-reactive protein at endoscopy (IQR), mg/l	3.1 (1.0-8.3)
Active smoker at endoscopy, n (%)	116 (33)

IQR: interquartile range

Fig 2a

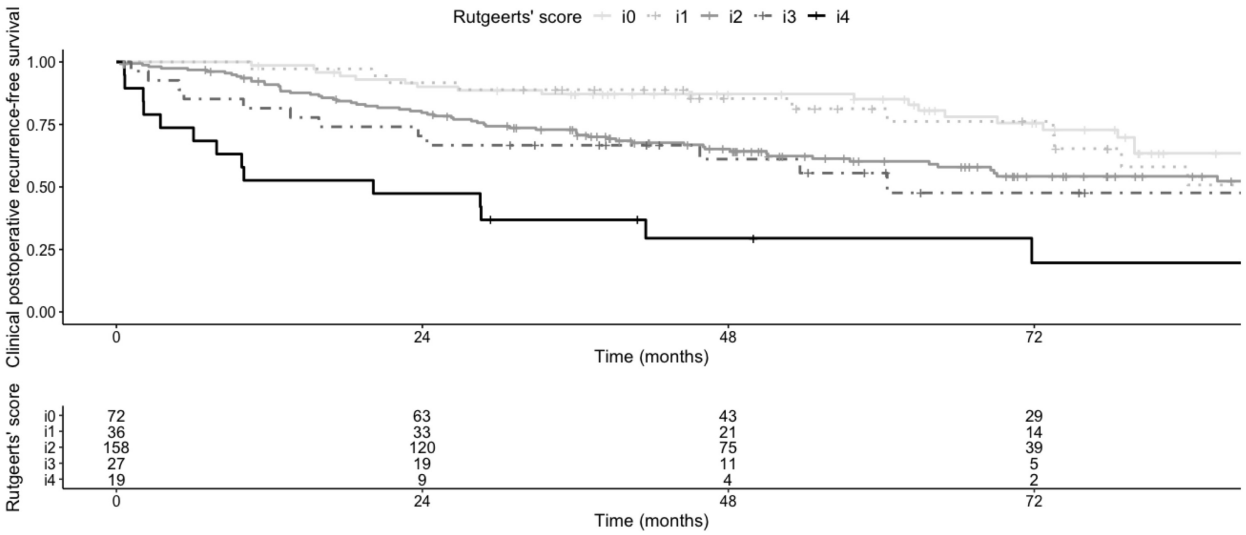

Rutgeerts' score i0 i1 i2 i3 i4
Clinical postoperative recurrence-free survival
1.00
0.75
0.50
0.25
0.00
0
24
48
72
Time (months)
Rutgeerts' score
i0 72 63 43 29
i1 36 33 21 14
i2 158 120 75 39
i3 27 19 11 5
i4 19 9 4 2
0
24
48
72
Time (months)

Fig 2b

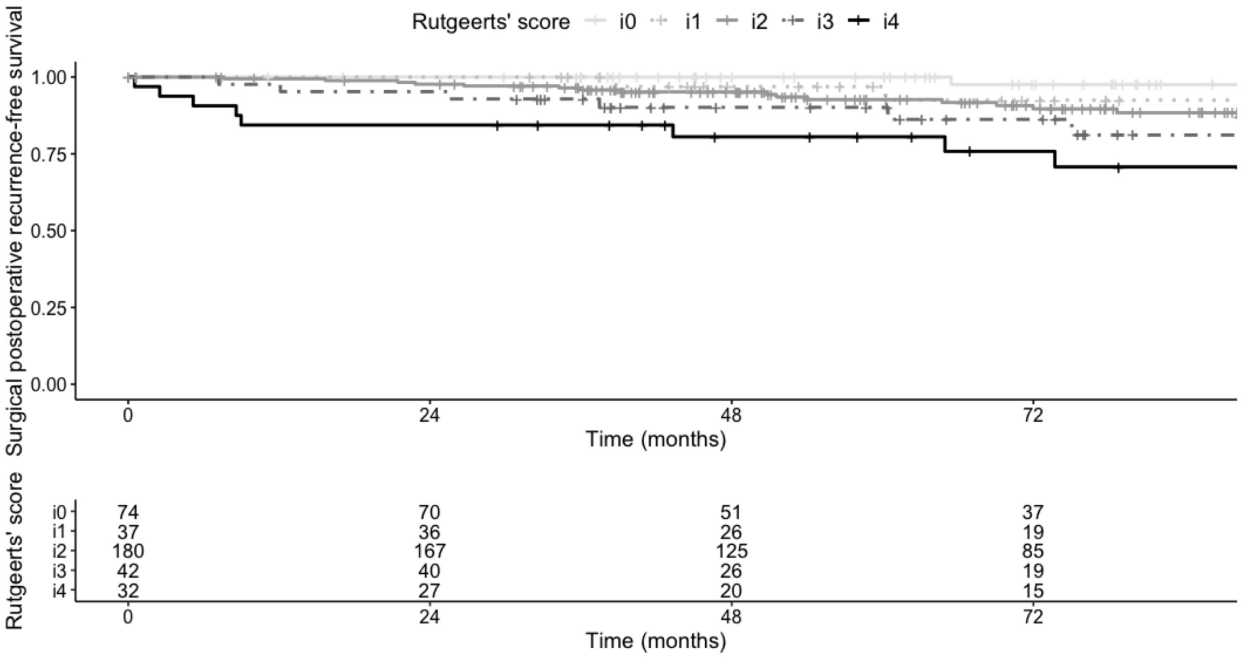

Rutgeerts' score i0 i1 i2 i3 i4
Surgical postoperative recurrence-free survival
1.00
0.75
0.50
0.25
0.00
0
24
48
72
Time (months)
Rutgeerts' score
i0 74 70 51 37
i1 37 36 26 19
i2 180 167 125 85
i3 42 40 26 19
i4 32 27 20 15
0
24
48
72
Time (months)

Fig 3a

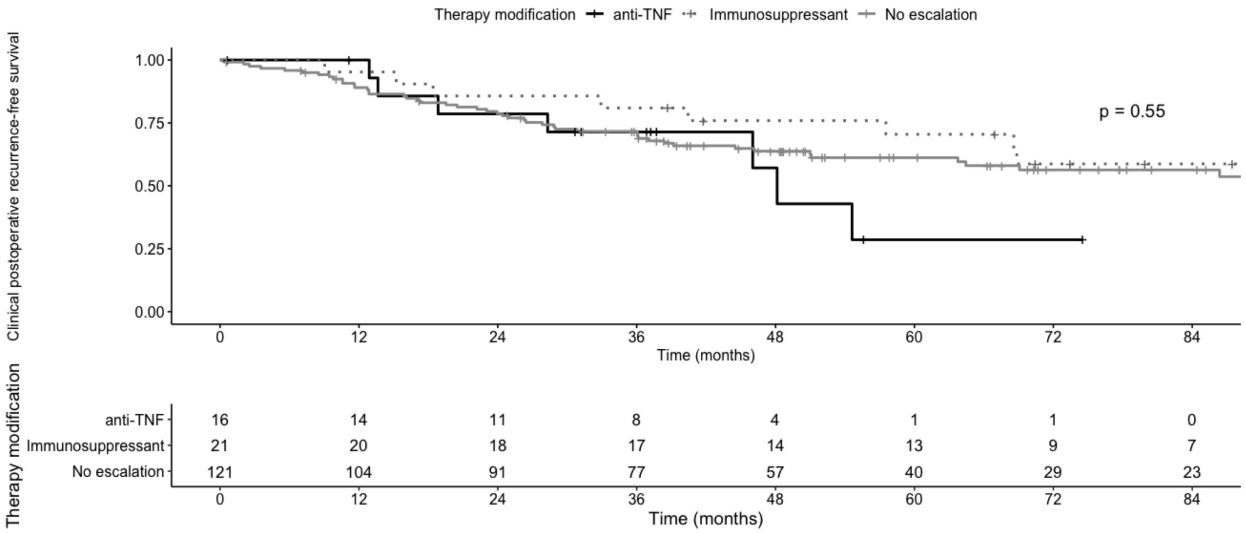

Therapy modification
anti-TNF
Immunosuppressant
No escalation
Clinical postoperative recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p = 0.55
0
12
24
36
48
60
72
84
Time (months)
Therapy modification
anti-TNF 16 14 11 8 4 1 1 0
Immunosuppressant 21 20 18 17 14 13 9 7
No escalation 121 104 91 77 57 40 29 23
0
12
24
36
48
60
72
84
Time (months)

Fig 3b

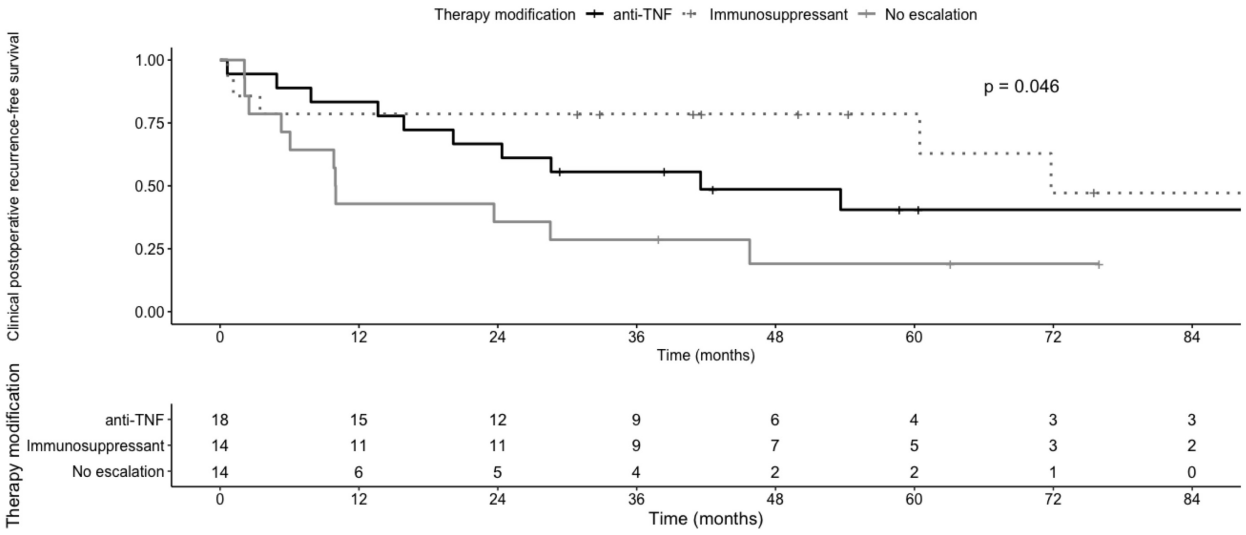
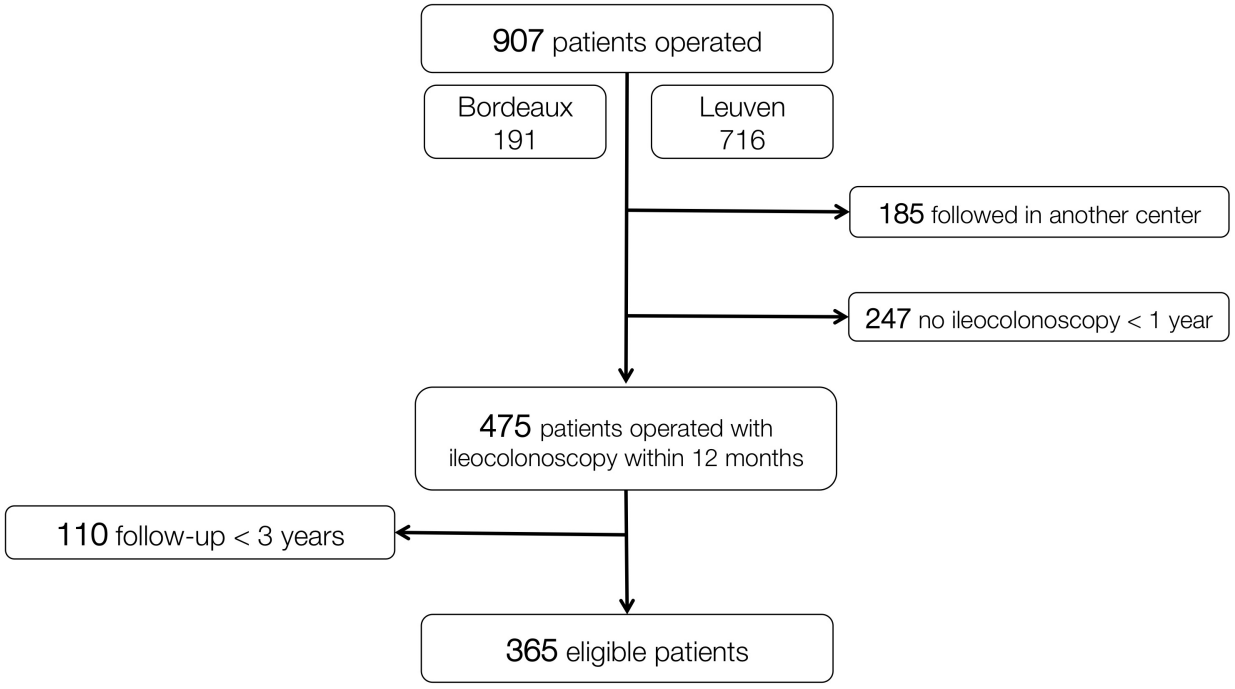

Therapy modification
anti-TNF
Immunosuppressant
No escalation
Clinical postoperative recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p = 0.046
0
12
24
36
48
60
72
84
Time (months)
Therapy modification
anti-TNF 18 15 12 9 6 4 3 3
Immunosuppressant 14 11 11 9 7 5 3 2
No escalation 14 6 5 4 2 2 1 0
Time (months)

Fig 1


907 patients operated
Bordeaux
191
Leuven
716
185 followed in another center
247 no ileocolonoscopy < 1 year
475 patients operated with
ileocolonoscopy within 12 months
110 follow-up < 3 years
365 eligible patients

Supplementary table 1: Modified Rutgeerts' score.

Category	Description
i0	No lesions in the distal ileum
i1	Less than 5 aphthous lesions in the distal ileum
i2	5 or more aphthous lesions with normal mucosa in-between, or skip areas of larger lesions or lesions limited to the ileo-colonic anastomosis
i2a	Lesions confined to the ileo-colonic anastomosis (including anastomotic stenosis) with or without less than 5 aphthous lesions in the distal ileum
i2b	More than 5 aphthous or larger lesions, with normal mucosa-in-between, in the distal ileum with or without anastomotic lesions
i3	More than 5 aphthous lesions with diffusely inflamed mucosa in between
i4	Large ulcers with diffuse mucosal inflammation in between or nodules or stenosis in the distal ileum

From *Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremas and Hiele M, Predictability of the Postoperative Course of Crohn's disease, Gastroenterology, 1990;99;956-963* and *Gecse K, Lowenberg M, Bossuyt P, Rutgeerts PJ, Vermeire S, Stitt L, et al. Sa1198 Agreement Among Experts in the Endoscopic Evaluation of Postoperative Recurrence in Crohn's Disease Using the Rutgeerts Score. Gastroenterology. 2014 May 1;146(5):S – 227.*

Predictive factors for clinical POR and surgical POR

After univariate analysis, occurrence of clinical POR during follow-up was associated to a RS ≥ i2 [HR 1.9 (1.3-2.8), p<0.01], to immunosuppressant exposure before surgery [HR 1.5 (1.1-2.1), p=0.02] or anti-TNF exposure before surgery [HR 1.8 (1.2-2.5), p<0.01], to smoking at endoscopy [HR 1.7 (1.1-2.4), p<0.01)] and CRP > 5 mg/L at endoscopy [HR 1.8 (1.2-2.7), p<0.01)]. Immediate thiopurine preventive therapy after surgery [HR 0.6 (0.4-1.0), p=0.04] and latero-lateral anastomosis [HR 0.6 (0.4-0.9), p=0.01] were negatively associated with clinical POR in univariable regression. Clinical POR was not associated with disease duration (p=0.41), previous ileocolic resection (p=0.30), active penetrating disease at surgery (p=0.05), or preventive therapy by anti-TNF after surgery (p=0.07) in univariate regression.

The multivariate Cox model identified exposure to anti-TNFs before surgery [HR 2.0 (1.4-2.9), p<0.01)], a RS ≥ i2 [HR 1.7 (1.1-2.5), p=0.01], smoking [HR 1.7 (1.2-2.4), p<0.01)] together with CRP > 5 mg/L at the time of endoscopy [HR 1.6 (1.1-2.3), p=0.02)] and the absence of a latero-lateral anastomosis [HR 1.9 (1.3-2.9), p<0.01)] as independent predictors for clinical POR.

After univariate analysis, surgical POR during follow-up was associated to a RS ≥ i2 [HR 2.6 (1.2-5.9), p=0.01], to smoking at endoscopy [HR 2.5 (1.4-4.6), p<0.01] and CRP > 5 mg/L at endoscopy [HR 2.5 (1.4-4.6), p<0.01)]. In multivariate analysis, surgical POR was independently associated to a RS ≥ i2 [HR 3.4 (1.0-11.3), p=0.05], smoking at endoscopy [HR 2.8 (1.4-5.5), p=0.01)] and CRP > 5 mg/L at endoscopy [HR 2.3 (1.1-4.5), p=0.02)].

After univariate and multivariate analysis, endoscopic dilatation during follow-up was only associated to a CRP > 5 mg/L at index endoscopy [HR 1.8 (1.0-3.1), p=0.05) for univariate analysis and HR 2.1 (1.2-3.5), p=0.01 in multivariate analysis, respectively].

Need to Know

Background: Little is known about rates of CD recurrence after surgery or the outcomes of therapy modification based on post-operative endoscopic findings.

Findings: Treatment with immunosuppressants or TNF antagonists in patients with an asymptomatic endoscopic post-operative recurrence of CD (Rutgeerts' score of i2) did not reduce long-term risk of clinical recurrence, but these treatments had a small effect in patients with higher scores (i3 or i4).

Implications for patient care: Patients with an asymptomatic mild endoscopic post-operative recurrence of CD (Rutgeerts' score of i2) might not benefit from treatment with immunosuppressants or tumor necrosis factor antagonists.