Risk of Late Postoperative Recurrence of Crohn's Disease in Patients in Endoscopic Remission After Ileocecal Resection, Over 10 Years at Multiple Centers

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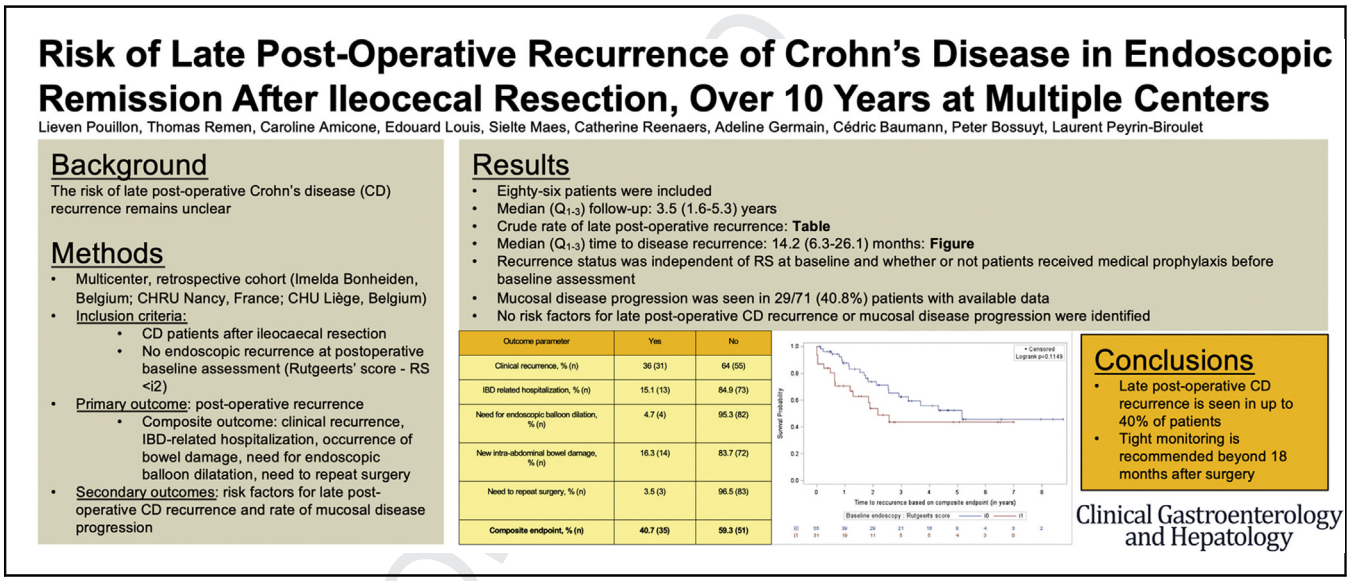

BACKGROUND & AIMS: **The risk of recurrence of Crohn's disease (CD) from 1 to 10 years after surgery despite initial endoscopic remission (late post-operative recurrence) is not clear.**

METHODS: **We performed a retrospective study, at 3 inflammatory bowel disease (IBD) centers in France and Belgium, of all patients with CD (n = 86) undergoing an ileocecal resection with curative intent from 2006 through 2016 who did not have endoscopic evidence for recurrence (Rutgeerts score less than i2) at their baseline assessment. Post-operative recurrence after baseline endoscopy was defined as a composite endpoint of at least 1 of the following: clinical recurrence, IBD-related hospitalization, occurrence of bowel damage, need for endoscopic balloon dilatation of the anastomosis, and need to repeat the surgery. Risk of mucosal disease progression was studied as a secondary outcome.**

Abbreviations used in this paper: CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; MRI, magnetic resonance imaging.

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RESULTS: **The median time between surgery and baseline endoscopy was 7 months (IQR, 5.7–9.5 months); 40 patients (46.5%) received medical prophylaxis in this period. The median follow-up time was 3.5 years (IQR, 1.6–5.3 years). Thirty-five patients (40.7%) had a late post-operative recurrence of CD, with a median time to disease recurrence after baseline endoscopy of 14.2 months (IQR, 6.3–26.1 months). Recurrence status did not differ significantly between patients with Rutgeerts scores of i0 (20/55) or i1 (15/31) at baseline ($P = .28$) and was independent of medical prophylaxis (16/40 with prophylactic therapy vs 19/46 without prophylactic therapy; $P = .90$). Mucosal disease progressed in 29 of the 71 patients (40.8%) with available data. We did not identify risk factors for late post-operative recurrence of CD or mucosal disease progression.**

CONCLUSIONS: **Among patients with CD treated by ileocecal resection, 40% of patients had a late recurrence, despite initial endoscopic remission, after a median follow-up time of 3.5 years. Tight monitoring of these patients is recommended beyond 18 months.**

Crohn's disease (CD) is a chronic, disabling inflammatory bowel disease (IBD).[1] Approximately half of the patients require surgery in the first decade after diagnosis, and 1 of 3 patients need multiple bowel resections during their disease course.[2] The Rutgeerts score grades the severity of signs of endoscopic CD recurrence after ileocecal resection, by focusing on the mucosa of the ileocolonic anastomosis and the neoterminal ileum, just proximal to the anastomosis.[3] In a landmark trial conducted in the prebiologic era, the Rutgeerts score proved to be the most important variable predicting symptomatic recurrence during follow-up in postoperative CD patients.[4] Nowadays, the score is well known and widely used to decide about treatment optimization in clinical practice, and as an endpoint for grading endoscopic recurrence in clinical trials.

It is recommended to perform ileocolonoscopy within the first year after surgery because this may affect treatment decisions.[5,6] The International Organization for the study of Inflammatory Bowel Disease agreed that Rutgeerts score of i0 (no endoscopic lesions) or i1 (between 1 and5 aphthous lesions in the neoterminal ileum) reflects endoscopic remission.[7] In general, such patients do not require new therapy, nor intensification of existing therapy.[8] Since most studies in postoperative CD patients aimed to assess the evolution of patients with Rutgeerts score of i2 or higher,[9,10] little is known about the long-term outcome of patients without endoscopic CD recurrence after ileocecal resection. Although the original paper of Rutgeerts et al[4] looked at clinical recurrence during follow-up in this subgroup, data about hospitalization, intra-abdominal bowel damage, and the need for endoscopic balloon dilatation or redo-surgery were lacking. The POCER trial suggested that early endoscopic remission does not preclude the need for long-term monitoring,[6] but it remains unclear whether all patients in endoscopic remission after ileocecal resection necessitate tight follow-up, and for how long. Although risk factors for early postoperative CD recurrence are well established,[11,12] no data exist about potential risk factors for late postoperative CD recurrence.

In this retrospective, multicenter study, we aimed to evaluate the risk of late postoperative CD recurrence according to a composite endpoint, in patients who are initially in endoscopic remission after ileocecal resection. Secondary goals were to compare the time to late postoperative CD recurrence according to Rutgeerts score at baseline endoscopy, to identify potential risk factors associated with late postoperative CD recurrence, and to evaluate the risk of mucosal disease progression based on endoscopy, fecal biomarker, and magnetic resonance imaging (MRI).

Materials and Methods

Study Aims

The risk of late postoperative CD recurrence was evaluated through a retrospective cohort study in 3 large-volume IBD centers in France (Nancy University Hospital, Nancy) and Belgium (Liège University Hospital, Liège and Imelda General Hospital, Bonheiden).

Patient Selection

All CD patients that underwent an ileocecal resection with curative intent between September 2006 and September 2016 were screened for eligibility in the participating centers. Only patients with absence of endoscopic signs of recurrence (defined as Rutgeerts score i0 or i1) at the ileocolonic anastomosis during baseline assessment were included. Baseline assessment was defined as the first endoscopy after surgery, taking place after month 3 but before the end of month 18 following ileocecal resection. Patients that underwent an ileocecal resection without curative intent, patients with an ileostomy, and patients younger than 18 years of age at the time of surgery were excluded from analysis.

Data Collection

Baseline characteristics were recorded at the moment of baseline endoscopy performed after month 3 and before the end of month 18 following ileocecal resection, and included age, sex, disease duration, age at diagnosis,

Montreal disease classification, smoking status, and previous surgery. Treatment courses with an immunomodulator (methotrexate, thiopurine, 6-mercaptopurine) or biological therapy (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab) between date of diagnosis and surgery, between surgery and baseline endoscopy, and until the end of follow-up, were registered. New or worsening IBD-related abdominal pain or diarrhea, IBD-related hospitalization, occurrence of new intra-abdominal fistulae, abscesses or strictures, the need for endoscopic balloon dilatation of the anastomosis, and the need to repeat the surgery were recorded during follow-up after baseline endoscopy, including the time of first event. Furthermore, results of all endoscopic assessments, fecal calprotectin levels, and MRI examinations after baseline were collected. End of follow-up was defined as the moment of the last follow-up visit or if redo ileocecal resection was performed.

Table 1. Baseline Characteristics at the Time of Endoscopy

Characteristic	Total (N = 86)
Age, y	38.4 (28.8–51.0)
Male	31 (36)
Disease duration, y	7.1 (1.7–20.0)
Age at diagnosis	
A1: <16 y	4 (4.7)
A2: 16–40 y	68 (79.1)
A3: >40 y	14 (16.3)
Disease location	
L1: ileal	56 (65.1)
L2: colonic	2 (2.3)
L3: ileocolonic	28 (32.6)
Associated upper digestive tract involvement	2 (2.3)
Disease behavior	
B1: inflammatory	4 (4.7)
B2: stricturing	47 (54.7)
B3: penetrating	35 (40.7)
Perianal disease	21 (24.4)
Active smoking	27 (31.4)
Previous surgery	17 (19.8)
Treatment with IMM and/or biological between time of diagnosis and ileocecal resection	
None	31 (36)
IMM	49 (57)
Anti-TNF (infliximab, adalimumab, certolizumab)	39 (45.3)
Vedolizumab	4 (4.7)
Ustekinumab	1 (1.2)
Treatment with IMM and/or biological between ileocecal resection and baseline endoscopy	
None	46 (53.5)
IMM	22 (25.6)
Infliximab	9 (10.5)
Adalimumab	14 (16.3)
Certolizumab	0 (0)
Vedolizumab	0 (0)
Ustekinumab	0 (0)
Rutgeerts score	
i0	55 (64.0)
i1	31 (36.0)

Values are median (interquartile range) or n (%).
IMM, immunomodulator; IQR, interquartile range; TNF, tumor necrosis factor

What You Need to Know

Background

Approximately half of patients with Crohn's disease (CD) require surgery in the first decade after diagnosis. Risk factors for early recurrence of CD after surgery are well established, but little is known about the risk of later recurrence.

Findings

Among patients with CD treated by ileocecal resection, 40% of patients had a late recurrence, despite initial endoscopic remission, after a median follow-up time of 3.5 years. No individual risk factors for late postoperative recurrence of CD or mucosal disease progression could be identified.

Implications for patient care

Time to recurrence of CD after resection exceeds 1 year after baseline endoscopy showing endoscopic response, so patients should be carefully monitored for more than 18 months after surgery.

Outcome Measures

Primary aim was to evaluate the risk of late postoperative CD recurrence, which was defined as a composite endpoint of at least 1 of the following during follow-up after baseline endoscopy: clinical recurrence (ie, new or worsening IBD-related abdominal pain or diarrhea), IBD-related hospitalization, occurrence of bowel damage (ie, new intra-abdominal fistulae, abscesses, or strictures), the need for endoscopic balloon dilatation of the anastomosis, and the need to repeat the surgery. Secondary aims were to (1) compare the time to late postoperative CD recurrence according to Rutgeerts score at baseline endoscopy, (2) to identify potential risk factors associated with late postoperative CD recurrence, and (3) to evaluate the risk of mucosal disease progression as defined by a composite mucosal endpoint of at least 1 of the following: endoscopic disease progression (ie, evolution to Rutgeerts score > i1), elevation of fecal biomarker (ie, fecal calprotectin level >250μg/g), and disease activity on MRI (ie, segmental Nancy score at the neoterminal ileum >2).

Statistical Analysis

Categorical variables were described as numbers and percentages, and continuous variables as mean ± SD or median and interquartile range (IQR), depending on their distribution. Pearson's chi-square test was used for univariate analysis involving categorical variables. Kaplan-Meier curves were used for intergroup comparisons of time to late postoperative CD recurrence. Univariate Cox regression analyses were used to identify potential risk factors for time-dependent late postoperative CD recurrence. Variables with

Table 2. Crude Rate of Late Postoperative CD Recurrence

Outcome Measure	Yes	No
Clinical recurrence	31 (36)	55 (64)
IBD-related hospitalization	13 (15.1)	73 (84.9)
Need for endoscopic balloon dilatation	4 (4.7)	82 (95.3)
New intra-abdominal bowel damage	14 (16.3)	72 (83.7)
Need to repeat surgery	3 (3.5)	83 (86.5)
Composite endpoint	35 (40.7)	51 (59.3)

Values are n (%).
CD, Crohn's disease; IBD, inflammatory bowel disease

a P value <.1 in the univariate analysis were candidates for the multivariate Cox model. The threshold for statistical significance was set at a P value<.05 in all tests. The statistical analysis was carried out using SAS software (version 9.4; SAS Institute, Inc., Cary, NC). All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline Characteristics

Out of a total number of 438 CD patients undergoing an ileocecal resection during the study period, 86 patients (n = 55 women; n = 27 active smokers) could be included. Main reasons for exclusion were Rutgeerts score ≥i2 at postoperative endoscopy and the lack of endoscopy within the prespecified time interval. Median time between CD diagnosis and ileocecal resection was 6.1 (IQR, 0.9–19.4) years. Seventeen (19.8%) patients had undergone previous surgery, while the majority (n = 55, 64%) had received treatment with immunomodulators or biologicals before ileocecal resection. Median time between surgery and baseline endoscopy was 7.0 (IQR, 5.7–9.5) months and 40 (46.5%) patients received medical prophylaxis with immunomodulators or biologicals in this period (Table 1).

Late Postoperative Crohn's Disease Recurrence

Median follow-up time after baseline endoscopy was 3.5 (IQR, 1.5–5.3) years. Based on the composite endpoint, late postoperative CD recurrence in the overall population was seen in 35 (40.7%) patients (Table 2). Recurrence status was comparable between patients with Rutgeerts score i0 (n = 20 of 55) or i1 (n = 15 of 31) at baseline endoscopy (P = .28), and independent whether or not patients had received medical prophylaxis between surgery and baseline endoscopy (16 of 40 with prophylactic therapy vs. 19 of 46 without prophylactic therapy; P = .90; Figure 1).

Time to Recurrence

Among the 35 patients with late postoperative CD recurrence, median time from baseline endoscopy to disease recurrence was 14.2 (IQR, 6.3–26.2) months. The proportion of patients with recurrence in the first year and first 3 years of follow-up was 17.4% (n = 15 of 86) and 36% (n = 31 of 86), respectively (Table 3). Kaplan-Meier analysis indicated no statistically significant differences between patients with Rutgeerts score i0 and those with Rutgeerts score i1 at baseline endoscopy (P = .11) (Figure 2). The survival analyses for each of the individual components of the composite endpoint are shown in Supplementary Figure 1.

Among the 16 patients with late postoperative CD recurrence who received medical prophylaxis between ileocecal resection and baseline endoscopy, median time to disease recurrence was 19.4 (IQR, 9.1–25.8) months. In the 19 patients with late postoperative CD recurrence that did not receive medical prophylaxis between ileocecal resection and baseline endoscopy, median time to disease recurrence was 11.0 (IQR, 5.9–30.5) months. Kaplan-Meier analysis indicated no difference in time to disease recurrence between patients who did or did not receive medical prophylaxis between ileocecal resection and baseline endoscopy (P = .39) (Supplementary Figure 2).

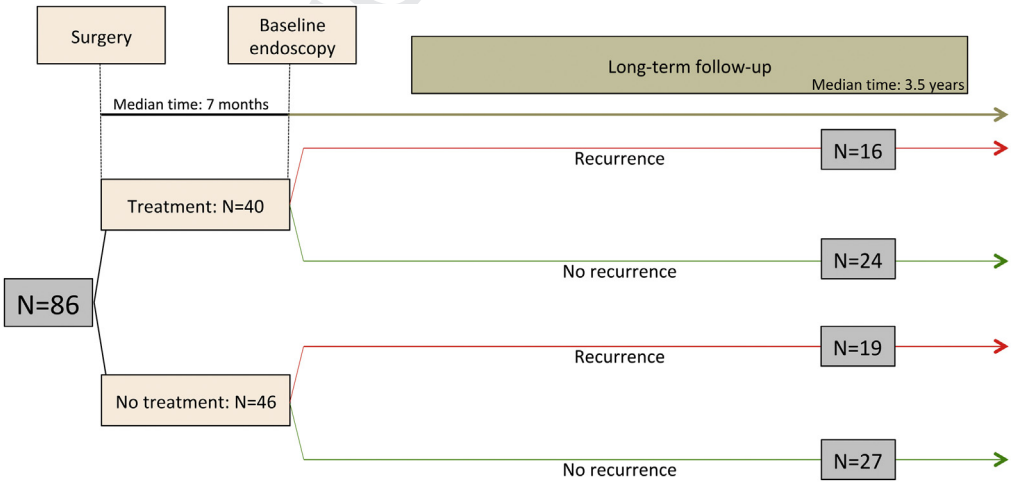

Figure 1. Late postoperative CD recurrence in patients with and without prophylactic treatment between ileocecal resection and baseline endoscopy.

Table 3. Postoperative CD Recurrence Events Over Time (in the Total Population and Stratified by Prophylactic Treatment and Rutgeerts Score at Baseline) (N = 86)

	Time Window								
	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9
Events	15	10	6	2	1	1	0	0	0
Censored	13	8	8	3	8	4	4	1	2
At risk	58	40	26	21	12	7	3	2	0
Rutgeerts score at baseline									
Prophylactic treatment: yes									
i0 (n = 28)									
Events	3	3	1	1	0	1	0		
Censored	2	2	4	3	6	1	1		
At risk	23	18	13	9	3	1	0		
i1 (n = 12)									
Events	2	3	2	0	0	0	0		
Censored	1	0	2	0	1	0	1		
At risk	9	6	2	2	1	1	0		
Prophylactic treatment: no									
i0 (n = 27)									
Events	3	3	3	1	1	0	0	0	0
Censored	8	2	0	0	1	2	0	1	2
At risk	16	11	8	7	5	3	3	2	0
i1 (n = 19)									
Events	7	1	0	0	0	0	0		
Censored	2	4	2	0	0	1	2		
At risk	10	5	3	3	3	2	0		

Risk Factors

No risk factor for late postoperative CD recurrence could be identified after univariate Cox regression analysis in the overall population, although there was a trend toward a higher risk for recurrence in patients with Rutgeerts score i1 at baseline compared with patients with Rutgeerts score i0 (hazard ratio, 1.71; 95% confidence interval, 0.87–3.35; $P = .12$) (Table 4). In the separate groups of patients that did and did not receive medical prophylaxis between ileocecal resection and baseline endoscopy, no risk factors could be identified either (Supplementary Tables 1 and 2).

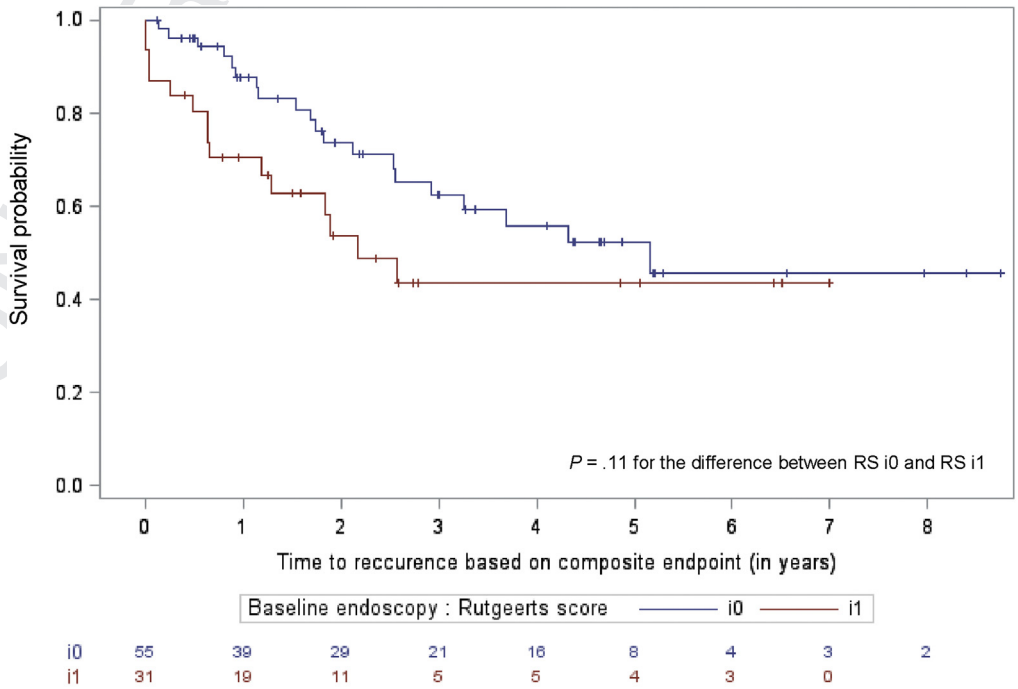

Figure 2. Time to CD recurrence after baseline endoscopy based on the composite endpoint in patients after ileocecal resection.

Table 4. Factors Associated With Late Postoperative CD Recurrence in the Overall Population

Risk Factor	N	Recurrence N	Univariate Regression HR	95% CI	*P* Value
Gender					.11[a]
Female	55	26	1		
Male	31	9	0.54	0.25–1.15	
Smoking status					.22[a]
Inactive	59	21	1		
Active	27	14	1.53	0.78–3.03	
Age at diagnosis[b]	86	35	1.00	0.98–1.03	.74[a]
Age at surgery[b]	86	35	0.99	0.97–1.02	.58[a]
Disease location					.94[a]
L1	56	21	1		
L2	2	0	0	N/A	
L3	28	14	1.13	0.57–2.23	
Disease behavior					.55[a]
B1	4	2	1		
B2	47	21	0.84	0.19–3.63	
B3	35	12	0.58	0.13–2.63	
Perianal disease					.66[a]
No	65	33	1		
Yes	21	2	0.84	0.38–1.85	
Previous surgery					.22[a]
No	69	27	1		
Yes	17	8	1.62	0.75–3.48	
Previous IMM and/or biological treatment					.53[a]
No	32	12	1		
Yes	54	23	1.25	0.62–2.52	
Baseline endoscopy					.12[a]
Rutgeerts score i0	55	20	1		
Rutgeerts score i1	31	15	1.71	0.87–3.35	
IMM and/or biological treatment between surgery and baseline endoscopy					.39[a]
No	46	19	1		
Yes	40	16	0.75	0.38–1.45	

CI, confidence interval; HR, hazard ratio; IMM, immunomodulator; N/A, not applicable.

[a]•••.

[b]HR of quantitative variables reflects the risk variation for 1-unit increase of the variable.

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Mucosal Disease Progression

In 71 of 86 patients, at least 1 objective measurement of mucosal inflammatory activity (endoscopy, fecal calprotectin, MRI) was available during follow-up. Based on a composite mucosal endpoint, disease progression was seen in 29 of 71 (40.8%) patients (Supplementary Table 3). Prevalence of mucosal disease progression during follow-up was comparable between patients with Rutgeerts score i0 (n = 19 of 48) and Rutgeerts score i1 (n = 10 of 23) at baseline endoscopy ($P = .75$), and independent whether or not patients had received medical prophylaxis between surgery and baseline endoscopy (13 of 35 with prophylactic therapy vs 16 of 36 without prophylactic therapy; $P = .53$).

Among the 29 patients with mucosal disease progression, median time from baseline endoscopy to progression was 24.1 (IQR, 13.5–38.4) months. Kaplan-Meier analysis indicated no difference between patients with Rutgeerts score i0 and those with Rutgeerts score i1 at baseline endoscopy ($P = .44$). We could not identify any risk factor for mucosal disease progression in the subgroup of patients with available data (Supplementary Table 4).

Discussion

This is the first study specifically looking at the risk of late postoperative recurrence in CD patients who are initially in endoscopic remission after ileocecal resection, and this by using a composite endpoint. With a median follow-up time of 3.5 years after baseline endoscopy, CD recurrence was seen in up to 40% of patients, and occurred more than 1 year after baseline endoscopy in the majority of those.

The POCER trial previously showed that patients with endoscopic remission (Rutgeerts score i0 or i1) 6 months after ileocecal resection are still at risk for endoscopic recurrence 1 year later, with progression seen in 41% of patients.[6] Our data show a very similar risk of late postoperative CD recurrence while using a different endpoint, including not only clinical but also more objective

parameters such as intra-abdominal bowel damage and the need for balloon dilatation or redo surgery. Moreover, because our study recorded the time to disease recurrence since baseline endoscopy, which adds to the time since surgery, it is clear that relevant CD relapse can still occur even beyond 18 months after ileocecal resection. Long-term tight monitoring of postoperative CD patients regardless of their endoscopic appearance at index colonoscopy remains therefore warranted.

Risk factors for early postoperative CD recurrence are well examined and include smoking, prior intestinal surgery, absence of prophylactic treatment, penetrating disease at index surgery, and perianal disease location.[13,14] We could not confirm any of these as specific risk factors for late postoperative recurrence. Although active smoking and prior intestinal surgery were more frequently associated with disease relapse, hazard ratios did not reach statistical significance. This could be due to a lack of statistical power; however, risk factors for early and late postoperative CD recurrence potentially differ. Indeed, the established risk factors for early disease recurrence might not be independent and only reflect disease severity or complicated disease course, making them correlate less with late disease recurrence. Prospective data in larger cohorts are needed to clarify this.

Most clinical algorithms support the use of prophylactic therapy in patients with a high risk of early postoperative CD recurrence, with step-up therapy in all patients if endoscopic recurrence is seen at colonoscopy.[15,16] Mainly anti–tumor necrosis factor therapy, alone or in combination with other treatment modalities, has shown to reduce endoscopic postoperative CD recurrence,[17] which has a predictive value for symptomatic recurrence and the need for future resection.[4,18] The heterogeneity of our cohort, including both patients that did and did not receive medical prophylaxis immediately after surgery, makes it difficult to estimate if recurrence rates reflect 'true' late postoperative recurrence or merely represent loss of response to the treatment. Nevertheless, crude recurrence rates were comparable in patients with and without prophylactic treatment between ileocecal resection and baseline endoscopy, and immunomodulators and biological therapy in the immediate postoperative period did not decrease the risk of late disease recurrence. Our composite primary endpoint, however, did not include endoscopic progression given the lack of systematic endoscopic follow-up in this retrospective cohort. Taken into account that most (n = 31 of 35) patients experiencing a relapse were symptomatic, this was in line with data from the prospective PREVENT trial, in which infliximab treatment only reduced endoscopic but not clinical recurrence.[19]

A recent paper of Rivière et al[20] showed that patients initiating medical prophylaxis immediately after surgery more often had Rutgeerts score ≤i1 at first endoscopic evaluation. In the follow-up of their cohort, patients with Rutgeerts score >i1 experienced more frequently postoperative CD recurrence (both clinical as judged by the need to repeat the surgery) than patients with Rutgeerts score ≤i1, a finding that remained unmodified when excluding the patients that initiated immediate postoperative prophylaxis.[20] However, the initiation of immunomodulators or anti–tumor necrosis factor therapy in patients with an asymptomatic endoscopic recurrence reflected by Rutgeerts score i2 did not lead to improved outcomes.[20] The true value of postoperative medication in asymptomatic patients after surgery remains thus uncertain. In this regard, it would have been interesting to study the effect of postoperative medical prophylaxis on bowel damage alone, but the relative low number of events withheld us from performing this specific subanalysis. Future studies on late postoperative CD recurrence should be conducted in larger cohorts, including more centers or using nationwide databases.

Mucosal disease progression, based on a composite secondary endpoint of endoscopy, fecal biomarker and MRI, was seen in 41% of patients. As this was a retrospective study with no standardized protocol during follow-up, data about mucosal disease activity were only available in a subgroup (n = 71) of patients, and might therefore suffer a selection bias. Indeed, patients with a clinical suspicion of disease relapse were more likely to undergo additional investigation with endoscopy, fecal calprotectin, or MRI.

Strengths of this study are its multicenter design and long follow-up time. In contrast to the initial cohort of Rutgeerts, data were registered in the biologic era and primary endpoint included objective parameters on top of clinical recurrence. Limitations are its retrospective design, and the relative low number of patients eligible for inclusion despite a large initial cohort of more than 400 patients that underwent ileocecal resection during the study period. This was partly explained by the lack of timely postoperative endoscopic evaluation in a subset of patients in which colonoscopy was often replaced by dosage of fecal calprotectin or MRI, thereby reflecting real-world practice and patients' preferences in the participating centers. Last, the time frame of which postoperative endoscopy assessment was eligible for inclusion was rather broad, potentially introducing a selection bias. Nevertheless, median time between surgery and baseline endoscopy was 7 months, with a narrow interquartile range (3.8 months), so the impact on the outcomes was estimated as low.

In conclusion, late postoperative CD recurrence was seen in up to 40% of patients despite initial endoscopic remission. Tight monitoring of these patients is recommended beyond 18 months after ileocecal resection. Prospective studies in large sets of patients are needed to clarify the specific risk factors for late postoperative

CD recurrence, including the effect of prophylactic therapy on late recurrence rates.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.05.027.

References

1. Peyrin-Biroulet L, Loftus EV, Colombel J-F, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010;105:289–297.
2. Olivera P, Spinelli A, Gower-Rousseau C, Danese S, Peyrin-Biroulet L. Surgical rates in the era of biological therapy. Curr Opin Gastroenterol 2017;33:246–253.
3. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut 1984;25:665–672.
4. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–963.
5. Gomollon F, Dignass A, Annese V, et al. European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohn's Colitis 2017;11:3–25.
6. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet 2015;385:1406–1417.
7. Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65:1447–1455.
8. Nguyen GC, Loftus EV, Hirano I, et al. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. Gastroenterology 2017;152:271–275.
9. Onali S, Calabrese E, Petruzziello C, et al. Post-operative recurrence of Crohn's disease: a prospective study at 5 years. Dig Liver Dis 2016;48:489–494.
10. Rivière P, Vermeire S, Irles-Depe M, 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 2019;17:1643–1645.
11. Buisson A, Chevaux J-B, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther 2012; 35:625–633.
12. Auzolle C, Nancey S, Tran-Minh M-L, et al. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study. Aliment Pharmacol Ther 2018;48:924–932.
13. Vuitton L, Koch S, Peyrin-Biroulet L. Preventing postoperative recurrence in Crohn's disease: what does the future hold? Drugs 2013;73:1749–1759.
14. Gionchetti P, Dignass A, Danese S, et al. European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. J Crohn's Colitis 2017;11:135–149.
15. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohn's Colitis 2017; 11:649–670.
16. Barnes EL, Lightner AL, Regueiro M. Perioperative and post-operative management of patients with Crohn's disease and ulcerative colitis. Clin Gastroenterol Hepatol 2020;18: 1356–1366.
17. Burr NE, Hall B, Hamlin PJ, Selinger CP, Ford AC, O'Connor A. Systematic review and network meta-analysis of medical therapies to prevent recurrence of post-operative Crohn's disease. J Crohns Colitis 2019;13:693–701.
18. Regueiro M, Kip KE, Baidoo L, Swoger JM, Schraut W. Post-operative therapy with infliximab prevents long-term Crohn's disease recurrence. Clin Gastroenterol Hepatol 2014; 12:1494–1502.e1.
19. Regueiro M, Feagan BG, Zou B, et al. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. Gastroenterology 2016;150:1568–1578.
20. Rivière P, Vermeire S, Irles-Depe M, et al. Rates of post-operative recurrence of Crohn's disease and effects of immunosuppressive and biologic therapies. Clin Gastroenterol Hepatol 2020 Apr 6 [E-pub ahead of print].

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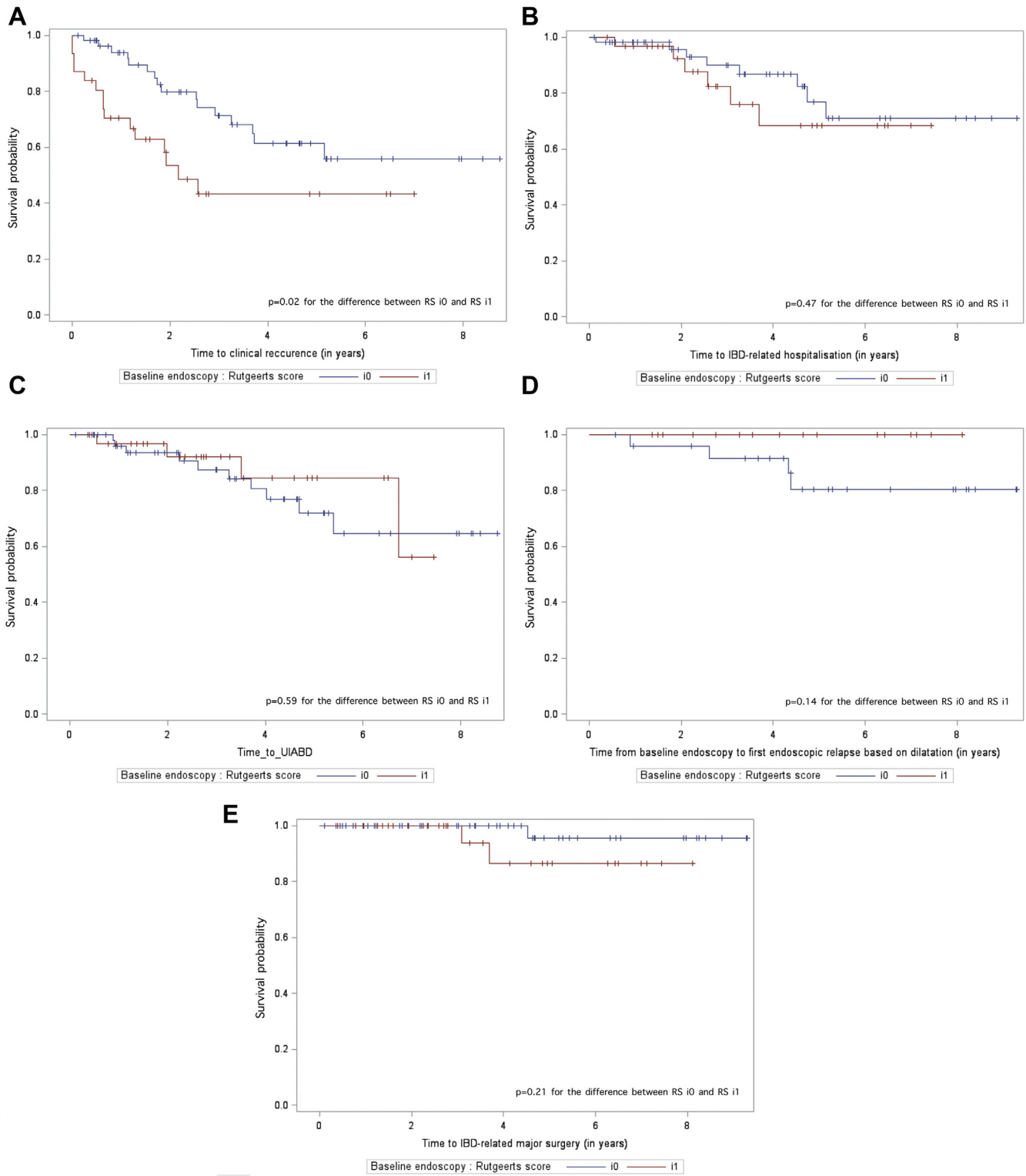
Conflicts of Interest
These authors disclose the following: Lieven Pouillon has received advisory board fees from Janssen and Takeda; presentation fees from AbbVie and Ferring; and personal fees from AbbVie, Ferring, Norgine, and Takeda. Peter Bossuyt has received grants and personal fees from Pfizer, Janssen, Mundipharma, and AbbVie; and personal fees from Takeda, Vifor Pharma, Hospira, MSD, Roche, Pentax, and BMS. Laurent Peyrin-Biroulet has received personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, and Theravance; has received grants from AbbVie, MSD, Takeda; and owns stock options from CTMA. The remaining authors disclose no conflicts.



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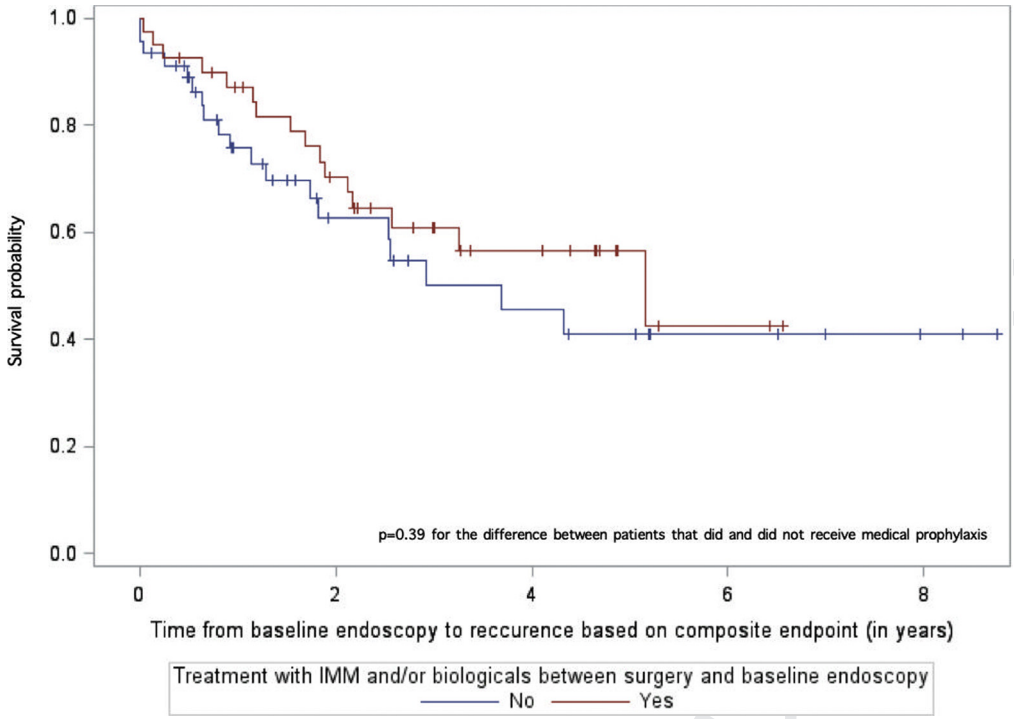
Supplementary Figure 1. (*A–E*) Time to Crohn's disease recurrence after baseline endoscopy for the individual components of the composite endpoint in patients after ileocecal resection with curative intent. UIABD, (previously) unknown intra-abdominal (bowel) damage. RS, Rutgeerts score.



Supplementary Figure 2. Time to Crohn's disease recurrence after baseline endoscopy based on the composite endpoint in patients after ileocecal resection. IMM, immunomodulator.

Supplementary Table 1. Factors Associated With Late Postoperative CD Recurrence in the Patients That Received Medical Prophylaxis Between Ileocecal Resection and Baseline Endoscopy

			Univariate Regression		
Risk Factor	N	Recurrence	HR	95% CI	*P* Value
Sex					.12[a]
Female	29	14	1		
Male	11	2	0.31	0.07–1.36	
Smoking status					.11[a]
Inactive	27	8	1		
Active	13	8	2.23	0.83–5.95	
Age at diagnosis[b]	40	16	0.99	0.94–1.05	.79[a]
Age at surgery[b]	40	16	0.99	0.95–1.04	.71[a]
Disease location					.31[a]
L1	18	5	1		
L2	2	0	0.60	0.02–12.79	
L3	20	11	2.12	0.72–6.22	
Disease behavior					.43[a]
B1	2	0	1		
B2	19	10	2.68	0.13–54.15	
B3	19	6	1.41	0.06–29.62	
Perianal disease					.93[a]
No	24	10	1		
Yes	16	6	1.05	0.37–2.95	
Previous surgery					.44[a]
No	30	11	1		
Yes	10	5	1.52	0.52–4.47	
Previous IMM and/or biological treatment					.63[a]
No	6	2	1		
Yes	34	14	1.43	0.32–6.32	
Baseline endoscopy					.13[a]
Rutgeerts score i0	28	9	1		
Rutgeerts score i1	12	7	2.16	0.80–5.83	

CI, confidence interval; HR, hazard ratio; IMM, immunomodulator.
[b]HR of quantitative variables reflects the risk variation for 1-unit increase of the variable.

Supplementary Table 2. Factors Associated With Late Postoperative CD Recurrence in the Patients Without Medical Prophylaxis Between Ileocecal Resection and Baseline Endoscopy

Risk Factor	n	Recurrence	Univariate Regression		
			HR	95% CI	*P* Value
Sex					.35[a]
Female	26	12	1		
Male	20	7	0.64	0.25–1.63	
Smoking status					.83[a]
Inactive	32	13	1		
Active	14	6	1.11	0.42–2.95	
Age at diagnosis[b]	46	19	1.01	0.98–1.04	.72[a]
Age at surgery[b]	46	19	0.99	0.97–1.02	.65[a]
Disease location					.47[a]
L1	38	16	1		
L2	0	N/A	N/A	NA	
L3	8	3	0.64	0.18–2.20	
Disease behavior					.35[a]
B1	2	2	1		
B2	28	11	0.33	0.07–1.55	
B3	16	6	0.33	0.06–1.69	
Perianal disease					.85[a]
No	41	17	1		
Yes	5	2	0.87	0.20–3.76	
Previous surgery					
No	39	15	1		.27[a]
Yes	7	4	1.87	0.62–5.65	
Previous IMM and/or biological treatment					.31[a]
No	26	10	1		
Yes	20	9	1.61	0.65–4.00	
Baseline endoscopy					.57[a]
Rutgeerts score i0	27	11	1		
Rutgeerts score i1	19	8	1.31	0.52–3.27	

CI, confidence interval; HR: hazard ratio; IMM: immunomodulator; N/A: not applicable.
[a]●●●.
[b]HR of quantitative variables reflects the risk variation for 1-unit increase of the variable.

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Supplementary Table 3. Crude Rate of Late Mucosal Disease Progression

Outcome Measure	Yes	No
Endoscopic progression (n = 42)	18 (42.9)	24 (57.1)
Elevated fecal calprotectin (n = 37)	12 (32.4)	25 (67.6)
MRI disease activity (n = 40)	8 (20.0)	32 (80.0)
Composite mucosal endpoint (n = 71)[a]	29 (40.8)	42 (59.2)

Values are n (%).
MRI, magnetic resonance imaging
[a]Total number of patients with at least 1 of the following: endoscopy, fecal calprotectin, MRI.

Supplementary Table 4. Factors Associated With Mucosal Disease Progression in the Subgroup of Patients With Available Data (n = 71)

Risk Factor	n	Recurrence	Univariate Regression		
			HR	95% CI	*P* Value
Sex					.71[a]
Female	46	20	1		
Male	25	9	0.86	0.39–1.89	
Smoking status					.18[a]
Inactive	48	18	1		
Active	23	11	1.69	0.79–3.61	
Age at diagnosis[b]	71	29	1.00	0.97–1.03	.85[a]
Age at surgery[b]	71	29	1.00	0.97–1.02	.73[a]
Disease location					.66[a]
L1	46	18	1		
L2	2	0	0.34	0.01–6.12	
L3	23	11	1.20	0.56–2.56	
Disease behavior					.18[a]
B1	3	2	1		
B2	39	19	0.79	0.18–3.39	
B3	29	8	0.37	0.08–1.77	
Perianal disease					.29[a]
No	55	21	1		
Yes	16	8	1.57	0.69–3.57	
Previous surgery					.53[a]
No	58	22	1		
Yes	13	7	1.31	0.56–3.08	
Previous IMM and/or biological treatment					.78[a]
No	28	10	1		
Yes	43	19	1.11	0.52–2.40	
Baseline endoscopy					.45[a]
Rutgeerts score i0	48	19	1		
Rutgeerts score i1	23	10	1.35	0.62–2.94	
IMM and/or biological treatment between surgery and baseline endoscopy					.59[a]
No	36	16	1		
Yes	35	13	0.82	0.39–1.71	

CI, confidence interval; HR, hazard ratio; IMM, immunomodulator; N/A, not applicable.

[a]•••.

[b]HR of quantitative variables reflects the risk variation for one unit increase of the variable

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