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

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ABBREVIATIONS

CD: Crohn's disease; IBD: inflammatory bowel disease; IOIBD: International Organization for the study of Inflammatory Bowel Disease; MRI: magnetic resonance imaging; SD: standard deviation; TNF: tumor necrosis factor

ABSTRACT

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.

Results: The median time between surgery and baseline endoscopy was 7 months (Q₁₋₃ 5.7–9.5 months); 40 patients (46.5%) received medical prophylaxis in this period. The median follow-up time was 3.5 years (Q₁₋₃ 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 (Q₁₋₃ 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.

KEY WORDS: Complications; Hemicolectomy; Relapse; Surveillance

INTRODUCTION

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 one out of three 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 pre-biologic era, the Rutgeerts' score proved to be the most important variable predicting symptomatic recurrence during follow-up in post-operative 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 since this may affect treatment decisions.^{5,6} The International Organization for the study of Inflammatory Bowel Disease (IOIBD) agreed that Rutgeerts' Score of i0 (no endoscopic lesions) or i1 (between 1-5 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. looked at clinical recurrence during follow-up in this subgroup,⁴ 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 post-operative CD recurrence are well-

established,^{11,12} no data exist about potential risk factors for late post-operative CD recurrence.

In this retrospective, multicenter study, we aimed to evaluate the risk of late post-operative 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 post-operative CD recurrence according to Rutgeerts' Score at baseline endoscopy, to identify potential risk factors associated with late post-operative CD recurrence, and to evaluate the risk of mucosal disease progression based on endoscopy, fecal biomarker, and magnetic resonance imaging (MRI).

METHODS

Study Aims

The risk of late post-operative CD recurrence was evaluated through a retrospective cohort study in three 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 below 18 years 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) and/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 and/or diarrhea, IBD-related hospitalization, occurrence of new intra-abdominal fistulae, abscesses and/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. Further more, 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.

Outcome Measures

Primary aim was to evaluate the risk of late post-operative CD recurrence, which was defined as a composite endpoint of at least one of the following during follow-up after baseline endoscopy: clinical recurrence (i.e. new or worsening IBD-related abdominal pain and/or diarrhea), IBD-related hospitalization, occurrence of bowel damage (i.e. new intra-abdominal fistulae, abscesses and/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 post-operative CD recurrence according to Rutgeerts' Score at baseline endoscopy, (2) to identify potential risk factors associated with late post-operative CD recurrence, and (3) to evaluate the risk of mucosal disease progression as defined by a composite mucosal endpoint

of at least one of the following: endoscopic disease progression (i.e. evolution to Rutgeerts' Score ≥ 1), elevation of fecal biomarker (i.e. fecal calprotectin level $>250\mu\text{g/g}$), and disease activity on MRI (i.e. segmental Nancy score at the neoterminal ileum >2).

Statistical Analysis

Categorical variables were described as numbers and percentages, and continuous variables as mean with standard deviation (SD) or median with 1st and 3th quartiles values (Q₁₋₃), 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 post-operative CD recurrence. Univariate Cox regression analyses were used to identify potential risk factors for time-dependent late post-operative CD recurrence. Variables with a *P*-value <0.1 in the univariate analysis were candidates for the multivariate Cox model. The threshold for statistical significance was set at a *P*-value <0.05 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 female; n=27 active smokers) could be included. Main reasons for exclusion were Rutgeerts' Score ≥ 2 at postoperative endoscopy and the lack of endoscopy within the prespecified time interval. Median time between CD diagnosis and ileocecal resection was 6.1 years (Q₁₋₃ 0.9-19.4 years). Seventeen (19.8%) patients had undergone previous surgery, while the majority (n=55, 64%) had received treatment with immunomodulators and/or biologicals before ileocecal resection. Median (Q₁₋₃) time between surgery and baseline endoscopy was 7.0 months (Q₁₋₃ 5.7-9.5 months) and 40 (46.5%) patients

received medical prophylaxis with immunomodulators and/or biologicals in this period (**Table 1**).

Late Post-operative Crohn's Disease Recurrence

Median follow-up time after baseline endoscopy was 3.5 years (Q₁₋₃ 1.5-5.3 years). Based on the composite endpoint, late post-operative 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 (20/55) or i1 (15/31) at baseline endoscopy (p=0.28), and independent whether or not patients had received medical prophylaxis between surgery and baseline endoscopy (16/40 with prophylactic therapy vs. 19/46 without prophylactic therapy; p=0.90; **Figure 1**).

Time To Recurrence

Among the 35 patients with late post-operative CD recurrence, median time from baseline endoscopy to disease recurrence was 14.2 months (Q₁₋₃ 6.3-26.2 months). The proportion of patients with recurrence in the first year and first 3 years of follow-up was, respectively, 17.4% (15/86) and 36% (31/86) (**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=0.11; **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 post-operative CD recurrence who received medical prophylaxis between ileocecal resection and baseline endoscopy, median time to disease recurrence was 19.4 months (Q₁₋₃ 9.1-25.8 months). In the 19 patients with late post-operative CD recurrence that did not receive medical prophylaxis between ileocecal resection and baseline endoscopy, median time to disease recurrence was 11.0 (Q₁₋₃ 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 ($p=0.39$; **Supplementary Figure 2**).

Risk Factors

No risk factor for late post-operative CD recurrence could be identified after univariate cox regression analysis in the overall population, although there was a trend towards a higher risk for recurrence in patients with Rutgeerts' Score i1 at baseline compared to patients with Rutgeerts' Score i0 (Hazard Ratio 1.71, 95% Confidence Interval 0.87-3.35, $p=0.12$; **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**).

Mucosal Disease Progression

In 71/86 patients, at least one 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 29/71(40.8%) patients (**Supplementary Table 3**). Prevalence of mucosal disease progression during follow-up was comparable between patients with Rutgeerts' Score i0 (19/48) and Rutgeerts' Score i1 (10/23) at baseline endoscopy ($p=0.75$), and independent whether or not patients had received medical prophylaxis between surgery and baseline endoscopy (13/35 with prophylactic therapy vs. 16/36 without prophylactic therapy; $p=0.53$).

Among the 29 patients with mucosal disease progression, median time from baseline endoscopy to progression was 24.1 months (Q₁₋₃ 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 ($p=0.44$). 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 post-operative 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 one year after baseline endoscopy in the majority of those.

The POCER trial previously showed that patients with endoscopic remission (RUTGEERTS' SCORE i0 or i1) six months after ileocecal resection are still at risk for endoscopic recurrence one year later, with progression seen in 41% of patients.⁶ Our data show a very similar risk of late post-operative 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, since 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 post-operative CD patients regardless of their endoscopic appearance at index colonoscopy remains therefore warranted.

Risk factors for early post-operative 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 post-operative 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 post-operative CD recurrence potentially differ. Indeed, the established risk factors for early disease recurrence might not be independent and only reflect

disease severity and/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 post-operative CD recurrence, with step-up therapy in all patients if endoscopic recurrence is seen at colonoscopy.^{15,16} Mainly anti-tumor necrosis factor (anti-TNF) therapy, alone or in combination with other treatment modalities, has shown to reduce endoscopic post-operative 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 post-operative 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 (31/35) 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. showed that patients initiating medical prophylaxis immediately after surgery more often had Rutgeerts' Score ≤ 1 at first endoscopic evaluation.²⁰ In the follow-up of their cohort, patients with Rutgeerts' Score >1 experienced more frequently post-operative CD recurrence (both clinical as judged by the need to repeat the surgery) than patients with Rutgeerts' Score ≤ 1 , a finding that remained unmodified when excluding the patients that initiated immediate post-operative prophylaxis.²⁰ The initiation of immunomodulators or anti-TNF therapy in patients with an asymptomatic endoscopic

recurrence reflected by Rutgeerts' Score i2, however, 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. Since 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 post-operative endoscopic evaluation in a subset of patients in which colonoscopy was often replaced by dosage of faecal calprotectin and/or magnetic resonance imaging, thereby reflecting real-world practice and patients' preferences in the participating centers. Lastly, the time frame of which post-operative 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 IQR (3.8 months), so the impact on the outcomes was estimated low.

In conclusion, late post-operative 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 post-operative CD recurrence, including the effect of prophylactic therapy on late recurrence rates.

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TABLES

Table 1. Baseline characteristics at the time of endoscopy

Characteristic	Total (n=86)
Age, y, median (Q ₁₋₃)	38.4 (28.8-51.0)
Male, n (%)	31 (36)
Disease duration, y, median (Q ₁₋₃)	7.1 (1.7-20.0)
Age at diagnosis, n (%)	
A1: < 16 years	4 (4.7)
A2: 16-40 years	68 (79.1)
A3: > 40 years	14 (16.3)
Disease location, n (%)	
L1: ileal	56 (65.1)
L2: colonic	2 (2.3)
L3: ileocolonic	28 (32.6)
Associated upper digestive tract involvement, n (%)	2 (2.3)
Disease behaviour, n (%)	
B1: inflammatory	4 (4.7)
B2: stricturing	47 (54.7)
B3: penetrating	35 (40.7)
Perianal disease, n (%)	21 (24.4)
Active smoking, n (%)	27 (31.4)
Previous surgery, n (%)	17 (19.8)
Treatment with IMM and/or biological between time of diagnosis and ileocecal resection, n (%)	
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, n (%)	
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, n (%)	
i0	55 (64.0)
i1	31 (36.0)

IMM: immunomodulator; IQR: interquartile range; TNF: tumor necrosis factor

Table 2. Crude rate of late post-operative CD recurrence

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

IBD: inflammatory bowel disease

Table 3. Post-operative CD recurrence events over time (in the total population and stratified by prophylactic treatment and Rutgeerts' Score at baseline)

Events and censoring occurring after baseline endoscopy (time window, y-y)			0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
Total population (N=86)											
		<i>Events</i>	15	10	6	2	1	1	0	0	0
		<i>Censored</i>	13	8	8	3	8	4	4	1	2
		<i>At risk</i>	58	40	26	21	12	7	3	2	0
Prophylactic treatment	Rutgeerts' score at baseline										
Yes	i0 (N=28)	<i>Events</i>	3	3	1	1	0	1	0		
		<i>Censored</i>	2	2	4	3	6	1	1		
		<i>At risk</i>	23	18	13	9	3	1	0		
	i1 (N=12)	<i>Events</i>	2	3	2	0	0	0	0		
		<i>Censored</i>	1	0	2	0	1	0	1		
		<i>At risk</i>	9	6	2	2	1	1	0		
No	i0 (N=27)	<i>Events</i>	3	3	3	1	1	0	0	0	0
		<i>Censored</i>	8	2	0	0	1	2	0	1	2
		<i>At risk</i>	16	11	8	7	5	3	3	2	0
	i1 (N=19)	<i>Events</i>	7	1	0	0	0	0	0		
		<i>Censored</i>	2	4	2	0	0	1	2		
		<i>At risk</i>	10	5	3	3	3	2	0		

Table 4. Factors associated with late post-operative CD recurrence in the overall population

Risk Factor	N	Recurrence	Univariate regression		
			N	HR	95% CI
Gender					0.11
Female	55	26	1		
Male	31	9	0.54	0.25-1.15	
Smoking status					0.22
Inactive	59	21	1		
Active	27	14	1.53	0.78-3.03	
Age at diagnosis*	86	35	1.00	0.98-1.03	0.74
Age at surgery*	86	35	0.99	0.97-1.02	0.58
Disease location					0.94
L1	56	21	1		
L2	2	0	0	N/A	
L3	28	14	1.13	0.57-2.23	
Disease behaviour					0.55
B1	4	2	1		
B2	47	21	0.84	0.19-3.63	
B3	35	12	0.58	0.13-2.63	
Perianal disease					0.66
No	65	33	1		
Yes	21	2	0.84	0.38-1.85	
Previous surgery					0.22
No	69	27	1		
Yes	17	8	1.62	0.75-3.48	
Previous IMM and/or biological treatment					0.53
No	32	12	1		
Yes	54	23	1.25	0.62-2.52	
Baseline endoscopy					0.12
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					0.39
No	46	19	1		
Yes	40	16	0.75	0.38-1.45	

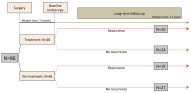
CI: confidence interval; HR: hazard ratio; IMM: immunomodulator; N/A: not applicable

* Hazard ratio of quantitative variables reflects the risk variation for one unit increase of the variable

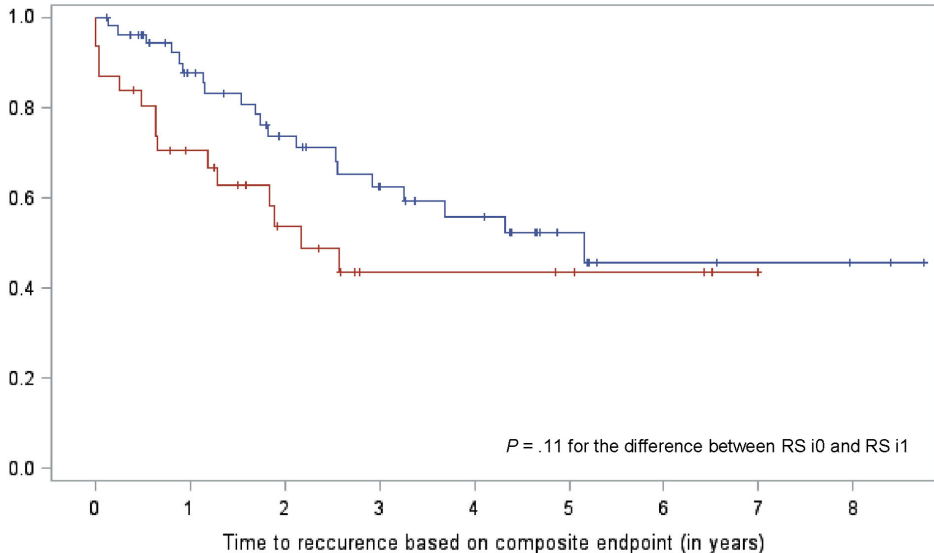
FIGURES - LEGENDS

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

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



Survival probability



Baseline endoscopy : Rutgeerts score — i0 — i1

i0	55	39	29	21	16	8	4	3	2
i1	31	19	11	5	5	4	3	0	