

Original article

Factors affecting the postoperative recurrence of Crohn's disease. New controversies with one centre's experience

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Introduction: Many patients with Crohn's disease have frequent recurrences, while others have long periods of remission after surgery. Determination of the risk factors of recurrence would be useful in identifying these high risk patients and to adopt suitable strategies during the surgical act and in the choice of post-surgical medical treatment.

Material and methods: A retrospective study was conducted on 78 patients with ileocolic Crohn's disease subjected to a first surgical resection, during the period from January 2000 to December 2005. The risk factors for endoscopic, radiological and surgical were subsequently analysed up to May 2009.

Results: A total of 41 patients (52.6%) had recurrences, being endoscopic in 17 (21.8%) of patients, radiological in 12 (15.4%) and surgical in 12 (15.4%). The mean time to first recurrence was 70.24 months. Recurrence was associated more to not performing anastomosis (77.7% vs 48.2%) during surgical resection. Although only the existence of postoperative complications ($P=.018$) was significantly associated with (68.4% vs 47.4%), as well as with the need for transfusion in the immediate post-operative period (67.8% vs 42.8%).

Conclusions: Transfusion of blood products is a risk factor for postoperative recurrence of Crohn's disease. But only postoperative complications are shown as an independent risk factor in the multivariate analysis. An adequate and safe surgical technique is a very important perioperative factor over which we have the influence to decrease these recurrences.

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Factores que afectan a la recurrencia postoperatoria de la enfermedad de Crohn. Nuevas controversias a través de la experiencia de un centro

R E S U M E N

Palabras clave:

Enfermedad de Crohn
Recurrencia postoperatoria
Factores de riesgo
Tratamiento quirúrgico

Introducción: Muchos pacientes con enfermedad de Crohn presentan recurrencias frecuentes mientras otros mantienen periodos prolongados de remisión después de la cirugía. Determinar los factores de riesgo de recidiva puede ser útil para identificar pacientes de alto riesgo y poder adoptar estrategias adecuadas durante el acto quirúrgico y en la elección del tratamiento médico postoperatorio.

Material y métodos: Estudio retrospectivo de 78 pacientes con enfermedad de Crohn ileo-cólica sometidos a una primera cirugía resectiva durante el periodo de enero de 2000 a diciembre de 2005; posteriormente se han estudiado los factores de riesgo de recurrencia endoscópica, radiológica y quirúrgica hasta mayo de 2009.

Resultados: 41 pacientes (52,6%) tuvieron recurrencia; siendo en 17 pacientes (21,8%) endoscópica, en 12 (15,4%) radiológica y en 12 (15,4%) quirúrgica. El tiempo medio de la primera recurrencia es de 70,24 meses. El no realizar anastomosis durante la cirugía resectiva parece tener más relación con la existencia de recidiva (77,7% vs. 48,2%). Aunque solo la existencia de complicaciones postoperatorias ($p = 0,018$) tiene relación significativa con la existencia de recurrencia (68,4% vs. 47,4%) así como la necesidad de transfusión en el periodo postoperatorio inmediato (67,8% vs. 42,8%).

Conclusiones: La transfusión de hemoderivados es un factor de riesgo para la recurrencia postoperatoria de la enfermedad de Crohn. Pero solo las complicaciones postoperatorias se muestran como factor de riesgo independiente en el análisis multivariable. Una técnica quirúrgica adecuada y segura es un factor perioperatorio muy importante en el que podemos influir para disminuir esta recidiva.

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Introduction

Crohn's disease is an inflammatory disease of the intestines. It had an incidence of 13 cases per 100 000 inhabitants in our health area in 2009. This disease has an unpredictable evolution and a high rate of recurrence despite the fact that a combined medical and surgical therapy is carried out. Around 80% of patients require surgery during their life¹ with a postoperative clinical recurrence of between 17% and 55% within 5 years and between 72% and 73% within 20 years. Recurrence requiring intervention occurs in between 11% and 32% of cases within 5 years and in between 20% and 40% within 10 years.^{2,3} It reaches approximately 50% twenty years after surgery. Recent data from endoscopic monitoring reports a recurrence ranging from 70% to 90% of cases one year after the operation⁴ and this has been associated with the development of complications and the need to undergo another operation. Therefore, an endoscopic assessment at 6-12 months (m) after surgery is recommended.⁵

Many prognostic factors have been researched and only smoking,^{6,7} ileocolonic disease⁸⁻¹⁰ and the extent of the disease^{7,10} have been found to increase the risk of recurrence. The rate of recurrence is greater after a resection with ileocolonic anastomosis than after a resection with ileostomy.^{11,12}

The objective of this study was to clarify the risk factors of postoperative recurrence in our patients who were treated separately from any clinical pharmacological trial.

Material and method

Patients and study design

A retrospective study was conducted on all the patients who underwent their first surgical resection for Crohn's disease from January 2000 to December 2005 in Department A and B of General Surgery of the *Complejo Hospitalario A Coruña* (A Coruña Hospital Complex). A follow-up of the endoscopic, radiological and surgical recurrence was then carried out from January 2000 to May 2009.

The exclusion criteria for this study were: disease located outside of the terminal ileum or the colon, the surgery during 2000-2005 was not the first abdominal surgery as a result of the disease, death after the operation (during hospitalisation) and lost to follow-up. A total of 84 patients with ileocolonic disease underwent surgery for the first time during this period. Four of them were lost to follow-up and another 2 died; one for suture dehiscence and the other for acute pulmonary oedema.

Three types of recurrence were defined: radiological recurrence diagnosed using barium enema or CT, endoscopic recurrence with aphthous ulcers in previously unaffected areas and recurrence which required subsequent surgical treatment. The need for postoperative surgery (during the hospitalisation period) or ileostomy reconstruction was not considered as a surgical recurrence. This is because the surgery was not caused by the disease but was secondary to postoperative complications or the previous surgical intervention.

It was not possible to diagnose recurrence by merely looking at the symptoms as the changes in intestinal habits due to surgery could not be easily distinguished from the symptoms of a new outbreak in the patients' clinical histories. It must be taken into account that the post-surgical diagnostic tests were not the same for all patients as it was an observational study. This may result in differences in the rate of recurrence with regard to other studies, but the figures reported here were those of our patients during the time period stated.

Statistical analysis

A total of 78 patients who were followed up for a mean period of 6.7 years were included in the statistical analysis. A descriptive statistical analysis of the variables was initially carried out using the statistical software SPSS 17.0 for Windows.

The cumulated recurrence and disease-free period were calculated using survival curves (Kaplan-Meier) for the whole study group and for each of the 21 variables studied. Patients were considered to be disease free during the 'surgery to diagnosis of recurrence' period and if no recurrences were noted, until the data was collected (May 2009).

In the *univariate analysis*, the log-rank test was used to test the null hypothesis or that the distributions of disease-free survival or cumulated recurrence were equal (1-disease-free survival) for each of the variables. Differences were considered to be statistically significant when $P < .05$.

A multivariate analysis was performed to identify the independent diagnostic factors using the variables that were found to be significant in the *univariate analysis* ($P < .05$) and those that were nearly significant ($P < .2$). The risk was calculated using the Cox regression model. Another analysis was carried out at a later point which included the variables found to be associated with post-surgical recurrence in the literature: smoking, course and time from onset of the disease to surgery.

Results

A total of 78 patients were included in the review. They were followed up for a maximum of 8 years and 3 months and a minimum of 3 years and 3 months after initial surgery. We found signs of recurrence in 40 patients (52.6%); being endoscopic in 17 patients (21.8%), radiological in 12 (15.4%) and surgical in 12 (15.4%). As it was a retrospective study, the figures of endoscopic and radiological recurrence are probably reduced as there was no systematic protocol for the

Table 1 – Causes of postoperative surgical recurrence of Crohn's disease

Cause	No.	%	Time after surgery, months
Intestinal obstruction	5	41.7	15, 33, 38, 68 and 70
Intra-abdominal abscess	2	16.7	54 and 57
Ileal perforation	2	16.7	25 and 37
LGIB	1	8.3	46
Stercoral fistula	1	8.3	45
Severe outbreak	1	8.3	48
Total	14	100	

radiological and endoscopic tests. The mean follow-up after surgery was 6.7 years (range 5.0-8.5 years).

Figure 1 shows the cumulative rate of recurrence at 12, 24, 36 months, 5 and 8 years after surgery. The most common cause of surgical recurrence was intestinal obstruction (41.7%). This occurred more than one year after surgery in all cases and coincided with the location of the previous anastomosis. A recurrence of the disease was found in 4 patients and a probable foreign body giant cell reaction linked to the suture material was reported in the other patient. These were, therefore, considered secondary to recurrence and not technical complications of the anastomosis. Table 1 shows the other causes of surgical recurrence.

The mean age at diagnosis for Crohn's disease was 33.28 years (range 12-75 years). The mean age when the patients underwent surgery was 38.3 years (range 13-75 years). The mean time from onset of the disease to surgery was 5.15 ± 6.5 years with a range of 0 to 27 years. The other epidemiological characteristics of all the variables studied are presented in Table 2.

The mean time to first recurrence was 70.2 months (CI 95%: 61.3- 79.1). Of the 12 patients who had a surgical recurrence,

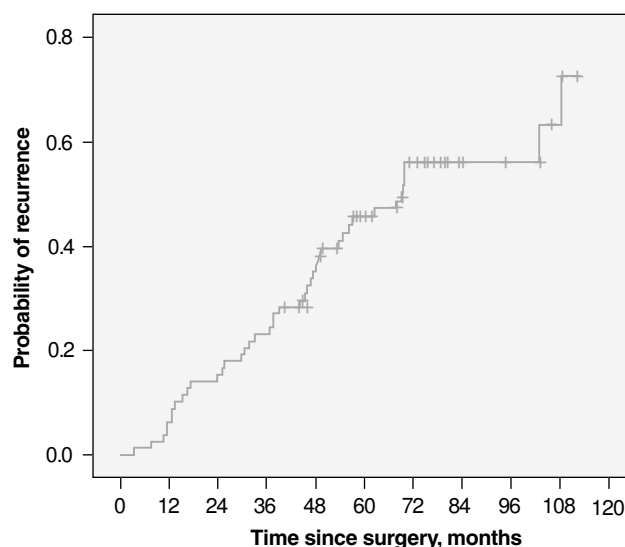


Figure 1 – Cumulated recurrence at 12, 24, 36 months, and 5 and 8 years after surgery. Cumulated recurrence at one year, two years, 3 years, 5 years and 8 years is 6.4%, 15.4%, 23.1%, 45.5% and 56% respectively.

Table 2 – Probability of postoperative recurrence for all the variables studied

Variable	No.	Recurrence	No recurrence	Mean ^e	Median ^f	P
<i>Time in years since onset^a</i>						.257
<3	37 (47.4%)	23 (62.2%)	14 (37.8%)	64.38	56.95	
<or equal to 3	41 (52.6%)	18 (43.9%)	23 (56.1%)	75.39	102.95	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Age^b</i>						.601
<21	21 (26.9%)	17 (66%)	7 (33.3%)	66.28	67.93	
21-44	39 (57.7%)	18 (46.2%)	21 (53.8%)	75.045	102.95	
>44	18 (25.6%)	9 (50.0%)	9 (50.0%)	65.95	56.95	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Age at surgery^c</i>						.401
<26	19 (24.4%)	14 (73.7%)	5 (26.3%)	63.12	53.64	
26-50	40 (51.2%)	18 (45.0%)	22 (55.0%)	74.9	102.95	
>50	19 (24.4%)	9 (47.4%)	10 (52.6%)	69.98		
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Sex</i>						.373
Male	44 (56.4%)	25 (56.81%)	19 (43.18%)	66.85	56.19	
Female	34 (43.6%)	16 (47.05%)	18 (52.94%)	74.17	69.54	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Smoking habit^d</i>						.386
Smoker	18 (23.1%)	9 (50%)	9 (50%)	67.92	67.93	
Non-smoker	40 (60.6%)	23 (57.5%)	17 (42.5%)	63.36	56.95	
Former smoker	13 (16.3%)	5 (38.4%)	8 (65.1%)	83.91	102.95	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Course</i>						.993
Perforating	45 (57.7%)	25 (55%)	20 (44%)	69.91	69.54	
Not perforating	33 (42.3%)	16 (48.5%)	7 (51.5%)	69.92	102.95	
<i>Leukocytosis</i>						.191
<9000	29 (37.2%)	13 (44.8%)	16 (55.2%)	76.13	102.95	
≥9.000	49 (62.8%)	28 (57.5%)	21 (42.9%)	65.88	56.2	
<i>Time scale</i>						.512
Urgent	35 (44.9%)	19 (54.28%)	16 (45.7%)	66.6	69.54	
Scheduled	43 (55.1%)	22 (51.16%)	21 (48.8%)	71.6	69.8	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Anastomosis</i>						.24
Yes	69 (88.5%)	34 (42.27%)	35 (50.7%)	66.6	69.8	
No	9 (11.5%)	7 (77.7%)	2 (22.2%)	61.6	53.64	
<i>Type</i>						.159
Term-term	7 (9%)	3 (42.86%)	4 (57.1%)	83.97	108.36	
Term-lat	39 (50%)	17 (43.59%)	22 (56.4%)	77.54	102.95	
Lat-lat	22 (28%)	14 (63.64%)	8 (36.4%)	55.23	46.69	
<i>Suturing</i>						.815
Manual	25 (32.1%)	13 (52%)	12 (8%)	68.75	69.8	
Mechanical	43 (55.1%)	21 (48.84%)	22 (51.2%)	73.81	102.95	
<i>Complications</i>						.018
Yes	19 (15.4%)	13 (68.42%)	6 (31.6%)	58.59	46.69	
No	59 (84.6%)	28 (27.46%)	31 (52.5%)	75.85	102.95	
Overall	78	41 (52.6%)	37 (47.4%)	70.22	69.54	
<i>Granuloma</i>						.06
Yes	21 (26.9%)	15 (71.4%)	6 (28.6%)	56.62	47.31	
No	55 (70.5%)	30 (54.5%)	36 (54.5%)	75.38	69.9	
<i>Reconstruction</i>						.997
Yes	17 (21.8%)	9 (52.94%)	8 (47.1%)	58.91	69.54	
No	59 (77.2%)	32 (54.3%)	27 (45.8%)	69.07	62.6	

Table 2 (Continuation)

Variable	No.	Recurrence	No recurrence	Mean ^e	Median ^f	P
Transfusion						.018
Yes	28 (35.9%)	19 (67.86%)	9 (32.1%)	57.1	46.69	
No	49 (64.1%)	21 (42.86%)	28 (57.1%)	78.64	102.95	
Treatment						.145
Yes	66 (84.6%)	38 (57.57%)	28 (42.4%)	66.8	59.95	
No	10 (12.8%)	3 (30%)	7 (70%)	83.5		
5-ASA						
Yes	63 (80.8%)	37 (58.73%)	26 (41.31%)	66.91	56.95	
No	12 (19.2%)	3 (25%)	9 (75%)	84.44		
Corticosteroids						
Yes	28 (35.9%)	17 (60.71%)	11 (39.9%)	63.36	54.78	
No	48 (64.1%)	24 (50%)	24 (50%)	71.83	69.8	
Immunosuppressive agents						
Yes	6 (7.7%)	4 (66.66%)	2 (33%)	39.62	31.67	
No	70 (92.3%)	37 (52.85%)	33 (47.1%)	70.44	69.5	
Infliximab						
Yes	0	0	0			
No	70	41 (58.57%)	29 (41.4%)	66.4	56.95	

^aThe median of 3 years was used as a reference for the cut-off point of time from onset.

^bThe percentiles 25 and 75, corresponding to 21 and 44 years old, were used as a reference for the cut-off point for age at diagnosis.

^cThe percentiles 25 and 75, corresponding to 26 and 50 years old, were used as a reference for the cut-off point for age at surgery.

^dPatients who had stopped smoking at least one year before surgery were considered to be former smokers; non-smokers were those who had never smoked and active smokers those who had smoked in the 12 months prior to surgery.

^{e,f}The mean and median are the mean and median of the recurrence-free survival time according to the different variables studied.

4 of them (5.5% over the total) had a second recurrence. This was endoscopic in 3 of them, and in the other case it involved an intra-abdominal abscess secondary to a new recurrence of the disease. Table 3 shows a summary of the cumulated recurrence at different points depending on the different variables.

The probabilities of recurrence depending on the different variables studied are also shown in Table 2. We can see that the group of patients who were under 21 years old at diagnosis tended to have a greater rate of postoperative recurrences, but this was not confirmed by calculating the P according to the log-rank test ($P=.601$).

In the patients with a disease evolution of less than 3 years, the mean disease-free interval was 64.38 months (CI 95%: 51.6-77.1) and when it was over or equal to 3 years, it was 75.4 months (CI 95%: 63.6-79.1). The group of patients under the age of 26 years at the time of surgery had a greater tendency to suffer postoperative recurrence.

Whether the course of the disease was perforating or non-perforating did not seem to have a statistically significant relationship with recurrence ($P=.993$). Leukocytosis was found to be nearly significantly associated with recurrences ($P=.191$). In contrary to what was found in the literature, recurrence of the disease seemed to be more closely associated with not performing an anastomosis in our series (77.7% compared to 42.3%), although it was not statistically significant due to the small number of cases in the group without anastomosis. There was a greater tendency for recurrence in latero-lateral

anastomosis, which was not confirmed by the univariate analysis either ($P=.159$).

Figure 2 shows a significant relationship between postoperative complications and the probability of disease recurrence (68.4% compared to 47.5%; $P=.018$). These complications were: abscess with no signs of fistula, bleeding, anastomotic fistula, suture dehiscence, obstruction and prolonged ileus. Table 4 shows that abscess, prolonged ileus and intestinal obstruction are the complications that are most closely associated with postoperative recurrence.

Patients who have a granuloma in the specimen were more likely to have a surgical recurrence than if no granuloma was found (71.3% compared to 54.4%), although it was not significant. The postoperative reconstruction of ostomies carried out during the initial surgery as well as those carried out during subsequent surgery did not appear to have an effect on the postoperative appearance of disease.

In the univariate analysis, only the presence of postoperative complications ($P=.018$) was found to be significantly linked to the presence of recurrence (68.4% compared to 47.5%), as well as the need for transfusion during the postoperative period (67.9% compared to 42.9%).

The multivariate analysis was carried out using the variables with a statistically significant value of P: transfusion and postoperative complications, and the variables that were found to be nearly significant with a $P<.2$ were added later: type of anastomosis ($P=.159$), presence of granuloma ($P=.06$) and medical treatment ($P=.145$). The multivariate analysis showed that

Table 3 – Probability of recurrence at different time intervals according to the different variables

Variable	No.	6 m	12 m	24 m	36 m	60 m	90 m
<i>Age at diagnosis</i>							
<21 years	21	0	0	0	0.238	0.492	0.661
21-24	39	0	0.510	0.128	0.205	0.430	0.430
<24 years	18	0.060	0.167	0.278	0.333	0.550	0.550
<i>Years since onset</i>							
<3 years	37	0	0.108	0.216	0.243	0.507	0.655
≥3 years	41	0.040	0.073	0.098	0.220	0.405	0.405
<i>Age at surgery</i>							
<26 years	19	0	0	0.105	0.158	0.526	0.704
26-50 years	40	0	0.050	0.150	0.250	0.397	0.484
>50 years	19	0.053	0.158	0.211	0.263	0.498	0.498
<i>Sex</i>							
Male	44	0	0.045	0.182	0.295	0.518	0.558
Female	34	0.02	0.088	0.118	0.147	0.375	0.561
<i>Smoker</i>							
Yes	18	0	0	0.056	0.167	0.342	0.671
No	40	0.025	0.125	0.250	0.300	0.527	0.60
Former smoker	13	0	0	0.077	0.154	0.316	0.316
<i>Course</i>							
Perforating	45	0	0.067	0.133	0.178	0.432	0.602
Not perforating	33	0.030	0.061	0.182	0.303	0.491	0.419
<i>Leukocytosis</i>							
<9000	29	0.034	0.103	0.103	0.172	0.317	0.471
≥9000	49	0	0.041	0.184	0.265	0.543	0.612
<i>Surgical time</i>							
Urgent	35	0	0.086	0.143	0.229	0.484	0.632
Scheduled	43	0.023	0.047	0.163	0.233	0.428	0.522
<i>Anastomosis</i>							
Yes	69	0.014	0.072	0.174	0.261	0.434	0.504
No	9	0	0	0	0	0.619	1
<i>Type of anastomosis</i>							
Term-term	7	0	0	0.143	0.143	0.286	0.286
Term-lat	39	0.026	0.077	0.103	0.154	0.370	0.440
Lat-lat	22	0	0.091	0.273	0.409	0.550	0.775
<i>Suturing</i>							
Manual	25	0	0.080	0.240	0.320	0.454	0.575
Mechanical	43	0	0.047	0.116	0.209	0.406	0.474
<i>Complications</i>							
Yes	19	0.053	0.158	0.263	0.316	0.684	0.789
No	59	0	0.034	0.119	0.203	0.386	0.491
<i>Type of complications</i>							
Fistula	4	0	0	0	0.500	1	1
Abscess	2	0	0	0	0.250	0.750	0.750
Dehiscence	2	0	0	0	0	0	0
Obstruction	2	0	0	0	0.500	1	1
Bleeding	2	0	0	0	0	0.500	1
<i>Granuloma</i>							
Yes	21	0.048	0.095	0.238	0.333	0.639	0.690
No	55	0	0.018	0.127	0.200	0.383	0.515
<i>Reconstruction</i>							
Yes	17	0	0	0.059	0.118	0.382	0.743
No	59	0.017	0.085	0.169	0.271	0.492	0.542

Table 3 (Continuation)

Variable	No.	6 m	12 m	24 m	36 m	60 m	90 m
Transfusion							
Yes	28	0.036	0.071	0.179	0.250	0.627	0.734
No	49	0	0.061	0.122	0.204	0.344	0.447
Treatment							
Yes	66	0.015	0.061	0.167	0.258	0.503	0.599
No	10	0	0.100	0.100	0.100	0.229	0.403

m indicates months.

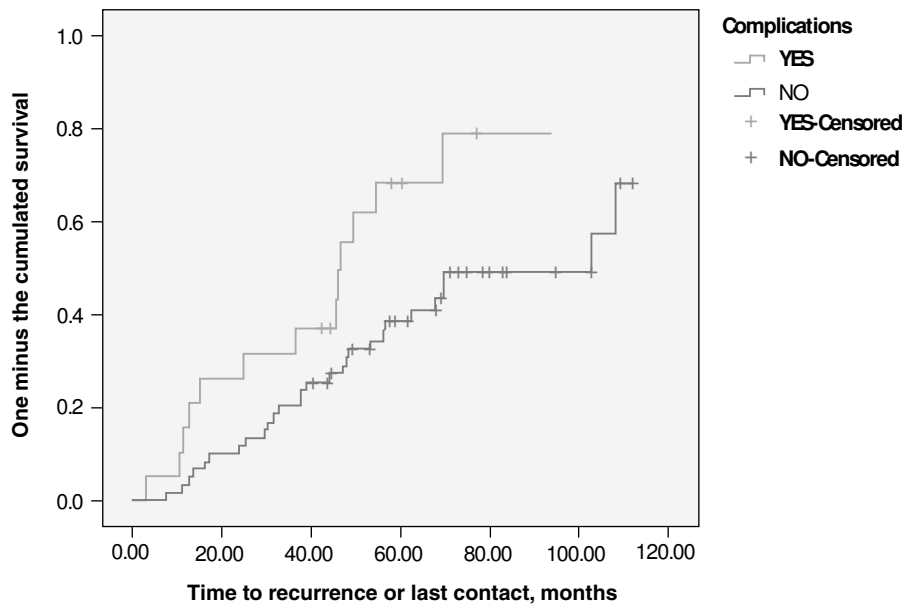


Figure 2 – This graph shows the recurrence of Crohn's disease and we can see a higher percentage of recurrence in patients who had postoperative complications than in those that did not.

transfusion was no longer significant ($P=.633$) and postoperative complications were still statistically significant ($P=.039$). The presence of granuloma in the specimen was not found to be statistically significant but it was very close ($P=.076$).

We included the variables preoperative smoking habit, time since onset of the disease and course in a later study in order to rule out that these variables were linked to the presence of complications and stop them from being confounding factors.

We found that neither the course nor time since onset of disease made postoperative complications lose significance as an independent risk factor. When smokers were included, it lost significance ($P=.058$), although we believe that this was due to the small sample size and not because these variables are related as the relative risk did not vary.

We included granuloma in this second multivariate analysis because we found that if it was not included, the

Table 4 – Type of postoperative complications and probabilities of recurrence according to each type of complication

	No. (%)	Recurrence (%) ^a	
Abscess	6 (7.7%)	4 (66.7%)	2 (33.3%)
Fistula	2 (2.6%)	1 (50%)	1 (50%)
Dehiscence	2 (2.6%)	0	2 (100%)
Obstruction	2 (2.6%)	2 (100%)	0
Prolonged ileus	3 (3.8%)	2 (66.7%)	1 (33.3%)
Bleeding	4 (5.1%)	4 (100%)	0
Total complications	19 (24.4%)	13 (68.42%)	6 (31.6%)
No. complications	59 (75.6%)	28 (27.46%)	31 (52.5%)
Total	78 (100%)	41 (52.6%)	37 (47.4%)

^aPercentage of total complications.

blood products transfusion variable remained significant in the analysis. Therefore, these two variables were strongly associated. We carried out a parallel analysis to check this using contingency tables and when calculating the chi-square value, we found that the presence of granulomas was associated with a higher chance of transfusion ($P=.044$). A transfusion was carried out in 52.4% of cases when granulomas were found and in 27.8% when they were not.

Discussion

The results of this study show that of the variables that may have an effect on postoperative recurrence only the presence of postoperative complications and blood products transfusions were significantly associated with an increased risk of recurrence during the first 8 years. The influence of postoperative complications in the recurrence of this disease was confirmed in the multivariate analysis but the presence of a transfusion was found to be no longer significant due to its association with granuloma. By excluding this associated variable from the analysis, blood products transfusion remained as an independent risk factor in the multivariate analysis.

The impact of age on recurrence after surgery has been studied in many series; patients who are diagnosed with the disease early tend to have a greater level of recurrence due to the longer follow-up period. In our study, in accordance with the majority of prior studies,¹³⁻¹⁹ neither age at diagnosis nor at surgery seemed to be predictive factors of postoperative recurrence, although it did tend to be higher the earlier the diagnosis was made and the earlier the patients underwent surgery.

In the prospective study by Pogglioli et al,¹⁷ an increased recurrence was found in patients who had been suffering from the disease for over 6 years. Sachar et al¹¹ found this increase in patients who had had the disease for under 10 years. Our results showed that recurrence-free survival was lower in patients who had had the disease for less than 3 years (64.4 compared to 75.4 months). These results could be linked to the fact that a short time period between diagnosis and surgery points to a more aggressive phenotype. As a consequence, we believe, as other authors do, that surgery should not be indicated in symptomatic patients who have had the disease for a short period of time due to the higher potential risk of early recurrence.²⁰

Being female has only been linked to a higher risk of recurrence in three studies. Whereas it has been put in doubt by many others,^{11,13-15,17,18} we found that the probability of recurrence was similar in both sexes.

Tobacco use has been widely studied in the pathogenesis of inflammatory diseases, and it been found to be associated with an increased risk of developing Crohn's disease and post-surgical recurrences, as in the studies by Cottone et al⁷ and Yamamoto et al.²¹ Furthermore, this last study reported that this risk was reduced by stopping smoking. Contrary to the literature and to the two important studies mentioned above, we found that the group of smokers had a higher probability of recurrence than non-smokers or former smokers

(57.5%, 50% and 38.4%) and that this increased probability disappeared after 60 months of follow-up. Although we extracted these data from a retrospective study which only studied the use of tobacco before surgery, we shall just pose the question and leave it open to discussion: may it be that the pathophysiological mechanism of tobacco has a greater effect on early recurrence of the disease than on overall postoperative recurrence?

Regarding the indication for surgery, we did not find an association with a perforating course or with the need for urgent surgery, just as in other studies.^{15,17,18} What was reported in the literature was an association between the type of initial presentation and the type of later recurrence.¹⁷ We also observed this comparing the types of recurrence, especially when it was a surgical recurrence.

The type of anastomosis is one of the most important aspects in the surgical management of Crohn's disease. The faecal flow from the large intestine over the new terminal ileum is involved in the anastomotic recurrence. Caprilli et al¹⁶ reported a higher risk of recurrence in termino-terminal anastomosis in a multicentre study but it was not statistically significant. In our series, latero-lateral anastomosis had a recurrence of 63.6% while it was 42.9% in termino-terminal anastomosis. This was not statistically significant but it was very close to being significant ($P=.159$). We also reported a recurrence of up to 77% when a primary anastomosis was not performed and 42.27% when it was; although it is true that the number of patients belonging to each group was very unequal. Nine cases did not undergo a primary anastomosis during the initial surgery, 2 of them had no recurrences, 4 had endoscopic recurrence and 3 surgical recurrence. One of the surgical recurrences was due to the perforation of the ileal stump two years after the primary surgery, resulting in a new endoscopic recurrence after two years. Another case was due to an intestinal obstruction secondary to recurrence of the disease in the remaining terminal ileum one year after the initial surgery. The last case was due to an abscess and stercoral fistula which was also caused by a recurrence of ileal Crohn's disease. The overall rate of recurrence was the same in patient undergoing a posterior ileocolonic reconstruction (52%) and those who did not (54%).

A recent meta-analysis of 8 studies showed that latero-lateral anastomosis is linked to fewer anastomotic leaks and postoperative complications compared to termino-terminal anastomosis.²² Another retrospective study²³ also reported a greater disease-free survival in manual latero-lateral anastomosis than in mechanical termino-terminal anastomosis. In our study the type of suture (mechanical or manual) did not seem to have an effect on the recurrence of the disease, regardless of the type of anastomosis employed.

There are contradictory publications in the literature on the impact that the presence of granuloma in the specimen has on postoperative recurrence.^{18,24,25} In our analysis, when granulomas were found in the specimen, the risk was 2.2 times higher and nearly statistically significant (CI 95%: 0.92-5.27).

It is generally considered that the immunosuppressive effect of blood products transfusions protects against the recurrence of Crohn's disease,²⁶ although many other studies do not agree

with this.²⁷ We did not find this protective effect in our study. In fact, we found a statistically significant association between transfusion and an increased recurrence of the disease ($P=.018$). In this analysis and in a parallel analysis with contingency tables, we can see that there is a significant relationship between the presence of granulomas and the need for transfusion. We have not actually found this association in the literature reviewed. We believe that it is possible that having granulomas may cause an occult bleeding with posterior anaemia and need for a preoperative transfusion.

There are other factors related with postoperative recurrence, but due to their characteristics, they were not included in this study: genetic factors and medical treatment. Of the different genetic variations studied, only polymorphism in the NOD2/CARD15 protein that forms part of a membrane receptor for gram + and gram - bacteria is associated with a higher immunological activity that increases the probability of recurrence.²⁸⁻³⁰ As for medical treatment, prophylaxis with 5-ASA and nitroimidazole antibiotic medication is beneficial, as well as combining it with immunosuppressive agents when there is a high risk of recurrence in the treatment of postoperative severe ileitis.³¹

Crohn's disease has been associated with a higher risk of postoperative complications and with the need for multiple anastomosis. There are few studies that look at whether these complications increase the risk of recurrence and only two have found this association.^{32,33} Here we found that it was an independent risk factor for recurrences in the univariate and multivariate analysis.

As a conclusion, blood products transfusion is a risk factor for the postoperative recurrence of Crohn's disease. But only postoperative complications were found to be an independent risk factor in the multivariate analysis. A possible explication for this could be that the secondary inflammatory reaction that causes postoperative complications may cause an autoimmune reaction at a later time that brings on a recurrence of Crohn's disease. If we examine the type of complications, the majority are secondary to performing an anastomosis. Anastomotic recurrence might not, therefore, only be explained by an early faecal reflux and bacterial overgrowth, this also may occur as a result of complications.

We, therefore, believe that if a patient with a not very aggressive form of the disease develops a complication for any reason after scheduled surgery, then he/she must be treated as a patient at high risk of recurrence and the medical treatment must be adapted to this new postoperative situation.

Conflict of interest

The authors affirm that they have no conflict of interest.

REFERENCES

- Olaison G, Sjodahl R, Tagesson C. Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. *Gut*. 1990;31:325-8.
- Hellberg R, Hultén L, Rosengren C, Ahren C. The recurrence rate after primary excisional surgery for Crohn's disease. *Acta Chir Scand*. 1980;146:435-43.
- Borley NR, Motensen NJ, Jewell DP. Preventing postoperative recurrence of Crohn's disease. *Br J Surg*. 1997;84:1493-502.
- Tytgat GN, Mulder CJ, Brummelkamp WH. Endoscopic lesions in Crohn's disease early after ileocecal resection. *Endoscopy*. 1988;20:260-2.
- Terdiman JP. Prevention of postoperative recurrence in Crohn's disease. *Clin Gastroenterol Hepatol*. 2008;6:616-20.
- Sutherland LR, Ramcharan S, Bryant H. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology*. 1996;110:424-31.
- Cottone M, Rosselli M, Orlando A, Oliva L, Puleo A, Cappello M, et al. Smoking habits and recurrence in Crohn's disease. *Gastroenterology*. 1994;106:643-8.
- Lock MR, Farmer RG, Fazio VW, Jagelman DG, Lavery IC, Weakley FL. Recurrence and reoperation for Crohn's disease: the role of disease location in prognosis. *N Engl J Med*. 1981;304:1586-8.
- Whelan G, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. *Gastroenterology*. 1985;88:1826-33.
- Williams JG, Wong WD, Rothenberger DA, Goldberg SM. Recurrence of Crohn's disease after resection. *Br J Surg*. 1991;78:10-9.
- Sachar DB, Wolfson DM, Greenstein AJ, Goldberg J, Styczynski R, Janowitz HD. Risk factors for postoperative recurrence of Crohn's disease. *Gastroenterology*. 1983;85:917-21.
- Rutgeerts P, Goobes K, Peeters M, Hiele M, Penninckx F, Aerts R, et-al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet*. 1991;338:771-4.
- Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99:956-63.
- Chardavoyne R, Flint GW, Pollack S, Wise L. Factors affecting recurrence following resection for Crohn's disease. *Dis Colon Rectum*. 1986;29:495-502.
- Wettergren A, Christiansen J. Risk of recurrence after resection for ileocolonic Crohn's disease. *Scand J Gastroenterol*. 1991;26:1319-22.
- Caprilli R, Corrao G, Taddei G, Tonelli F, Torchio P, Vissicido A. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). Prognostic factors for postoperative recurrence of Crohn's disease. *Dis Colon Rectum*. 1996;39:335-41.
- Poggioli G, Laureti S, Selleri S, Brignola C, Grazi GL, Stocchi L, et-al. Factors affecting recurrence in Crohn's disease. Results of a prospective audit. *Int J Colorectal Dis*. 1996;11:294-8.
- Anselme PF, Wlodarczyk J, Murugasu R. Presence of granulomas is associated with recurrence after surgery for Crohn's disease: experience of a surgical unit. *Br J Surg*. 1997;84:78-82.
- Burgmann T, Clara I, Graff L, Walker J, Lix L, Rawsthorne P, et-al. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis-how much is irritable bowel syndrome? *Clin Gastroenterol Hepatol*. 2006;4:614-20.
- Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of long-term enteral nutrition on clinical and endoscopic recurrence after resection for Crohn's disease: A prospective, non-randomized, parallel, controlled study. *Aliment Pharmacol Ther*. 2007;25:67-72.

21. Yamamoto T, Keighley MR. The association of cigarette smoking with a high risk of recurrence after ileocolonic resection for ileocecal Crohn's disease. *Surg Today*. 1999;29:579-80.
22. Simillis C, Purkayastha S, Yamamoto T, Strong SA, Darzi AW, Tekkis PP. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. *Dis Colon Rectum*. 2007;50:1674-87.
23. Muñoz-Juárez M, Yamamoto T, Wolff BG, Keighley MR. Wide-lumen stapled anastomosis vs. conventional end-to end anastomosis in the treatment of Crohn's disease. *Dis Colon Rectum*. 2001;44:20-5.
24. Glass RE, Baker WN. Role of the granuloma in recurrent Crohn's disease. *Gut*. 1976;176:233-42.
25. Chambers TJ, Morson BC. The granuloma in Crohn's disease. *Gut*. 1979;20:269-74.
26. Peters WR, Fry RD, Fleshman JW, Kodner JJ. Multiple blood transfusions reduce the recurrence rate of Crohn's disease. *Dis Colon Rectum*. 1989;32:749-53.
27. Gooszen HG, Silvis R. Protective effect of blood transfusions on postoperative recurrence of Crohn's disease in parous women. *Neth J Med*. 1994;45:65-71.
28. Yamamoto S, Ma X. Role of Nod2 in the development of Crohn's disease. *Microbes Infect*. 2009;11:912-8.
29. Bevins CL, Stange EF, Wehkamp J. Decreased Paneth cell defensin expression in ileal Crohn's disease is independent of inflammation, but linked to the NOD2 1007 fs genotype. *Gut*. 2009;58:882-3.
30. Salucci V, Rimoldi M, Penati C. Monocyte-derived dendritic cells from Crohn patients show differential NOD2/CARD15-dependent immune responses to bacteria. *Inflamm Bowel Dis*. 2008;14:812-8.
31. Cunningham MF, Docherty N, Coffey JC, Burke JP, O'Connell PR. Postsurgical recurrence of ileal Crohn's disease. An update on risk factors and intervention points to a central role for impaired host-microflora homeostasis. *World J Surg*. 2010;34:1615-26.
32. Holzheimer RG, Molloy RG, Wittmann DH. Postoperative complications predict recurrence of Crohn's disease. *Eur J Surg*. 1995;161:129-35.
33. Scarpa M, Angriman I, Barollo M, Polese L, Ruffolo C, Bertin M, et al. Role of stapled and hand-sewn anastomoses in recurrence of Crohn's disease. *Hepatogastroenterology*. 2004;51:1053-7.