

Factors affecting recurrence in Crohn's disease

Results of a prospective audit

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Abstract. It has been suggested that certain clinical and morphological features can modify the outcome of Crohn's disease, particularly regarding recurrence after surgery. A series of 233 patients was followed prospectively. They underwent a resectional surgical procedure for both primary and recurrent Crohn's disease during a fifteen-year period with a minimum follow-up of eighteen months. Possible risk factors for recurrence were studied. They included duration of disease before primary surgery, the type of clinical presentation at onset (whether "Perforating" or "Non-perforating"), the initial anatomical location, the presence of microscopic disease at the resection edges, the type of surgical procedure (anastomosis vs stoma), post-operative surgical complications and the age of the patient. The duration of the disease before the initial operation was the only significant factor related to the recurrence rate.

Résumé. On a suggéré que certaines données cliniques et morphologiques étaient susceptibles de modifier l'évolution de la maladie de Crohn, en particulier quant à l'incidence des récurrences après chirurgie. Une série de 233 patients ont été suivis prospectivement. Au cours d'une période de 15 ans, ces patients ont subi deux interventions de résection soit, la résection du foyer primaire et la résection d'une récurrence de la maladie de Crohn. Le suivi minimum de ces patients est de 18 mois. Les facteurs de risque d'une récurrence ont été étudiés. Parmi ceux-ci on note la durée de l'évolution de la maladie avant la chirurgie primaire, le mode de présentation clinique au début (maladie transmurale ou non transmurale) le siège initial, la présence de lésions microscopiques sur les tranches de section, le type de geste chirurgical (anastomose versus stoma), la survenue de complications postopératoires et l'âge du patient. Seule la durée d'évolution avant le geste chirurgical initial a été établie comme représentant un facteur significatif en faveur d'une récurrence.

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The literature of the last 30 years has been full of retrospective analyses of series of patients with Crohn's disease treated by surgery. Several factors predisposing to recurrence have been investigated such as early age of onset of disease, duration of the disease before surgery, presence of histological inflammation at the resection margins, location of the disease and many others. There have, however, been very few prospective studies investigating factors predisposing to recurrence with an analysis of their long-term influence.

In 1978 we established a prospective post-operative surveillance of patients undergoing surgery for Crohn's disease in an attempt to identify factors predictive of risk of recurrence.

Methods

From January 1 1978 to December 31 1993, 336 patients were surgically treated for Crohn's disease. Sixty-two had their primary operation performed elsewhere, and were excluded from analysis owing to inadequate morphological and clinical data concerning the primary operation. 274 patients underwent a primary surgical procedure for Crohn's disease at our Institution. Forty-one were excluded for reasons including loss to follow-up [11], non-resectional procedure (strictureplasty, 18), and follow-up of less than 18 months. This left 233 patients followed from 18 to 204 months after primary resectional surgery. 129 (55.3%) were male and 104 (44.7%) female.

The following parameters were investigated as possible predictive factors of recurrence: the duration of the disease prior to primary surgery, the age of the patient at onset of disease, the presence of microscopic disease at the resection margins, the initial anatomic location of the disease (according to Farmer's classification) [1], the type of disease at onset, perforating and non-perforating [2] the type of operation performed (anastomosis vs stoma) and the post-operative complication rate.

Recurrence was defined as the need for re-operation. The relationship between recurrence and the above factors each investigated as an independent variable was determined by the chi squared test using Yates correction where appropriate. A value for *p* of less than 0.05 was considered as statistically significant. Cumulative recurrence rates, expressed as probability, were calculated using the Kaplan Meyer life-table analysis [3]. Multi-

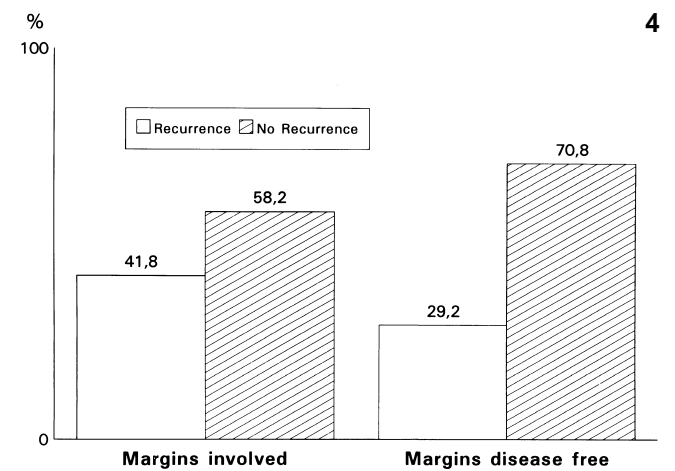
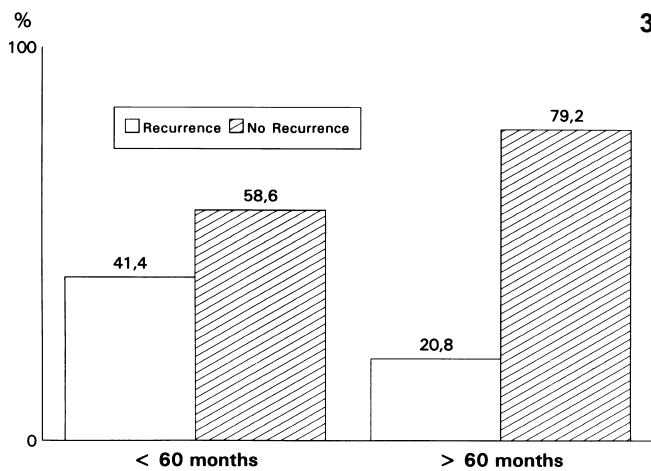
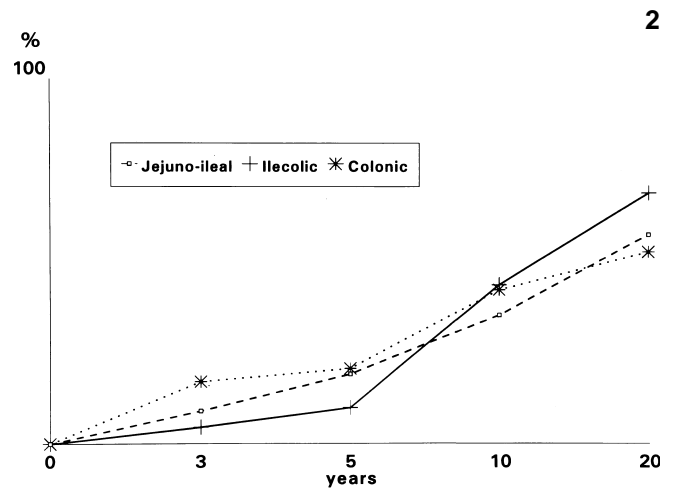
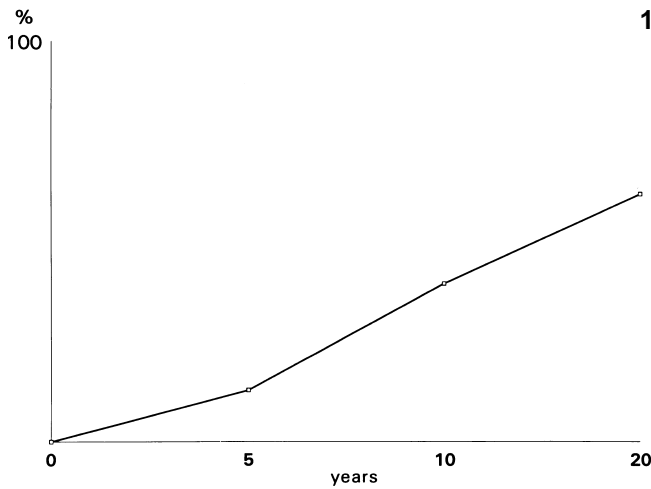


Fig. 1. Overall probability of recurrence after 5 (12.7%), 10 (39.1%), and 20 years (61.3%)

Fig. 2. Probability of recurrence according to the initial localization of the disease: no differences were found

Fig. 3. Correlation between duration of the disease before surgery and recurrence rate: there was a higher rate of relapse in patients with a disease lasting less than 69 months

Fig. 4. Correlation between presence or absence of microscopic inflammation at the resection margins and recurrence rate. Although there is a tendency towards a higher recurrence rate if margins are involved, the cumulative recurrence rate does not show any statistically significant difference

ivariate analysis with Stepwise Logistic Regression (SLR) was used to examine the joint effects of these parameters on recurrence rate.

Results

Ileocolic disease was present in 160 (68.6%) patients, jejunio-ileal disease in 29 (12.4%) patients, and colonic disease in 44 (20.0%) patients. The mean age of the patients was 27.7 ± 1.1 years at the onset of the disease and 35.6 ± 1.2 years at the time of the first operation.

Recurrence requiring further surgery occurred in 81 patients, giving a “crude” recurrence rate of 34.3%. Using Kaplan Meyer life-table analysis, the probability of recurrence was 12.7% at 5 years, 39.1% at 10 years and 61.3% at 20 years (Fig. 1). The probability of recurrence according to the initial location of the disease did not show any particular differences (Fig. 2).

Univariate analysis

Duration of the disease before surgery. The average interval between onset of symptoms and the first operation was 69.3 ± 6.7 months. Using this interval as a “cut-off value” of higher versus lower probability of recurrence, there was a significant correlation between recurrence and a shorter duration of the disease prior to initial surgery ($P=0.0009$) (Fig. 3).

Age at onset of the disease. Cumulative recurrence rates were calculated for those under and those over 34 years, which was the median age at the time of first operation. There was no statistically significant difference in the two groups. We did not find a significant correlation even using a three age group classification (patients over 39 years (oldest tertile), under 28 years (youngest tertile) and those between 28 and 39 years).

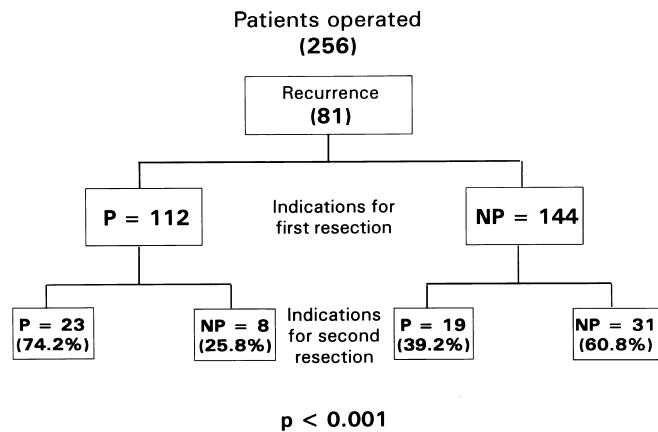


Fig. 5. Distribution of perforating and non perforating indications for surgery at first and second operation. (The figure has been arranged following that of Greenstein et al. [2])

Presence of microscopic disease at the resection margins. All the specimens were examined retrospectively by one pathologist (W. F. G.). Both the proximal and the distal margins were reviewed. Complete data were available in 226 of the 233 patients. There were 43 patients with active disease at one or both resection margins. In these, recurrence occurred in 17 (39.5%). Of the 183 patients with both margins disease free, 55 (30%) developed recurrence. There was no statistically significant difference between these groups.

Initial anatomical localization of the disease. The recurrence rates for primary ileocolic, jejunio-ileal and colonic involvement were 6.1%, 19.1% and 11.2% respectively. These rates showed no statistically significant differences. Although not significant in the overall analysis, recurrence (within 36 months) was significantly greater for colonic involvement (23.5%) compared with 7.9% and 13% for ileocolic and jejunio-ileal disease respectively, $P < 0.05$ (Fig. 5).

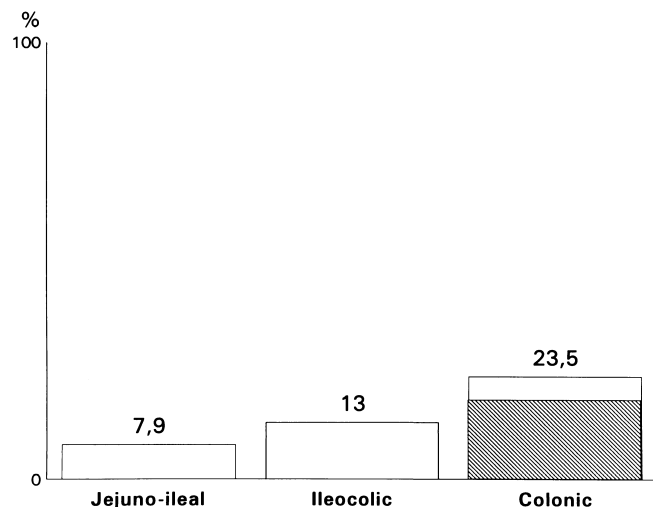


Fig. 6. Early recurrence rate is significantly higher in colonic disease. Among this group of patients, recurrence occurred in 93% of the cases in those who underwent a segmental colonic resection (shaded area)

“Perforating” or “non-perforating” disease. The patients were divided into two groups according to the presence or absence of abscess and fistula, (“perforating” and “non-perforating” disease, 2) This parameter proved to be not significant ($P = 0.08$) as a prognostic factor for recurrence. We also considered whether or not the type of recurrence was the same as the disease pattern found at the time of the first surgery. Out of the 233 patients in whom the indication for the first resection was assessed, perforating disease was present in 105 and non-perforating in 128 patients. A second resection was subsequently required in 81 patients, 31 of whom had originally presented with perforating disease. The indication for second resection was perforating disease in 23 out of these 31 patients, suggesting that patients with perforating disease tend to relapse similarly ($P < 0.01$), (Fig. 6).

Stoma or anastomosis. A stoma was performed in 30 patients, all in those presenting with colonic disease. There was no significant difference in the recurrence rate between patients who required a stoma and those having one or more anastomoses (22.7% vs 31.8%) (Fig. 7).

Post-operative complications. Post-operative complications after the first operation occurred in 26 (11.1%) patients. The most frequent was sepsis, including abscess, fistula or anastomotic leakage (17 [65.4%]). The relative risk for recurrent disease was not significantly higher in these patients than in those who had no postoperative complication.

Multivariate analysis

All the above variables were submitted to a Multivariate Analysis using Stepwise Logistic Regression. This failed to show any statistically significant correlation between any of these and the subsequent recurrence rate.

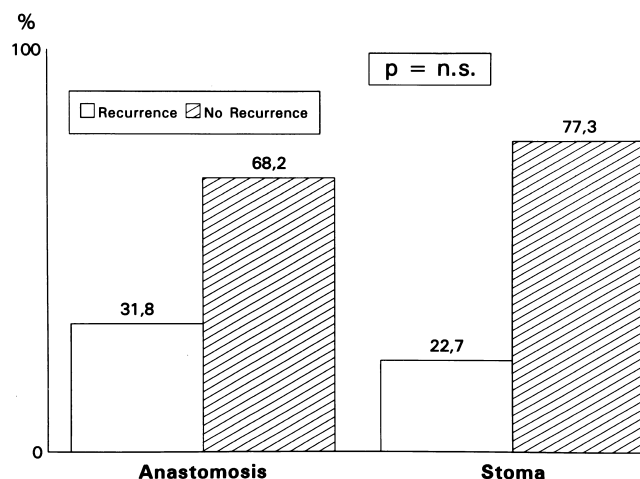


Fig. 7. Correlation between type of operation performed and recurrence rate: no differences were found

Table 1. Types of operations performed

Jejuno-ileal resection	63
Ileo-colic resection	157
Strictureplasty	
Alone	21
Plus resection	43
Total abdominal colectomy	
With ileostomy	9
With ileo-rectal anastomosis	12
Total proctocolectomy with permanent ileostomy	12
Segmental colonic resection:	
With colostomy	9
With colo-rectal anastomosis	16

Discussion

The present study included a large series of patients who had been followed prospectively. Of the 274 patients having their first operation in our unit only 11 (%) were lost to follow-up. By excluding patients who did not have a resectional procedure e.g. strictureplasty, we attempted to obtain as homogeneous a group as possible given the general variance of distribution of disease, mode of presentation etc.

Both univariate and multivariate analysis have shown remarkably little correlation between recurrence and the variables examined. With the exception of duration of disease before first operation, none was a significant indicator. These results are at variance with some reports in the literature where there is a remarkable inconsistency in outcomes reported.

Differing definitions of recurrence of Crohn's disease create difficulties in comparing reports in the literature and may be responsible for some discrepancy. Lennard-Jones and Stalder [4] defined recurrence according to three criteria, including: the reappearance of symptoms, relapse of symptoms with radiological evidence of recurrence, and the need for a re-resection. The first two are more subjective and may overestimate the occurrence of relapse. Conversely, using the criterion of re-resection will tend to underestimate it. Using re-resection as the criterion for recurrence, reports in the literature have cited an incidence ranging from 17% to 58% [4–20]. Our own data lie within this large range.

Our finding of a relationship between recurrence and duration of the disease before the primary operation has been reported by several authors despite differences in selected cut off of interval between the onset of disease and surgery. For example, Sachar et al. [21] used a much longer interval of more or less than 10 years and found a significantly higher recurrence rate in the population with a shorter duration of disease (65% vs. 23% respectively). In contrast, however, a recent prospective study from the same institution [22] failed to show any statistically significant correlation between the duration of the disease and the recurrence rate, after a 3 year follow-up, an observation also reported by several other authors [10, 14, 23–30]. It is likely that these difference are explained by the arbi-

trary “cut off” point for duration of disease which varies from study to study.

Early age of onset of the disease has been reported by some authors to be a risk factor for recurrence [4, 6, 14, 21, 31, 32] and others have suggested that colonic disease is significantly correlated [15, 18]. Our findings illustrate the difficulty in accepting results from retrospective studies although it did appear from our data that early recurrence (i.e. within 36 months) was related to colonic disease at presentation. This might be explained by the fact that over 93% of these occurred in patients initially submitted to a segmental colonic resection. Generally high recurrence rates have been reported by others after colectomy whether segmented or total with ileorectal anastomosis. Thus Longo et al. [22] and Allan et al. [37] give rates for the former of 62% and 67% and for the latter of 67% and 53% with no statistically significant difference between segmented to total colonic resection, the former remaining an appropriate operation for short colonic skip lesions. This is supported by the lack of correlation of the presence of microscopic disease at the resection margins with recurrence as reported extensively in the literature [18, 38–43] indicating wide intestinal resection to be of no value. While the results of the present study confirmed the finding of Greenstein et al. [2] that patients presenting with perforating disease tend to have the same pattern when they recur, there was no indication that the rate of recurrence was increased. In this regard our results were similar to those in the Cleveland Clinic series [44] from which it was felt that the Greenstein classification was an “unpredictable guide to recurrence after surgery”.

In the light of the large body of evidence suggesting that recurrence after a stoma-creating operation is lower than following intestinal anastomosis [17, 21, 22, 45], it was surprising that no such correlation was found in the present study. This might be due to the small number of patients [30] having a stoma and perhaps to a somewhat lower recurrence rate in those undergoing anastomosis than reported by others.

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