

## Postoperative Complications Predict Recurrence of Crohn's Disease

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### ABSTRACT

**Objective:** To find out if any of six variables influenced the incidence and timing of recurrence after a first resection for Crohn's disease.

**Design:** Open study.

**Setting:** University hospital, Germany.

**Subjects:** 104 surviving patients of 106 who underwent a first resection for Crohn's disease between January 1976 and December 1990.

**Main outcome measures:** Association between 6 variables (age, sex, site of diseased bowel, histological evidence of Crohn's disease, indication for operation, and incidence of postoperative complications) and incidence and time of recurrence after the first operation.

**Results:** Patients were followed up for a mean of 4.5 years (range 1-16). Presentation with acute perforation was associated with a higher incidence of recurrence (10/14 compared with 26/90), chi square 7.90,  $p = 0.005$ ) and more than doubled the risk of that recurrence developing with six years (log rank chi square 11.7,  $p = 0.02$ ); the same was true for development of a postoperative complication for which the corresponding figures were 14/26 compared with 22/78, chi square 4.59,  $p = 0.03$ , and log rank chi square 6.1,  $p = 0.01$ .

**Conclusion:** These data support the hypothesis that there may be two types of Crohn's disease: an aggressive type that perforates and is prone to early relapse, and one that develops more slowly with an obstructive pattern, and which relapses less often and after a longer disease free interval. The development of postoperative complications is a previously unrecognised risk factor for early recurrence in Crohn's disease.

### RÉSUMÉ

**But:** Déterminer si parmi six variables étudiées certaines pourraient influencer l'incidence et le moment des récurrences après une première résection pour maladie de Crohn.

**Type d'étude:** Ouverte.

**Provenance:** Hôpital universitaire, Allemagne.

**Patients:** Cent quatre patients survivants sur 106 ayant eu une première résection pour maladie de Crohn entre Janvier 1976 et Décembre 1990.

**Principaux critères de jugement:** L'association entre 6 variables (l'âge, le sexe, le segment intestinal concerné, les signes histologiques de maladie de Crohn, l'indication opératoire et l'incidence des complications opératoires) d'une part et l'incidence et le moment des récurrences après la première intervention d'autre part.

**Résultats:** Les patients ont été suivis pendant quatre ans et demi en moyenne (extrêmes 1-16). Les perforations aiguës inaugurales s'accompagnaient d'un risque plus élevé de récurrence (10/14 contre 26/90,  $\chi^2:7.90$ ,  $p = 0.005$ ) et faisaient plus que doubler le risque que la récurrence survienne dans les six années suivant la première intervention (log rank  $\chi^2:11.7$ ,  $p = 0.02$ ); cela était également vrai pour les complications postopératoires pour lesquelles les chiffres étaient de 14/26 contre 22/78,  $\chi^2:4.59$ ,  $p = 0.03$  et log rank  $\chi^2:6.1$ ,  $p = 0.01$ .

**Conclusion:** Ces données sont en faveur de l'hypothèse selon laquelle il pourrait y avoir deux types de maladie de Crohn: une forme agressive qui donne lieu à des perforations et qui est susceptible de récidiver précocement, et une qui évolue plus lentement sur un mode obstructif, et qui récidive moins souvent et après une période de quiescence plus longue. La survenue de complications postopératoires est un facteur de risque de récurrence de maladie de Crohn qui n'avait pas été encore identifié jusque là.

### INTRODUCTION

One of the most important characteristics of Crohn's disease is that it recurs, despite apparently definitive resections which remove all macroscopically involved bowel. The aetiology of the disease is still not clear and little is known of the factors responsible for recurrent disease. It is hoped that a fuller understanding of the pathophysiological mechanisms responsible for the condition will lead to the development of therapeutic regimens to cure the condition.

In the interim, it is important to identify factors that might influence the risk of recurrence after resection (34). Such efforts in the past, however, have usually identified variables that are not amenable to change.

Frequent recurrences and a high incidence of postoperative infective complications may indicate that altered immunological competence is an important aetiological factor. It has been suggested that impaired immunological responses may be secondary to poor nutrition which often accompanies active disease

Table I. Variables assessed for their effect on recurrence after excisional surgery for Crohn's disease

●	Age at operation
●	Sex
●	Anatomical position of resected bowel
●	Indication for operation
●	Microscopic disease at resection margin
●	Postoperative complication

(14). Several studies have focused attention on a possible viral or bacterial cause of the disease and have also indicated that there may be alterations in immune function, although a specific pathogen has not yet been isolated (36). At least one study, however, has shown a close correlation between the severity of perioperative immune dysfunction and the risk of recurrent disease (16). As immunological abnormalities seem to have a role in the pathogenesis of Crohn's disease, we have examined the possibility that such dysfunction might be reflected in a predisposition to the development of postoperative infective complications, which would therefore act as an indicator of the likelihood of early recurrence.

## PATIENTS AND METHODS

Between January 1976 and December 1990, 122 patients underwent their first operation for Crohn's disease at the Justus-Liebig University, Giessen, Germany. Of these patients 106 (87%) underwent primary resection of diseased bowel; 104 survivors were followed up prospectively and they are reported here. The two operative deaths were patients who presented with toxic megacolon, perforation and peritonitis, and died of fulminant sepsis after resection of the colon.

The influence of six variables present at the time of first operation were evaluated with respect to their influence on the development of recurrence within a mean period of 4.1 postoperative years (range 1–16) (Table I). As most patients were referred to this tertiary referral centre shortly before surgical treatment, and a precise record of previous treatment was not always available, no attempt was made to correlate either preoperative duration of disease or medical treatment with postoperative recurrence rates.

Prophylactic steroids were not used postoperatively, although 5-amino salicylic acid compounds were given to all patients who had large bowel disease and had undergone a large bowel resection with restoration of gastrointestinal continuity. Patients were followed up at a special clinic, at which recurrence

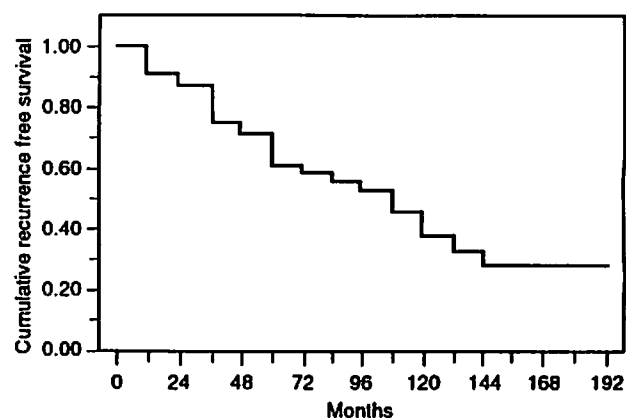


Fig. 1. Kaplan-Meier cumulative recurrence free survival curve (expressed as a probability) in 104 patients who had bowel resections for Crohn's disease.

was defined as the development of clinical symptoms that required either medical or surgical treatment and had been confirmed by either definite radiological or histological evidence of recurrent disease (5). Although all patients with symptoms were investigated, no effort was made to screen for asymptomatic recurrence.

Patients who underwent local procedures including treatment of perianal complications of Crohn's disease which did not involve resection of bowel were not included in the study. At operation, all grossly visible involved bowel was resected, and no bypass procedure was done. No patient underwent stricture plasty at the time of resection.

### Statistical analysis of results

Independent variables were cross-tabulated to ascertain their influence on recurrence. Cumulative recurrence rates were calculated by the life-table methods of Kaplan and Meier (18), and comparisons between them were made using Gehan's generalised Wilcoxon procedure and log rank chi square analysis (10, 26). Multivariate analysis with a Cox regression model for censored data (4) was used to examine the joint effects of these clinical characteristics on recurrence rates. All statistical analyses were made with the STATA® computer program (Computer Resource Centre, Santa Monica, USA).

## RESULTS

All 104 patients who survived the primary bowel resection for Crohn's disease were followed up for a mean of 4.1 years (range 1–16). A total of 38 recurrences were recorded. The mean recurrence free survival was 4.25 years (range 1–12), and the cumulative 5 and 10 year recurrence free survival rates were 61% and 38%, respectively (Fig. 1).

Table II. Association between type of operation and recurrence in 104 patients undergoing resection for Crohn's disease

Operation	No. (%) of patients	No. (%) with recurrence	Chi square	p value
Small bowel resection alone	24 (23)	6 (17)	0.78	0.28
Large bowel resection alone	46 (44)	19 (53)	1.14	0.28
Combined small and large bowel resection	34 (33)	11 (31)	0.01	0.91

Table III. Association between indications for operation and recurrence in 104 patients undergoing resection for Crohn's disease

Indication for operation	No. (%) of patients	No. (%) with recurrence	Chi square	p value
Stenosis	44 (42)	12 (33)	1.30	0.25
Fistula or abscess	18 (17)	6 (17)	0.02	0.90
Inflammatory mass	17 (16)	3 (8)	1.77	0.18
Acute perforation	14 (13)	10 (28)	7.90	0.005
Uncontrolled on medical treatment	11 (11)	5 (14)	0.22	0.64
Total	104	36	—	—

There were 20 recurrences in the 56 men (36%), and 16 in the 48 women (33%). Recurrence free survival curves were similar for the two groups (log rank  $\chi^2 = 0.01$ ,  $p = 0.9$ ). The mean age of the study group was 31 years (range 13–72). Cumulative recurrence rates were calculated for three age groups; patients over 35 years (oldest quartile), those under 23 years (the youngest quartile), and those between 23 and 35 years. There were no significant difference in recurrence rates among the three groups.

The types of operation are shown in Table II. There were no significant differences in the incidence of recurrent disease in the three groups. Continuity of the gastrointestinal tract was restored in all patients who underwent isolated small bowel resection and in 28 of 34 patients who had a combined small and large bowel resection. Nineteen patients who had isolated large bowel disease had subtotal colectomy with end ileostomy.

Histological examination of the resection margins showed the presence of active disease in 28 (27%) specimens. There was a tendency towards a higher recurrence rate if active disease was identified in 13 patients (46%) compared with those with clear margins (18; 27%), but the cumulative 10 year recurrence free survival for the two groups was not significantly different (0.39) for disease free margins compared with (0.33) if the margins were involved (log rank  $\chi^2 = 1.4$ ,  $p = 0.24$ ).

Indications for operation are shown in Table III. Recurrence free survival curves were significantly different when expressed as a function of indication for

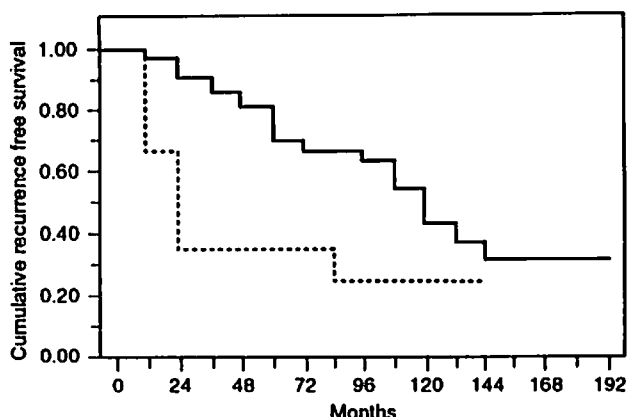


Fig. 2. Cumulative recurrence free survival in patients operated on for acute perforation (broken line), or for any other indication (solid line) (Wilcoxon Gehan  $z = 4.0$ ,  $p < 0.01$ ; logrank  $\chi^2 = 8.1$ ,  $p < 0.01$ ).

operation (log rank  $\chi^2 = 11.7$ ,  $p = 0.02$ ). In particular, patients who presented with acute perforation had a significantly increased risk of recurrent disease, with a relative risk of 2.3 (Fig. 2) and a significantly higher incidence of recurrence ( $p = 0.005$ ).

There were 26 postoperative complications (Table IV). Fourteen patients who developed a postoperative complication subsequently developed recurrent disease and had a significantly shorter disease free survival (Fig. 3). The relative risk for recurrent disease in these patients was twice that of those who had no postoperative complication. Seventeen of the 26 complications were due to infection of the wound or another site, but compared with all

Table IV. Association between postoperative complications and recurrence in 104 patients undergoing resection for Crohn's disease

Complication	No recurrence	Recurrences (predicted)	Total
None	56	22 (28)	78
Infection	9	8 (5)	17
Fistula	3	3 (2)	6
Anastomotic leak	0	2 (0)	2
Pulmonary embolus	0	1 (0)	1
	68	36	104

Pearson chi square (4) 8.8  
with  $p = 0.084$   
Fischer's exact test  
 $p = 0.039$   
Log Rank chi square (4)  
 $p < 0.001$

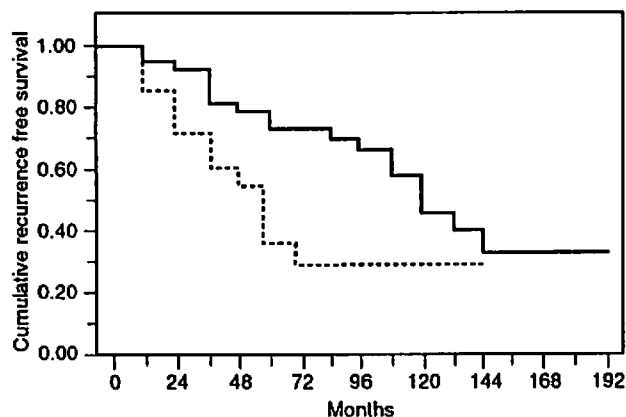


Fig. 3. Cumulative postoperative recurrence free survival in patients with a trouble no postoperative complication (solid line) compared with those who developed a postoperative complication (broken line) (Wilcoxon Gehan  $z = 2.7$ ,  $p = 0.01$ ; log rank  $\chi^2 = 6.1$ ,  $p = 0.01$ ).

patients who developed postoperative complications, this did not represent an independent risk factor (log rank  $\chi^2 = 1.5$ ,  $p = 0.21$ ). Patients with complications did, however, develop more recurrences than those who did not ( $p = 0.03$ ).

From a series of Cox model interactions using age, sex, anatomical location, indication for operation, and postoperative complications, only perforation leading to bowel resection and the development of a postoperative complication made significant contributions to the model.

## DISCUSSION

We have examined the effect of six clinical variables on the development of recurrence in 104 patients who underwent resection of bowel for complications of

Crohn's disease. Although there were only 36 recurrences in the group after a mean follow-up of 4.1 years, our findings confirm existing reports which have suggested that certain indications for operation may be followed by more frequent and earlier recurrences. We also found that the development of a postoperative complication seems to be a risk factor in the development of recurrent disease.

Although postoperative recurrence is a characteristic feature of Crohn's disease, there has been little agreement about such issues as frequency, rate, and risk factors for recurrent disease, partly because of differences in operative techniques and the statistical methods used to analyse results. The lack of an accepted definition of recurrence in Crohn's disease also makes it difficult to compare studies that have attempted to identify risk factors (2, 29). Several authors have defined recurrence as the reappearance of disease that required reoperation, as this provides a finite endpoint for the assessment of recurrence (9, 21, 33). Such studies tend to underestimate recurrence, however, as they do not include patients who have clinical recrudescence with subsequent remissions that are either spontaneous or induced by medical treatment (33). Frikker et al. reported a rate of 4% a year of further resection for the first seven years after initial resection, and 1.9% a year for the next 10 years (9), and Whelan reported the median duration of remission before re-operation as 8.3 years (33). In studies that defined recurrence as the presence of endoscopic or histological evidence of disease, a one year recurrence rate of up to 72% has been reported (28), which does not differ significantly from the 10 year recurrence rate of 77%. From this we conclude that Crohn's disease almost always recurs within the first year of operation. In the present study, in which recurrence was defined as the presence of radiological or histological evidence of symptomatic disease, we found a 10 year cumulative recurrence rate of 62%, which compares favourably with recurrence rates of up to 76% in studies using the same criteria (3, 15).

Although contrasting results have been published about the extent to which recurrence is influenced by the anatomical site of disease, several reports have suggested that localised small bowel disease has the best prognosis, with a recurrence rate of 32%–38% after resection (2, 9). In contrast, other reports have suggested that colonic disease is associated with the best prognosis (5, 17). Most agree, however, that ileocolic disease has a poor prognosis, with 10 year cumulative recurrence rates of up to 60%, and rates of further resection of up to 45% (2, 21, 33). Several authors have failed to show any association between the site of disease and subsequent recurrence

(7, 32, 33). In a large study of 438 patients with Crohn's disease who were operated on at the Cleveland Clinic, Whelan et al. reported a 10 year reoperation rate for ileocolic disease of 53%, compared with 45% for colonic or anorectal disease and 44% for small intestinal disease. The estimated time to recurrence was, however, not significantly different among the three groups (33). We report a 25% recurrence rate for small bowel disease, compared with 41% for large bowel and 32% for combined disease. This difference was not significant (7, 32, 33).

Much controversy still surrounds the reports of Sachar and others which have suggested that Crohn's disease may be divided into two clinical types: an aggressive perforating form which includes acute perforation, fistulation, and abscess formation, which requires earlier operation and is followed by a faster rate of recurrence. The second form follows a slower obstructive pattern, and is associated with recurrence of fever and a longer disease free interval (30, 31). In a retrospective study of 770 patients who underwent primary resection, Greenstein et al. reported that the risk of further operation doubled in those who had presented initially with perforating disease compared with those operated on for other indications. Subsequent operative intervention also tended to be for the same indications (12). They noted that (in keeping with the findings of Farmer et al.) the indication for operation in Crohn's disease depended on the anatomical site of the disease (8), and patients with ileitis more commonly present with non-perforating disease while those with ileocolitis are more likely to present with perforation. These findings suggest that differences in recurrence rates at different anatomical sites may be more immediately related to the indication for operation rather than the distribution of the disease. Whelan et al., however, did not find a significant correlation between perforation and abscess formation as an indication for surgery, although they noted that internal fistulation as an indication for surgery was associated with a higher likelihood of recurrence and a shorter median time to recurrence (33). Others have, however, failed to find any correlation between indication for operation and subsequent recurrence rates (7, 17, 24). We found that neither fistulation nor abscess formation was a significant risk factor for recurrent disease. Patients who presented with acute perforation, however, had double the risk of recurrent disease. These data seem to support evidence that a sub-group of patients with Crohn's disease who present with perforation may be at increased risk of early recurrence.

Although the aetiology of recurrent Crohn's disease is unknown, it is clear that the pathological process affects the entire gastrointestinal tract at a micro-

scopic and subcellular level, although macroscopically inflammatory lesions seem to be localised (6, 11, 13). Recurrent disease is likely to indicate progression of latent pre-existing disease rather than development of new lesions. As a result, the importance of excising apparently healthy bowel on each side of diseased bowel has been questioned. Several recent reports have suggested that recurrence is not influenced by residual microscopic disease in the resection margins and lead to calls for more conservative surgery (3, 22, 25). Our findings are in keeping with those of Cooper and Williams and Pennington et al., who reported a slight but not significant trend towards earlier recurrences when the margin was involved with active disease. Others have reported a definite association between recurrent disease and the presence of active microscopic disease in the resection margins (1, 35). Although our results tend to support evidence which suggests the presence of microscopic disease in the resection margin does not significantly affect recurrence, further studies are needed to resolve the issue.

The results of this study suggest that patients who developed a postoperative complication were at increased risk of recurrent disease, but we did not attempt to define the nature of this association. It is therefore not clear when the development of a postoperative complication directly increased the risk of recurrent disease, or simply acted as an indicator of increased risk, possibly as a result of impaired immune function. Crohn's disease is associated with various immunological abnormalities (23), including alterations in lymphocyte numbers and function (27), the appearance of lymphocytotoxic antibodies (20), and abnormal suppressor activity (19). Because immunological mechanisms are likely to be involved in the pathogenesis of the disease it is reasonable to postulate that those patients with pronounced defects in immune function are also more likely to develop recurrent disease. Heiman & Aufses reported higher symptomatic recurrence rates in patients with severe preoperative lymphopenia compared with patients with normal lymphocyte counts before operation (16). Perioperative immune dysfunction might also predispose to the development of postoperative infective complications. One could postulate that those patients with pronounced defects in immune function not only have a higher risk of recurrent disease, but might also be at increased risk of developing postoperative complications, particularly infective ones. We noted a significant correlation between the development of a postoperative complication and subsequent early recurrence (Fig. 3). To our knowledge, such an association has not previously been reported. Although wound infection and other forms

of infection accounted for 65% of our postoperative complications, the development of an infective complication was not a significant risk factor for recurrent disease, when viewed in isolation. This finding may more accurately reflect the relatively small numbers of patients in this study, and suggests that further study is indicated. The data suggest, however, that patients who develop complications after resection are at increased risk of early recurrent disease and may benefit from more intensive surveillance, allowing earlier evaluation and treatment of recurrent disease.

In conclusion, these data confirm the findings of previous studies which showed that age, sex, and the presence of active disease in the resection margins do not play a significant part in predicting the risk of recurrence in Crohn's disease. The data further support the hypothesis that Crohn's disease may be either a slow obstructive disease, or an aggressive perforating type which is more prone to recurrence. The development of a postoperative complication seems to be followed by an accelerated rate of recurrence after operation and may indicate altered immune function. The confirmation of these two clinical patterns in Crohn's disease may have important prognostic, therapeutic, and possibly pathological implications.

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