Factors affecting recurrence after surgery for Crohn’s disease

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Abstract

Although in Crohn’s disease post-operative recurrence is common, the determinants of disease recurrence remain speculative. The aim of this study was to examine factors affecting post-operative recurrence of Crohn’s disease. A Medline-based literature review was carried out. The following factors were investigated: age at onset of disease, sex, family history of Crohn’s disease, smoking, duration of Crohn’s disease before surgery, prophylactic medical treatment (corticosteroids, 5-aminosalicylic acid [5-ASA] and immunosuppressants), anatomical site of involvement, indication for surgery (perforating or non-perforating disease), length of resected bowel, anastomotic technique, presence of granuloma in the specimen, involvement of disease at the resection margin, blood transfusions and post-operative complications. Smoking significantly increases the risk of recurrence (risk is approximately twice as high, especially in women and heavy smokers). Quitting smoking reduces the post-operative recurrence rate. A number of studies have shown a higher risk when the duration of the disease before surgery was short. There were, however, different definitions of ‘short’ among the studies. Prophylactic corticosteroids therapy is not effective in reducing the post-operative recurrence. A number of randomized controlled trials offered evidence of the efficacy of 5-ASA (mesalazine) in reducing post-operative recurrence. Recently, the thera-peutic efficacy of immunosuppressive drugs (azathioprine and 6-mercaptopurine) in the prevention of post-operative recurrence has been investigated and several studies have reported that these drugs might help prevent the recurrence. Further clinical trials would be necessary to evaluate the prophylactic efficacy of immunosuppressants. Several studies showed a higher recurrence rate in patients with perforating disease than in those with non-perforating disease. However, evidence for differing recurrence rates in perforating and non-perforating diseases is inconclusive. A number of retrospective studies reported that a stapled functional end-to-end anastomosis was associated with a lower recurrence rate compared with other types of anastomosis. However, prospective randomized studies would be necessary to draw a definite conclusion. Many studies found no difference in the recurrence rates between patients with radical resection and non-radical resection. Therefore, minimal surgery including strictureplasty has been justified in the management of Crohn’s disease. In this review, the following factors do not seem to be predictive of post-operative recurrence: age at onset of disease, sex, family history of Crohn’s disease, anatomical site of disease, length of resected bowel, presence of granuloma in the specimen, blood transfusions and post-operative complications. The most significant factor affecting post-operative recurrence of Crohn’s disease is smoking. Smoking significantly increases the risk of recurrence. A short disease duration before surgery seems, albeit to a very minor degree, to be associated with a higher recurrence rate. 5-ASA has been shown with some degree of confidence to lead to a lower recurrence rate. The prophylactic efficacy of immunosuppressive drugs should be assessed in future. A wider anastomotic technique after resection may reduce the post-operative recurrence rate, though this should be investigated with prospective randomized controlled trials.

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Key words: Crohn’s disease; Post-operative recurrence; Predictive factors; Resection; Surgery

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INTRODUCTION

Crohn’s disease is a chronic inflammatory gastrointestinal disorder with an unpredictable clinical course characterized by the high incidence of recurrence. Nearly 80% of patients with Crohn’s disease require surgery during their lifetime[1]. Post-operative recurrence rates defined by clinical symptoms are 17-55% at 5 years, 32-76% at 10 years and 72-73% at 20 years[2-14]. The rates of recurrence requiring re-operation are 11-32% at 5 years, 20-44% at 10 years and 46-55% at 20 years[2-14]. Thus, the re-operation rate tends to steadily increase with time, reaching approximately 50% at 20 years after surgery. Although in Crohn’s disease post-operative recurrence is common, the determinants of disease recurrence remain speculative. Several patients with Crohn’s disease experience frequent recurrences while others have prolonged periods of remission after surgery.
Identifying risk factors for post-operative recurrence would be useful to spot patients at a high risk of future recurrence and to determine strategies for medical treatment after surgery. A number of factors have been evaluated as potentially influencing the recurrence rates after surgery for Crohn’s disease[14-39]: age at onset of disease, sex, family history of Crohn’s disease, smoking, duration of Crohn’s disease before surgery, prophylactic medical treatment (corticosteroids, 5-amino salicylic acid [5-ASA] and immunosuppressants), anatomical site of involvement, indication for surgery (perforating or non-perforating disease), length of resected bowel, anastomotic technique, presence of granuloma in the specimen, involvement of disease at the resection margin, blood transfusions and post-operative complications. A Medline-based literature review was carried out to examine factors affecting post-operative recurrence of Crohn’s disease.

**Age at onset of disease**

Many studies examined the impact of age on the recurrence rate after surgery. Naturally, patients with early onset of disease seem to have a higher recurrence rate because of a longer follow-up duration. A younger age at onset of disease has been linked to a higher recurrence rate in several studies[18,20,32-34] but not others[17,20,21,26,28,30]. Thus, the reports about the importance of age have been conflicting and different studies have yielded contradictory results. In summary, age does not seem to be a definite predictive factor of post-operative recurrence.

**Sex**

A few studies have suggested that the sex of the patient influences the risk of recurrence after surgery, with slightly increased recurrence rates reported for both men[35] and women[32,38,39]. In many other studies, the recurrence rate was similar for both men and women[15-17,20,21,26,29,30].

**Family history of Crohn’s disease**

There have been only a few reports examining the relationship between family history of Crohn’s disease and the recurrence rate after surgery[17,38]. Chardavoyne et al.[17], found family history of Crohn’s disease did not influence the recurrence rate. Our recent study found that patients with a family history had a higher recurrence rate[38].

**Smoking**

There has been increasing speculation as to the role of cigarette smoking in the pathogenesis of inflammatory bowel diseases, since smokers are over-represented in groups of patients with Crohn’s disease and under-represented in patients with ulcerative colitis[40-43]. Not only is smoking associated with an increased risk of developing Crohn’s disease, but several studies have demonstrated a significantly increased risk of recurrence after surgery[18,20,21,26,28,30]. Sutherland et al.[44] reported that the 5- and 10-year recurrence rates were significantly higher in smokers (36% and 70%) than in non-smokers (20% and 41%; odds ratio, 2.1; P = 0.007). When patients were stratified by sex, the increased risk was more apparent in women (odds ratio, 4.2; 95% confidence interval [CI], 2.0-4.2) than in men (odds ratio, 1.5; 95% CI, 0.8-6.0). Lindberg et al.[45], found that heavy smokers (>10 cigarettes/day) had an increased risk of operation at least once; odds ratios for heavy smokers compared with non-smokers after 5 and 10 years were 1.14 and 1.24, respectively (P = 0.03 and P = 0.017). The risk of further operations was even higher and after 10 years the odds ratio was 1.79 (P = 0.015). Cottone et al.[46], conducted multivariate analyses to examine predictive factors for three types of recurrence (clinical [symptomatic], endoscopic and surgical [reoperation] recurrences) after surgery for Crohn’s disease. They found that smoking was an independent significant factor for clinical recurrence (odds ratio, 1.46; 95% CI, 1.1-1.8), endoscopic recurrence (odds ratios, 2.2; 95% CI, 1.2-3.8) and surgical recurrence (odds ratio, 2.0; 95% CI, 1.2-2.3). Breuer-Katschinski et al.[47], studied 346 patients with Crohn’s disease and found that 73% of smokers and 39% of non-smokers required one or more operations. The 5- and 10-year recurrence rates were 43% and 64% for smokers, which were significantly higher than 26% and 33% for non-smokers (odds ratio, 3.1; P<0.00). For the 5- and 10-year recurrence rates the relative risk estimates for smokers versus non-smokers were 3.1 (95%CI, 1.7 - 5.8) and 6.7 (95%CI, 2.7-6.8). When stratified by sex, the increased risk for the recurrence was recognized in both sexes. For the number of cigarettes smoked a dose-response effect was obvious in women. Timmet et al.[48], found that at 48 wk after surgery for Crohn’s disease, the relapse rate [Crohn’s disease activity index (CDAI) > 150 or an increase of CDAI of > 60] was 30% in non-smokers compared with 53% in smokers (odds ratio, 2.1; P = 0.02). Ex-smokers did not have an increased risk; the relapse rate was 35%, which was similar to 30% in non-smokers. In my research in the UK[46], after resection for ileocecal Crohn’s disease the 5- and 10-year recurrence rates were 35% and 55% for smokers compared with 19% and 36% for non-smokers (odds ratio, 2.3; P = 0.007). When smokers were further divided into two sub-groups according to the number of cigarettes smoked per day, the cumulative recurrence rate was higher in heavy smokers (15 or >15 cigarettes/d) compared with mild smokers (<15 cigarettes/d). In my another study[49], after resection (colectomy and ileorectal anastomosis) for Crohn’s colitis the 5-, 10- and 15-year recurrence rates were 25%, 46%, and 52% for smokers and 11%, 15%, and 18% for non-smokers (odds ratio, 3.0; P = 0.005). When smokers were further divided into two sub-groups according to the number of cigarettes smoked per day, the cumulative recurrence rate was higher in heavy smokers (15 or >15 cigarettes/d) compared with mild smokers (<15 cigarettes/d). In my another study[49], after resection (colectomy and ileorectal anastomosis) for Crohn’s colitis the 5-, 10- and 15-year recurrence rates were 25%, 46%, and 52% for smokers and 11%, 15%, and 18% for non-smokers (odds ratio, 3.0; P = 0.005). In the multivariate analyses, only smoking was an independent significant factor for poor outcome after surgery for Crohn’s colitis. Our recent study[50] examined the impact of quitting smoking on re-operation for recurrence after surgery for Crohn’s disease. We found that patients who quit smoking were less likely to have undergone one, two and three re-operations for recurrence (odds ratio, 0.25; 95% CI, 0.15-0.41; odds ratio, 0.30; 95% CI, 0.16-0.57 and odds ratio, 0.25; 95% CI, 0.10-0.71). These data indicate that patients with Crohn’s disease who stop smoking reduce the risk of re-operation for recurrence after surgery. In contrast, two studies failed to find significant correlations between smoking and the recurrence rate after surgery for Crohn’s disease, though in those studies the number of patients included was small and the detailed data concerning smoking were not presented[51,52]. In summary, smoking significantly increases the risk of recurrence after
surgery for Crohn’s disease (risk is approximately twice as high), especially in women and heavy smokers. Quitting smoking is associated with a lower recurrence rate compared with that in smokers. Because many patients with Crohn’s disease are unaware of the risks that smoking has on their disease[55,59], education and encouragement of patients to stop smoking are necessary in the management of Crohn’s disease[55,59]. The mechanism of the effect of smoking on Crohn’s disease is as yet unclear. Potentially important mechanisms include immune modulation, gut vascularity, gut mucous composition, gut permeability and perturbation in eicosanoid production[40-45].

**Duration of disease before surgery**

An association between duration of disease before the first operation and early recurrence has been suggested previously[15,17,21,28,33,38,60]. A number of studies have shown a higher risk with a short history of disease[15,23,28,33,36,64]. In one prospective study, Poggioli et al.[28], found that duration of disease less than 6 years prior to surgery was associated with higher the recurrence rates compared to patients with an illness of longer than 6 years prior to surgery. Another study[67] found that recurrent disease was more likely to occur in patients with a duration of disease of between 3 and 10 years before surgery. Sachar et al.[18], found significantly higher recurrence rates in patients with disease duration less than 10 years. This has not been universal and other groups have failed to find a relationship between pre-surgical disease duration and recurrence[16,18,21,26,30].

Differences in the definition of ‘short duration’ hamper comparison among the studies. In our previous study[15], we selected the arbitrary intervals of 1 year between the onset of disease and surgery, 1 and 10 years and more than 10 years and found that recurrent disease was significantly associated with short duration of disease prior to primary surgery. It is not clear why a short duration of disease prior to surgery emerges as such a powerful association with recurrent disease in our study. It may be that a short interval between diagnosis and primary surgery is indicative of a more aggressive disease phenotype. However, it would seem unreasonable to defer surgery in a symptomatic patient with a short history of disease, merely because of the potential risk of early recurrence.

**Prophylactic medical treatment (corticosteroids, 5-ASA and immunosuppressants)**

Many studies report that corticosteroids therapy is ineffective in reducing recurrence of Crohn’s disease[61-66]. Several randomized controlled trials have demonstrated that 5-ASA (mesalazine) is effective in reducing the frequency of post-operative recurrence and in decreasing the severity of the lesions[40-45]. Caprilli et al.[67], studied 110 patients operated on for Crohn’s disease by the first intestinal resection. Patients were randomly allocated to receive mesalazine (2.4 g/d) or no treatment at all. The cumulative proportion of recurrence at 6, 12, and 24 mo was significantly lower in the mesalazine group than in untreated group (P = 0.002). At 24 mo the cumulative proportions of endoscopic recurrence were 0.52 and 0.85, respectively. At the same time, the cumulative proportions of symptomatic recurrence were 0.18 and 0.41 (P = 0.006). The cumulative proportions of the severe recurrence was also significantly lower in the mesalazine group (0.17 vs 0.38; P = 0.021). It was estimated that 5-ASA prevents 39% of all recurrences and 55% of the severe recurrences. In a double-blind, multicenter clinical trial[68], 87 patients were treated with 3 g/d mesalazine (Pentasa) or with placebo within 1 mo after surgery. Seventeen clinical relapses (seven in the mesalazine group) were recorded. After 12 mo, the endoscopic lesions were less frequent and less severe in the mesalazine group than were those in the placebo group (P<0.008). The overall rate of severe recurrence (on endoscopy or radiological documentation) was 24% in the mesalazine group and 56% in the placebo group (P<0.004). In another randomized controlled trial[69], 163 patients who underwent a surgical resection were randomized to a treatment group (1.5 g mesalazine twice a day) or a placebo control group within 8 wk of surgery. The follow-up period was a maximum of 72 mo. The symptomatic recurrence rate in the treatment group was 31% (27 of 87) compared with 41% (31 of 76) in the control group (P = 0.031). The relative risk of developing recurrent disease was 0.628 (90% CI, 0.40-0.97) for those in the treatment group (P = 0.039) using an intention-to-treat analysis and 0.532 (90% CI, 0.32-0.87) using an efficacy analysis.

The endoscopic and radiological rate of recurrence was also significantly decreased with relative risks of 0.654 (90% CI, 0.47-0.91) in the effectiveness analysis and 0.635 (90% CI, 0.44-0.91) in the efficacy analysis. These results[67-69] suggest that high-dose (2.4-3.0 g/d) 5-ASA therapy early in the post-operative period may be the most effective regimen. A meta-analysis[70] was conducted to assess the effectiveness of 5-ASA in maintaining remission of quiescent Crohn’s disease. Fifteen randomized, controlled trials of 5-ASA maintenance therapy involving a total of 2 097 patients were selected for the analysis. Therapy with 5-ASA significantly reduced the risk of symptomatic relapse (pooled risk difference, -6.3%; 95% CI, -10.4% to -2.1%). The pooled risk difference was significant in the post-surgical setting (-13.1%; 95% CI, -21.8% to -4.5%) but not in the medical setting (-4.7%; 95% CI, -9.6% to 2.8%). Multivariate model predicts that the probability of symptomatic relapse significantly decreases with 5-ASA treatment, by increasing proportion of patients with ileal disease, with prolonged disease duration, and with surgically induced remission.

Immunosuppressive drugs (azathioprine and 6-mercaptopurine [6-MP]) are effective in the setting of steroid dependence and steroid resistance, as well as for the treatment of perianal and fistulizing Crohn’s disease unresponsive to antibiotics[14,66,68]. Recently, therapeutic efficacy of azathioprine and 6-MP in the prevention of post-operative recurrence in patients with Crohn’s disease has been investigated. In a prospective, open-label, randomized study[63], 142 patients received azathioprine [2 mg/(kg·d)] or mesalamine (3 g/d) for 24 mo. The risk of clinical relapse was comparable in the azathioprine and mesalamine groups. No difference was observed with respect to surgical relapse between the two groups. In a sub-group analysis, azathioprine was more effective than mesalamine in preventing clinical relapse in patients with previous intestinal resections (odds ratio, 4.83; 95% CI, 1.47-15.8). The study concluded that while
no difference was observed in the efficacy of azathioprine and mesalamine in preventing clinical and surgical relapses after conservative surgery, azathioprine is more effective in those patients who have undergone previous intestinal resection. In another randomized trial[73], 131 patients received 6-MP (50 mg), mesalamine (3 g) or placebo daily. The clinical recurrence rates (intent to treat) at 24 mo were 50% (95%CI, 34-68%), 58% (95%CI, 41-75%) and 77% (95%CI, 61-91%) in patients receiving 6-MP, mesalamine and placebo, respectively. The endoscopic recurrence rates were 43% (95%CI, 28-63%), 63% (95%CI, 47-79%) and 64% (95%CI, 46-81%) and the radiographic recurrence rates were 33% (95%CI, 19-54%), 46% (95%CI, 29-66%) and 49% (95%CI, 30-72%), respectively. 6-MP was more effective than placebo (P<0.05) in preventing the clinical and endoscopic recurrence. The study concluded that 6-MP (50 mg/d) may be considered as a maintenance therapy after ileocolonic resection for Crohn’s disease. Thus, azathioprine and 6-MP might help prevent post-operative recurrence of Crohn’s disease. However, further clinical trials would be necessary to evaluate the efficacy of immunosuppressants in preventing clinical relapse after surgery for Crohn’s disease.

Anatomical site of involvement
Three main sites (small bowel, large bowel and ileocolonic region) of gastrointestinal involvement have been discussed as clinical patterns in Crohn’s disease. A number of studies examined the impact of anatomical site of disease on the recurrence and reported the different results[14,15,19,27,30]. The risk of recurrence was highest in patients with small bowel disease[39,31,74] and ileocolonic disease[27,30]. In one study[77], patients with predominantly large bowel disease (n = 56) were found to have a higher rate of re-resection (45%) when compared with 32% in patients with small bowel involvement (n = 94) and with 35% in patients with both small and large bowel involvement (n = 37) (P = 0.04)[77]. Other studies failed to find any significant impact of the site of disease on the recurrence rate[15,16,19,28]. Thus, the use of ‘anatomical site of involvement’ as a factor for post-operative recurrence is of limited value in clinical practice.

Indication for surgery
Crohn’s disease has two different clinical forms, a relatively aggressive ‘perforating’ type and a more indolent ‘non-perforating’ type. Greenstein et al.[79], defined a perforating disease as acute free perforation, sub-acute perforation with abscess or chronic perforation with internal or external fistula from findings at laparotomy. This definition has been widely used in clinical practice. Several studies examined the relationship between the type of disease and post-operative recurrence. Aeberhard et al.[78], found that the median interval between the first and second operation was 1.7 years for patients with perforating disease, which was significantly shorter than 13 years for patients with non-perforating disease. Lautenbach et al.[79], studied 88 patients who had undergone at least two resections for Crohn’s disease to elucidate predictors of early post-operative recurrence. A perforating indication for initial surgery (P<0.001) was found to be an independent predictor of early post-operative recurrence after initial surgery. The indication for initial surgery was predictive of the indication at a subsequent surgery for the recurrence (P = 0.001). The other study found that patients with fistulizing type of symptoms were at a high risk of early recurrence after surgery[73]. In contrast, the postoperative recurrence rates were similar for patients with perforating and non-perforating diseases in other studies[26-28,30,60,79,80]. Evidence for differing the recurrence rates in perforating and non-perforating diseases is inconclusive. There may be concordance between patients initially presenting with perforating vs non-perforating disease and the pattern of disease recurrence[82,28,75,79]. However, McDonald et al.[79], reported that patients were no more likely to have the same indication for surgery at the time of the second resection or the third resection compared with the initial resection.

Length of resected bowel
Several studies have suggested that the recurrence is more common after resection of a long length of diseased bowel[77,80]. Other studies found that the length of resected small and large bowel made no difference to the rates of recurrence[5,14,26]. Thus, the length of resected bowel does not seem to be a definite predictive factor of post-operative recurrence.

Anastomotic technique
The type of anastomosis following resection is one of the important issues in the surgical management of Crohn’s disease. The fecal stream is implicated in anastomotic recurrence in Crohn’s disease following bowel resection[26]. Relative obstruction with stasis and bacterial overgrowth is also recognized contributory factors to recurrent Crohn’s disease[14,83]. Therefore, the stapled functional end-to-end technique may reduce the risk of obstruction at the anastomosis because of a wider anastomotic lumen. One retrospective study[84] examined 27 patients who underwent conventional sutured end-to-end anastomosis and 42 who underwent stapled functional end-to-end anastomosis following bowel resection for Crohn’s disease. In the stapled group, only one patient (2%) required re-operation for recurrence. By contrast, 14 patients (43%) in the sutured group required 15 further resections for recurrence. The median follow-up duration was 23 mo for the stapled group compared with 52 mo in the sutured group. Our retrospective study[85] studied 45 patients who underwent conventional sutured end-to-end anastomosis and 78 underwent conventional stapled end-to-end anastomosis. In the stapled group only one patient required re-operation for ileocolonic anastomotic recurrence compared with 26 in the sutured group. The cumulative 1-, 2- and 3-year ileocolonic recurrence rates requiring surgery in the stapled group were 0%, 0% and 3%, which were significantly lower than 5%, 11% and 24% in the sutured group (P = 0.007 by log-rank test). The median duration of follow-up was 34 mo in the stapled group compared with 92 mo in the sutured group (P<0.01). A case-control comparative analysis of patients with Crohn’s disease from two major inflammatory bowel disease centers (Mayo clinic and Birmingham) treated with wide-lumen stapled anastomosis (n = 69) and a matched (age and gender) group treated with conventional sutured end-to-end anastomosis...
(n = 69) was conducted. A total of 55 patients developed recurrent symptoms, 39 (77%) in the conventional sutured end-to-end anastomosis and 16 (24%) in the wide-lumen stapled anastomosis group. The median follow-up was 70 mo for the sutured group and 46 mo for the stapled group. After conventional sutured end-to-end anastomosis 18 re-operations were required and after wide-lumen stapled anastomosis three re-operations were necessary. The cumulative re-operation rate for anastomatic recurrence was significantly lower (P = 0.017 by log-rank test) for the wide-lumen stapled anastomosis group. One prospective study comparing the long-term results of stapled and hand-sewn anastomoses reported a lower recurrence rate after the stapled anastomosis. Thus, the stapled functional end-to-end anastomosis was associated with a lower incidence of post-operative anastomotic recurrence than the conventional sutured end-to-end anastomosis in the surgical management of Crohn’s disease. Caprilli et al., reporting on prognostic factors for the recurrence of Crohn’s disease in a multicenter study, found a trend towards a higher rate of endoscopic recurrence after end-to-end anastomosis compared to side-to-side or end-to-side anastomosis. Recent retrospective study compared the post-operative recurrence rate after a hand-sewn end-to-side or side-to-side isoperistaltic anastomosis (n = 30) and stapled functional end-to-end anastomosis (n = 76) and found that there were 5 recurrences (16.7%) in the hand-sewn group and 2 recurrences (2.6%) in the stapled group. The other study compared the recurrence rate after stapled side-to-side ileocolonic anastomosis (n = 12) to those after stapled end-to-side (n = 36) or hand-sewn side-to-side anastomosis (n = 36). The stapled side-to-side anastomosis group obtained a better symptom-free survival than the stapled end-to-side group (P = 0.04). In the stapled and hand-sewn side-to-side groups the re-operation rates were significantly lower than in the stapled end-to-side group (P = 0.01 and P = 0.05, respectively). A longer follow-up showed a significantly lower incidence of re-operation for recurrence in the stapled and hand-sewn side-to-side anastomosis compared to the stapled end-to-side anastomosis group. Thus, a wider anastomosis may delay the onset of the symptomatic recurrence and be associated with a lower early recurrence rate after resection for Crohn’s disease. Furthermore, the incidence of complications after the stapled anastomosis is low and the procedures are quick and easy. Therefore, the stapled functional end-to-end anastomosis may be the anastomotic configuration of choice following resection for Crohn’s disease. However, most of the previous studies were non-randomized trials. The follow-up duration was inevitably shorter and the number of patients was smaller in the stapled anastomosis group because the stapled technique has been introduced recently. Multicenter prospective randomized study with a larger number of patients and a longer follow-up duration would be needed to find an absolute evidence of difference between the stapled functional end-to-end anastomosis and the other types of anastomosis.

Presence of granuloma in the specimen

There are contradictory reports in the literature regarding the impact of identifiable granuloma in the resection specimen on the recurrence. Anseline et al., found that granuloma in the specimen was significantly associated with the recurrence. Other authors reported a decreased rate of the recurrence in patients who had granulomas in their specimen. Some groups have shown that microscopic disease in the specimen increases the rate of anastomotic recurrence of ileocolonic Crohn’s disease. Several reports have reported that the wide resection of normal bowel uninvolved microscopically (radical resection) was associated with a lower recurrence rate than non-radical resection. However, many studies have shown no difference in the recurrence rates between patients with radical resection and non-radical resection. Fazio et al., carried out a randomized controlled trial to investigate the impact of resection margins on the recurrence of Crohn’s disease in the small bowel. Patients who underwent ileocolonic resection for Crohn’s disease (n = 152) were randomly assigned to two groups in which the proximal line of resection was 2 cm (limited resection) or 12 cm (extended resection) from the macroscopically involved area. Patients also were classified by whether the margin of resection was microscopically normal (category 1), contained non-specific changes (category 2), were suggestive but not diagnostic for Crohn’s disease (category 3) or were diagnostic for Crohn’s disease (category 4). The median follow-up time was 55.7 mo. Disease recurred in 29 patients: 25% of patients in the limited resection group and 18% of patients in the extended resection group. In 90 patients in category 1 with normal tissue, the recurrence occurred in 16, whereas in the 41 patients with some degree of microscopic involvement, the recurrence occurred in 13. The recurrence rates were 36% in category 2, 39% in category 3 and 21% in category 4. No group differences were statistically significant. The recurrence of Crohn’s disease is unaffected by the width of the margin of resection from macroscopically involved bowel. Thus, the recurrence rates also do not increase when microscopic Crohn’s disease is present at the resection margins. Therefore, extensive resection margins are unnecessary.

As the recurrence was independent of microscopic involvement of the resection margins in many studies, there has been an increasing tendency toward minimal surgery in the treatment of Crohn’s disease. Strictureplasty conserves bowel and minimizes the risk of developing the short bowel syndrome. Nowadays, strictureplasty has become an established surgical option in the management of obstructive Crohn’s disease. It is particularly suitable for patients at a risk of short bowel syndrome. After strictureplasty the segment of inflamed bowel is left in situ, because the sutures are placed through the diseased bowel. However, the most recurrences after strictureplasty occur at non-strictureplasty sites and the recurrence rate at the strictureplasty sites has been reported to be only 2.8-3.7%.

Blood transfusions

The immunosuppressive effect of blood transfusions may modify the progression of Crohn’s disease. The effect of peri-operative blood transfusions on the recurrence of Crohn’s disease was investigated in several studies. Williams and Hughes examined 60 patients with Crohn’s disease.
disease who underwent small bowel resection. Twenty-eight patients received blood transfusions. The patients who received peri-operative blood transfusions had a significantly lower recurrence rate. Five years after the bowel resection, the cumulative recurrence rate in transfused patients was 19% compared with 59% in controls. Peters et al., studied 79 patients with Crohn’s disease who underwent intestinal resection. In 45 patients who received multiple red blood cell transfusions, the recurrence developed in 22% by 36 mo and the median time to the recurrence was 35 mo. In 34 patients who did not receive multiple transfusions, the recurrence was found in 44% by 36 mo and the median time to the recurrence was 20 mo (P<0.04). The recurrence in patients with disease limited to the small bowel or to the colon was not significantly affected by the transfusion status. However, the recurrence developed in only 10% of multiply transfused patients with ileocolonic disease by 36 mo, whereas the recurrence developed in 45% of the patients who were not multiply transfused (P = 0.057). Gooszen and Silvis studied 148 patients with Crohn’s disease, 62 males and 86 females (49 non-parous and 37 parous females). Eighty-seven patients received peri-operative blood transfusions. Overall, blood transfusions showed no effect on the recurrence. Peri-operative transfusions seemed to protect against recurrent disease after colonic resection. Transfusions had a beneficial effect in parous females (P = 0.068) and after correction for the type of operation this beneficial effect was significant (P = 0.026). After peri-operative blood transfusions parous females had a similar prognosis regarding the recurrent Crohn’s disease to that of non-parous females and males. In contrast, other studies failed to find any significant effect of peri-operative blood transfusions on the post-operative recurrence of Crohn’s disease. A recent pooled analysis studied 622 patients with a primary and complete resection of macroscopic disease. Three hundred thirty-one patients (53%) received blood in the peri-operative period and the mean follow-up duration was 72.8 mo. For the overall sample, the 5-year recurrence rates were 26.9% for the transfused group and 25.2% for the non-transfused (P = 0.456). When the data were stratified by age, gender, disease location and length of resection, no difference in the 5-year recurrence rates between transfused and non-transfused patients could be detected. This pooled analysis found no protective effect of blood transfusions on the post-operative recurrence of Crohn’s disease.

**Post-operative complications**

Crohn’s disease is frequently associated with possible risk factors for post-operative complications; intestinal obstruction, pre-existing septic complications, impaired nutritional status, chronic corticosteroid medication and the need for multiple anastomoses. There have been only a few reports about the relationship between the postoperative complications and recurrence rate. Poggioli et al., found no relationship, but Holzheimer et al., and Scarpal reported that the development of post-operative complications was associated with a high recurrence rate.

**DISCUSSION**

Smoking significantly increased the risk of recurrence after surgery for Crohn’s disease, especially in women. The effect of smoking was dose-dependent. Giving up smoking was associated with a lower probability of recurrence compared with smokers. A short disease duration before surgery seems, albeit to a very limited extent, to be associated with a higher recurrence rate, though the definition of short duration is different depending on the study. A number of randomized controlled trials offer encouraging evidence of the efficacy of 5-ASA in reducing post-operative recurrence. Recent studies have reported that immunosuppressive drugs were useful in the prevention of post-operative recurrence. However, further clinical trials would be necessary to evaluate the efficacy of immunosuppressants. Several authors found that perforating disease was associated with a higher recurrence rate compared with non-perforating disease, though evidence for differing the recurrence rates in perforating and non-perforating diseases is inconclusive. A number of retrospective studies found that a stapled functional end-to-end anastomosis was associated with a lower recurrence rate compared with other anastomotic techniques. However, prospective randomized trials would be necessary to find an absolute evidence of difference between the stapled functional end-to-end anastomosis and the other types of anastomosis. The following factors were not predictive of post-operative recurrence: age at onset of disease, sex, family history of Crohn’s disease, anatomical site of disease, length of resected bowel, presence of granuloma in the specimen, peri-operative blood transfusions and post-operative complications.

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