

Surgical recurrence in Crohn's disease: Are we getting better?

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achieved with the increased use of immunosuppressive medications in CD. Consequently, the question arises if we are getting better as a result of novel medical and surgical strategies.

Key words: Crohn's disease; Surgical recurrence; Recurrence; Inflammatory bowel disease

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Core tip: Crohn's disease still remains a challenging chronic inflammatory disorder, both for colorectal surgeons and gastroenterologists. There is still a considerable risk for recurrent surgery following intestinal resection, although recent evidence suggests a declining number of recurrence rates. Consequently, the question arises if we are getting better as a result of novel medical and surgical strategies.

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Abstract

Crohn's disease (CD) still remains a challenging chronic inflammatory disorder, both for colorectal surgeons and gastroenterologists. The need for recurrent surgery following primary intestinal resection is still considerable, though recent evidence suggested a declining rate of recurrence. Several conflicting surgical parameters have been identified that might impact on the postoperative outcome positively, such as access to the abdomen, anastomotic configuration or type of disease. Additionally, promising results have been

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease, and patients have a lifetime risk of intestinal resection of up to 80%^[1]. Although a population-based study reported an early use of immunosuppressants over an 18-year period was associated with a significant reduction in the cumulative probability of surgery^[2], other studies revealed that the number of surgical procedures remained unchanged over the time, despite the more frequent use of infliximab^[3,4].

Unfortunately, surgery is not curative and clinical

as well as endoscopic disease recurrence occurs frequently soon after first surgical intervention. In addition, the need to undergo a repeat operation for CD can reach 50% during a follow up period of over 10 years^[5]. Notably, most of the available data concerning re-operation rates was collected retrospectively, before the era of biologicals, thus might not entirely reflect the current situation.

In contrast to a number of previous published studies, Riss *et al*^[6] recently reported a surgical recurrence rate of 8.6% after a mean follow-up period of over 8 years. So the question arises whether novel treatment strategies alter the process of recurrence and give hope to affected patients. To date, there is a lack of data on predictors of recurrent surgery in CD. Current predictors such as smoking, young age of onset, family history, jejunal involvement and specific types of fistula, which correlate with a higher rate of surgical recurrence, might be complemented by predictive markers related to therapy^[7,8].

CHANGING SURGICAL STANDARDS

CD is a chronic disorder and can usually be managed conservatively for a certain time period. However, patients refractory to medical treatment will require surgery to remove affected bowel segments or strictureplasty to overcome a stenosis. Although these surgical standards have not changed for years, several studies revealed that the timing of surgery, the type of access to the abdomen and the surgical technique itself could have an impact on the postoperative outcome and the course of disease.

In a series of 116 consecutive patients, who underwent primary ileocolic resection for CD, urgent indication for surgery was significantly associated with the necessity of repeated intestinal resection^[6,9]. Additionally, Greenstein *et al*^[10] showed that perforating CD represented a more aggressive type of disease leading to a higher number of reoperations and even shorter time-periods between the procedures.

Laparoscopic surgery in CD can be challenging but is being more commonly performed, especially for ileocolic resections^[11-13]. It has proven short-term benefits such as decreased wound-infection rates, shorter hospital stay and faster recovery of bowel function even in complicated CD^[14]. However, its long term effect on disease recurrence and late bowel obstruction is still under debate^[15]. A meta-analysis comparing laparoscopic vs open surgery for CD indicated a reduced rate of surgery for recurrence in the laparoscopic group^[16]. Given that statistical significance was driven by one study mainly^[17], further well-designed clinical trials are mandatory to define the impact of laparoscopic surgery in CD on the need to undergo repeat surgery for disease recurrence.

Both the elective as compared to the acute indication and the laparoscopic vs the open procedure

are known to reduce the systemic inflammatory response syndrome (SIRS). It could be envisioned that a reduced SIRS in the perioperative course could reduce CD-associated pathological hyper-inflammation affecting the healing process of the anastomoses.

The type of anastomotic configuration following bowel resection in CD also seems to influence the postoperative outcome. Although, a stapled side-to-side anastomosis was previously widely considered as an inappropriate technique in CD, due the inflamed and thickened tissue and the potential higher risk for leakage, its safe use and its feasibility was demonstrated in large series^[11]. In addition, it was discussed whether a wide anastomotic lumen with less stool stasis and better blood supply, leads to an improved postoperative course with a reduced rate of anastomotic disease recurrence. Notably, a case-controlled study comparing wide-lumen stapled anastomosis with conventional sutured end-to-end anastomosis found a significant lower rate of symptomatic recurrences and reoperations in the stapled group^[18]. Furthermore, Simillis *et al*^[19] conducted a meta-analysis comparing end-to-end hand sewn anastomosis with other types of anastomotic configuration after intestinal resection for CD. Overall postoperative complications, including anastomotic leaks and length of hospital stay, were reduced in the side-to-side stapled group, although there was no significant difference in terms of surgical recurrences. Consequently, a wide-lumen stapled side-side anastomosis offers potential short-term benefits, but its beneficial effect on disease recurrence in Crohn's patients is not sufficiently confirmed.

CHANGING MEDICAL PARADIGM

Personalized medical therapy represents a keystone in the treatment of patients with CD. Currently, postoperative medical prophylaxis should be chosen individually for each single patient, according to a specific risk profile, such as smoking, penetrating disease or early endoscopic recurrence after routine ileocolonoscopy 6 to 12 mo following surgery. No clear guidelines recommending the routine application of specific immunosuppressive medication currently exist. This situation highlights the important role of close follow-up examinations by specialized gastroenterologists.

The introduction of immunosuppressants has led to significant improvements in the treatment of CD^[20]. It has been demonstrated that the postoperative exposure to azathioprine/6-mercaptopurine for more than 36 mo led to a significant reduction of reoperation rates after intestinal resection^[6,21]. This treatment benefit was effective even in the high-risk group of smokers. A recent meta-analysis reported Azathioprine and 6-mercaptopurine to be more effective in the prevention of postoperative clinical and endoscopic

recurrence in CD compared to placebo. Unfortunately, they were also associated with considerable adverse events^[22]. Surgical recurrence was not addressed in this investigation. In contrast, Ardiszone *et al*^[23] conducted a randomized controlled trial and did not observe any difference between azathioprine and mesalamine in preventing recurrent surgery. Further studies will be required to compare the effectiveness of azathioprine and 6-mercaptopurine with anti-tumor necrosis factor- α (TNF- α) antibodies in preventing disease relapse after intestinal resections.

Targeting TNF- α has become a major issue in maintaining long-term remission and significantly enriched therapeutic strategies in CD within the last decade. Infliximab, a monoclonal chimeric anti-TNF- α antibody, is effective in CD^[24] and induces remission even in patients not responding to conventional treatment^[25]. There are promising data that targeted therapy prevents postoperative endoscopic and clinical recurrence, which would further imply that escalation of disease could be limited at an early point, and eventually decreasing surgical interventions to reset disease activity. Regueiro *et al*^[26] randomly assigned 24 patients either to postoperative infliximab or placebo treatment. After 1 year, 9.1% had endoscopic recurrence compared to 84.6% in the placebo group. Furthermore, these encouraging results were confirmed by Sorrentino *et al*^[27], by performing a prospective study in 12 consecutive patients that were free of clinical and endoscopic disease recurrence at 24 mo under infliximab treatment. Once biological therapy was stopped, 10 out of 12 patients developed endoscopic recurrence, which could be limited by low-dose maintenance therapy.

Another milestone in biological therapy of CD was achieved with the implementation of adalimumab, a human, monoclonal anti-TNF- α antibody, which was expected to be less immunogenic than infliximab. Notably, adalimumab was more effective than azathioprine and mesalamine at preventing postoperative endoscopic recurrence of CD in a randomized trial^[28].

Nevertheless, there is a considerable lack of efficient data regarding the usefulness of biologicals (infliximab/adalimumab) in postoperative CD. Most published studies did not address the end-point surgical recurrence and enrolled a low number of patients only. Its routine prophylactic use after surgery to prevent recurrence is debatable taking into account missing large randomized controlled trials, its high medical cost and the potential side effects. The decision to use biologicals postoperatively should be made individually, according to the clinical history and risk stratification of each patient.

CONCLUSION

The impact of surgery on postoperative disease recurrence is still under debate. Most available studies

were designed retrospectively and do not provide high quality data to justify absolute recommendations. Few reports exist which indicate that a minimal invasive approach does not only offer short-term benefits, but might also delay repeat surgery for recurrence. A wide-lumen stapled side-to-side anastomotic configuration could potentially reduce the postoperative complication rate and the need for recurrent resection. Additionally, it is important to avoid postoperative complications, which represents another strong risk factor for surgical recurrence.

In our study, we have intended to implement all those strategies. We have used the technique of side-to-side anastomoses, endeavoring to perform elective rather than emergency surgery and a high rate of laparoscopic approaches. We now suggest that those factors could contribute to the favorable outcome with a low re-operation rate as this combination showed some success. It must certainly be stated that careful clinical observation after surgery and risk-stratified individual medical prophylactic therapy guided by experienced gastroenterologists is a keystone to providing the best care for these complex patients. In this line, the introduction of anti-TNF agents has definitely changed the treatment strategies in CD patients and improved the course of disease in a number of patients. Further randomized controlled trials will define the exact role of routine use of postoperative immunosuppressive medications.

In the future, it will be of great importance to further identify predictive factors for recurrence to allow us to select the appropriate patients who may benefit most from prophylactic medical treatment.

Finally, we are getting better in treating our patients, both surgically and medically, but we are still looking for a way to see a light in the end of the tunnel.

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