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Timing of individualized surgical intervention in Crohn's disease

Xia K *et al.* Timing of surgery in CD

Abstract

Crohn's disease (CD) is a gastrointestinal tract chronic inflammatory disorder with an increasing incidence worldwide. Comprehensive therapy for CD focuses on symptom control and healing the intestinal mucosa to improve the quality of life and prevent complications. Surgical intervention plays a vital role in comprehensive therapy. However, deciding the optimal timing for surgical intervention has long been a focus of controversy. This review provides insights into the timing of surgery for CD and guides clinicians in daily treatment.

Key Words: Crohn's disease; Surgical intervention; Timing of surgery; Individualization; Therapy

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Core Tip: Surgical intervention plays an important role in the comprehensive treatment of Crohn's disease (CD). However, the timing of surgery has always been a major controversial point. This review focuses on the main surgical indications for CD and the clinical factors that may influence surgical timing decisions. We also emphasize the value of early surgery in treating CD.

⁶ INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire digestive tract, especially the terminal ileum and proximal colon^[1,2]. The course of CD is protracted, characterized by alternating active and remission stages. The epidemiologic patterns of CD depict that the prevalence and hospitalization rates are currently rising gradually worldwide, contributing to an increasing burden on healthcare systems^[3-6]. The underlying cause of CD is still unknown but includes a variety of factors, including genetic susceptibility, environmental triggers, immune regulation, and gut microbial

imbalance^[7-9]. CD is prone to various complications due to penetrating and chronic intestinal inflammatory response, including intestinal obstruction, bowel perforation, fistula, or intra-abdominal abscess^[10,11]. After diagnosis, approximately 50% and 70% of CD patients develop complications within five or ten years, respectively^[12,13].

Recently, the launch of new biological agents has breathed new life into the clinical treatment of CD, while surgical intervention still plays an indispensable role^[14-16]. The cumulative surgery rate for CD patients is 16.6%, 35.4%, 53%, and 94.5% for 1, 5, 10, and 30 years, respectively, after the onset of the disease^[17]. The choice of optimal timing for surgical intervention has always been a focus of controversy. Some scholars advocate for early surgical intervention if drugs fail to achieve good results. Nevertheless, the recurrence after surgery is almost inevitable, and approximately 40% of CD patients require reoperation^[18]. Other scholars prefer to avoid early surgery only if it is necessary to resect the intestinal segments that cause complications following the principle of intestinal conservation. However, post-operative complications significantly increase due to poor nutritional status and severe abdominal infection^[19]. This review mainly focuses on the choice of individualized surgical intervention timing for CD patients.

SURGICAL INDICATIONS FOR CD

According to the relevant literature and clinical experience, we summarize the main surgical indications for CD, which involve serious complications of CD (Figure 1), failure of medical therapy, and growth retardation in children.

Serious complications of CD

Intestinal obstruction: Intestinal obstruction is a common and serious complication of CD, especially fibrosis-associated intestinal stricture^[20]. Lin *et al*^[21] revealed that approximately 70% of CD patients inevitably develop fibrosis-associated intestinal stricture a decade following diagnosis. Medical treatment is frequently ineffective in patients who develop intestinal obstruction, and surgical resection is primarily required

in that case^[22,23]. Certainly, with the development of endoscopic technology, endoscopic balloon dilation is also an appropriate treatment option ² when the length of strictures is ≤ 5 cm, non-angulated, and with a sizeable intestinal cavity large enough to allow balloon dilators in the absence of contraindications such as the presence of fistula, abscess, or malignancy^[24,25]. Furthermore, acute inflammatory obstruction can be frequently relieved by medical therapy. If conservative therapy is ineffective, surgical intervention should be considered to relieve the obstruction.

Intra-abdominal abscess: Intra-abdominal abscess is an important clinical complication of CD, the cause of which may be spontaneous or secondary to surgery^[26,27]. The current first-line therapy for CD, complicated by intra-abdominal abscess, is percutaneous abscess drainage with systemic antibiotics^[28,29]. However, surgical intervention should be considered actively if the symptoms of sepsis do not improve after drainage, abscess ruptures with severe peritonitis, or multiple abscesses cannot be drained. Intestine resection appears to be inevitable in most CD patients presenting intra-abdominal abscess^[30,31].

Fistula: Therapy for fistula has always been a complex clinical challenge. Simple enteral fistula without infection and clinical symptoms can be healed by a medical treatment such as enteral nutrition or biological agents^[32,33]. For other complex enteral fistulae, including spontaneous enteroenteral or enteroexternal fistula formed after abscess drainage, the possibility of self-healing is low, and surgery should be adopted^[34,35]. CD patients with severe fistula are often accompanied by loss of digestive fluid, resulting in disturbance of internal environmental balance, secondary infection, and malnutrition. Therefore, the infection should be readily controlled, and adequate nutritional support provided before elective surgery^[36,37]. Yzet *et al*^[38] recently reported successful cases of endoscopic treatment for enteroexternal fistula, which was feasible with short-term effectiveness.

Perianal lesions: Perianal lesions are common complications of CD, with perianal fistula and abscess being one of the most common^[39,40]. The management of symptomatic simple perianal fistula and complex perianal fistula employs a multidisciplinary approach, which includes antibiotics, biological therapies, and surgery^[41,42]. Furthermore, stem cell therapy is also an effective option for complex perianal fistula in CD patients^[43,44]. As for the treatment of perianal abscess, surgical drainage and antibiotic therapy are preferred.

Perforation, massive bleeding, or canceration: The incidence of CD complicated by acute perforation is low. However, emergency surgical intervention is often required if it occurs^[45]. When complicated by massive bleeding, the location of bleeding should be identified, and treatments such as drug, endoscopic, or interventional hemostasis should be actively adopted. Emergency surgery is required if the above treatments fail and massive bleeding continues^[46,47]. In addition, CD complicated by canceration is an absolute indication for surgery^[48].

Failure of medical therapy: Surgical intervention may be considered when drug therapy fails, and symptoms such as intolerance to severe side effects and ineffectiveness to various biological agents are difficult to control.

Growth retardation in children: Pediatric CD often presents as a triad of abdominal pain, diarrhea, and weight loss, characterized by growth retardation^[49,50]. Therefore, the pediatric treatment of CD induces and maintains clinical remission of the disease and optimizes nutrition and growth as soon as possible^[51]. Surgery should be performed before puberty for prepubertal or early pubertal patients with severe malnutrition resulting in growth arrest^[52]. Since the rate of post-operative recurrence is still high, drug therapy is required to maintain remission after surgery^[53].

CLINICAL FACTORS AFFECTING THE TIMING OF SURGERY

Surgical intervention for CD aims to deal with complications and improve the quality of life of patients, as they tend to be in poor general conditions. Therefore, except for emergencies such as massive bleeding and acute perforation, adequate preoperative preparation should be completed to improve the efficacy of surgery. As a clinician, more attention should be paid to following the clinical factors to minimize perioperative complications.

Nutritional support

Malnutrition is one of the prominent clinical manifestations of CD. Our team recently published a study indicating that CD patients were at higher nutritional risk than healthy people^[54]. It can hinder wound healing and increase the risk of incision infection, hernia, and anastomotic leak^[55]. Therefore, nutritional status is recognized as an independent risk factor for post-operative complications. Yamamoto *et al*^[56] revealed that patients with preoperative low albumin levels (< 30 g/L) had a 2.6-fold increased incidence of post-operative complications, similar to Shah *et al*^[57]. Another study indicated that preoperative optimization with nutritional support reduced the overall rate of post-operative complications of CD^[58]. Thus, perioperative nutritional support is vital for CD patients, while enteral nutrition should be adopted when the intestinal state permits. Appropriate enteral nutrition can improve the nutritional status, protect the intestinal mucosal barrier, and induce clinical remission^[59,60]. It is a well-established and recommended first-line induction therapy in pediatric CD with remission rates of up to 80%^[61].

Infection control

A recent study by Bachour *et al*^[62] revealed that abdominal infection was associated with an increased risk of surgical post-operative recurrence of CD. Tzivanakis *et al*^[63] indicated that the presence of preoperative abdominal abscess formation was identified as an independent predictor of anastomotic-associated complications. If the risk factor is present before surgery, the risk of anastomotic complications can be increased to 14%.

Therefore, CD patients with abdominal abscesses can often be first managed with antibiotics and percutaneous drainage, while definitive surgical intervention should be performed after the infection has been controlled^[64].

Drugs effects

Whether preoperative CD treatment with tumor necrosis factor inhibitors (TNFis) increases the risk of post-operative complications remains controversial. TNFis may compromise immunity, collagen production, and angiogenesis resulting in infective post-operative complications and altered wound healing^[65,66]. In addition, TNF- α is a key cytokine in collagen production and angiogenesis, with animal studies confirming its role in wound healing^[67]. However, previous studies have confirmed that preoperative TNFi exposure was not correlated with post-operative infectious complications^[68-70] (Table 1).

Azathioprine is commonly used as an immunosuppressant for treating CD and may not increase the risk of post-operative complications. Although azathioprine has demonstrated efficacy in preventing post-operative recurrence, there is no significant decrease in the need for surgery or intestinal complications from CD^[71,72] (Table 1). Furthermore, CD patients are frequently treated with steroids before surgery. Nguyen *et al*^[73] indicated that preoperative steroids were correlated with a higher risk of post-operative sepsis (Table 1). Therefore, steroids should be minimized or discontinued six months before surgery.

VALUE OF EARLY SURGICAL INTERVENTION IN THE TREATMENT OF CD

Early surgery for CD is commonly performed within a short time after diagnosis, while the time frame is still inconclusive^[74,75]. An *et al*^[76] defined early surgery as patients who had undergone upfront surgery for CD due to an acute complication of those who underwent surgery within six months of diagnosis. Interestingly, this study revealed that patients with ileocolonic CD may have a better prognosis if undergoing early surgical intervention, with fewer admissions to the hospital and reduced overall

operation rates. Aratari *et al*^[77] also defined early surgery when performed at the time of CD diagnosis, when these patients underwent surgery for the acute or subacute presentation of CD. Meanwhile, late surgery was defined as patients with an established diagnosis of CD who underwent surgery during the course of the disease on account of intestinal complications or refractoriness to medical therapy. Early surgery may significantly prolong the time of clinical recurrence of CD compared to late surgery. Considering the lack of evidence from these retrospective studies, the conclusions warrant further verification.

Early surgical intervention may benefit patients with localized CD, which refers to intestinal CD affecting < 30 cm in extent. This usually applies to an ileocaecal location but also isolated colonic disease, or conceivably to proximal small intestinal disease^[78]. Ponsioen *et al*^[79] indicated that early laparoscopic surgery for localized CD could improve the overall quality of life of patients and reduce the rate of recurrence and reoperation. A long-term follow-up study by Stevens *et al*^[80] during the LIR! C-trial revealed that most patients with localized CD who underwent early surgery were free of anti-TNF treatment, and none required a second surgery. Conversely, almost half of the patients who underwent anti-TNF treatment moved on to a Crohn-related resection. Furthermore, de Groof *et al*^[81] revealed that mean CD total direct healthcare costs per patient at one year were lower in the group who underwent early surgery compared with the anti-TNF group. Early surgical intervention is a reasonable and cost-effective treatment option for patients with localized CD.

China has a high incidence of hepatitis and tuberculosis. However, anti-TNF treatment may increase the risk of opportunistic infections^[82,83]. Early surgery instead of anti-TNF treatment can reduce opportunistic infections. Additionally, early surgical resection of localized lesions may improve the response to post-operative anti-TNF treatment, the curative effect of which is better than the initial therapy^[84,85].

CONCLUSION

CD is a refractory disease with a high misdiagnosis rate, a tendency for lifelong recurrence, and a high rate of operation and reoperation. Surgical intervention is a key part of the comprehensive treatment of CD. Inappropriate timing of surgery may lead to catastrophic post-operative complications, increasing the risk of surgery and prolonging hospital stays. Therefore, clinicians need to evaluate the severity and type of CD as well as the effectiveness of medical therapy and choose the timing of surgical intervention based on individual circumstances to ensure the maximum benefit for CD patients. Maybe in the future, with the deepening of multi-omics researches such as radiomics, metabolomics and microbiome, it will provide more favorable basis for individualized timing of CD surgery and identify the early changes of CD related acute lesions.

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