Early Laparoscopic Ileal Resection for Localized Ileocecal Crohn's Disease: Hard Sell or a Revolutionary New Norm?

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Abstract

Background: Despite reductions in surgical rates that have been observed with earlier use of biological therapy, surgery still constitutes an important tool in the therapeutic armamentarium in Crohn's disease (CD), particularly in patients with stenotic and penetrating phenotypes. In these scenarios, early surgical intervention is recommended, as bowel damage is present and irreversible, leading to lower efficacy with biologics. **Summary:** The concept of early surgery in CD supposes the possible advantages of better surgical outcomes in luminal CD after initial resection. Optimal timing of surgical intervention is associated with better postoperative outcomes, whilst delays can lead to more technically difficult and extensive procedures, which may result in an increase in postoperative complication rates and higher rates of stoma formation. Furthermore, data from the LIRIC trial have demonstrated that early surgery in luminal localized inflammatory ileocecal CD is an adequate alternative to medical therapy, with lower societal costs in the long term. In this review, we discuss the position of early resection in ileocecal CD by

critically reviewing available data, describing the ideal patients to be considered for early surgery, and weighing the potential advantages and disadvantages of an early surgery paradigm. **Key Messages:** While early surgery may not be the right choice for every patient, the ultimate decision regarding whether surgical or medical therapy should come first in the treatment paradigm must be individualized for each patient based on the disease characteristics, phenotype, risk factors, and personal preference. This highlights the importance of the multidisciplinary team, which remains a key pillar in deciding the overall management plan for patients with CD.

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Introduction

It is universally accepted that Crohn's disease (CD) is commonly associated with a progressive course, which evolves from the presence of luminal inflammation, which left uncontrolled develops towards fibrotic stenosis of affected bowel segments, potentially culminating in perforation, abscesses, and fistulas [1]. Despite significant advances in medical management over the last 2 decades,

a substantial proportion of patients still develop progression of their disease [2–7]. The impact of newer therapies has been demonstrated in several population-based studies, which have shown an association between the timely use of effective medical therapy and an overall reduction in the need for surgical procedures. For instance, a large Danish study by Rungoe et al. [8] described an increase in the use of immunomodulators and biological agents, associated with a reduction in the proportion of patients who needed surgery during the same period. Despite these reductions in surgical rates associated with the prompt use of biological therapy globally [9], surgery still remains an important tool in our therapeutic armamentarium, particularly in patients with stenotic and penetrating phenotypes of CD [10].

Accepted indications for surgery in ileocecal CD include long, “cold,” fibrotic stenoses which are not amenable to endoscopic intervention, penetrating disease with symptomatic internal or enterocutaneous fistula(s), development of neoplasia, or medically refractory disease either in the form of primary nonresponse or secondary nonresponse to biologics [11–13]. Optimal use of biologics includes strategies that have been shown to enhance their effectiveness such as early intervention, treat-to-target strategies, and tight monitoring of disease control. Delays in optimization of biological therapy or multiple switches to other agents with different mechanisms of action in inadequate responders may be associated with time delays leading to fibrosis and bowel damage.

Optimal surgical management of CD includes the option to employ minimally invasive techniques, which are currently considered the gold standard in surgery for CD [14]. Although feasible, laparoscopic surgery or other minimally invasive techniques (i.e., single port) for complicated CD (e.g., associated fistulas, inflammatory masses, and extensive disease) can be associated with higher rates of complications and a greater need for conversion to open procedures and stomas, mostly if not performed in high-volume centers [10, 15, 16]. Therefore, the concept of early surgery in CD must include the possible advantages of better overall surgical outcomes in luminal CD, and some studies have demonstrated the value of early surgery in comparison with medical therapy [17–19]. The aim of this review is to discuss the positioning of early surgical resection in ileocecal CD by critically reviewing available data, describing the ideal patients to be considered for early surgery, and putting forward its possible advantages and disadvantages.

Defining Timing of Early Surgery: How Early Is Early?

Overall, in population-based studies and referral centers, there appears to have been a reduction in surgical resection rates in patients with CD when biological therapy is introduced in a timely fashion [8, 9, 20]. However, there is a suggestion that this may not be an absolute true decrease in need for surgery, but rather that the persistence of medical therapy leads to a delay in surgical timing. Along with this delay, surgeons have reported the need for more extensive procedures due to increased severity at the time of resection [15]. The concept that perioperative biologic therapy decreases the length of surgical resections has been disputed. For example, a study from the Netherlands demonstrated that in CD patients undergoing ileocecal resections, the length of resection specimens did not decrease over time [21], despite a significant increase in the use of biologics and the time from diagnosis to surgery in patients with previous anti-TNF use (median 39.0 months, IQR 12.0–86.0, $\rho = 0.175$, $p = 0.014$). Furthermore, there was no significant decrease in the length of resected specimens in patients with previous exposure to biologics (median 20.0 cm, IQR 12.0–30.0, $\rho = 0.107$, $p = 0.143$). These findings lead to speculation whether biologics can truly avoid surgery or simply delay the procedures without reducing disease extension.

Key to this discussion is what constitutes the ideal definition of early surgery? Should the definition be based on a set period of time after diagnosis or should it be based on phenotypic features characteristic of early disease, considering the natural progression of CD? It is important to consider that progression of disease behavior from luminal inflammation towards stenotic or penetrating lesions does not occur at the same pace in all patients. Some will present with early stricturing or penetrating complications which may necessitate immediate surgical intervention but is not necessarily early surgery [22]. Therefore, “early” indication for surgery should not be based on a certain timeframe from diagnosis in terms of years or months but rather in the specific phenotype. Therefore, it is important to differentiate between early surgical intervention from early surgery. For the purposes of this discussion, early surgery should be defined as surgical resection performed for luminal inflammatory disease, with no previous resections (not related to postoperative recurrence), not complicated by fibrotic stenoses or perforation in which surgery is inevitable.

Several studies have described the long-term natural course of CD after early surgery, defined using time from

Table 1. Disease and patients' characteristics for an ideal indication for early surgical intervention in CD

Disease characteristics	Patients' characteristics
Localized disease (ileocecal region and proximal small bowel)	Adequate nutritional status
Luminal (inflammatory) phenotype, Montreal classification B1, refractory to medical therapy	No previous or recent use (within 6 weeks) of corticosteroids
Short segment of inflammatory disease (20 cm or less)	Nonobese (low visceral fat)
Strictureing (B2) or penetrating (B3) CD at the time of diagnosis	No large incisions from previous open abdominal surgery
	ASA class I and II

ASA, American Society of Anesthesiology; CD, Crohn's disease.

diagnosis. A study from Italy evaluated the natural history of CD patients comparing early (at the time of diagnosis) with delayed surgery [23]. Cumulative clinical recurrence was lower in the early surgery group (hazard ratio = 0.57; 95% CI: 0.35–0.92, $p = 0.02$). However, there was no difference between the groups in terms of reoperation or in the need for immunomodulators. Another study from Hungary also demonstrated that early limited surgery leads to a reduction in the need for corticosteroids and biologics over time, but similarly, no impact on surgical recurrence was observed [24]. A study from Portugal compared postoperative outcomes of patients who had surgery <6 months from diagnosis with patients that were treated with immunosuppressants. The rates of unfavorable outcomes were similar between the groups; however, patients with early surgery required more reoperations over long-term follow-up (50 vs. 27%, $p < 0.001$) [25]. Reoperation rates are challenging to interpret in this retrospective study due to the bias by indication for requiring early surgery in patients who have more complex disease within 6 months of diagnosis. Thus, there is clearly heterogeneity in defining early surgery, ranging from requiring resection at diagnosis to within 6 months of diagnosis and to surgery in the absence of disease progression. Furthermore, overcoming bias by indication for early surgery is difficult in cohort designs or retrospective analyses.

Table 1 illustrates important features of an ideal patient that should be considered for early surgical intervention, considering all phenotypes. In terms of disease characteristics, it includes patients with localized luminal disease, who are refractory to optimal medical therapy. Patients with fibrotic strictures and/or penetrating disease (internal or external fistulas) are also good candidates for surgery before biologics, as response to med-

ical therapy is low in these scenarios. Indeed, treatment with a biologic for patients who have established mechanical disease-related complications may be inappropriate, as treatment targets of either stricture resolution or fistula closure range from unlikely to impossible to achieve, therefore exposing patients to potential drug-related adverse events including immunization and anti-drug antibody formation. As surgery can also be associated with important postoperative complications, those with lower risks for adverse postsurgical events include patients with a low American Society of Anesthesiology (ASA) class, with adequate nutrition, no previous or recent (within 6 weeks) corticosteroids, those without associated obesity, and patients without previous open abdominal surgery with wide incisions [11, 12]. These characteristics would make an ideal scenario for the indication of early surgery for inflammatory luminal CD with expected adequate postoperative outcomes.

Rethinking Early Surgical Intervention versus Early Surgery: The Impact of LIRIC Trial Data

It is clear that a diagnostic delay in CD can lead to significant bowel damage by the time initial therapeutic decisions must be made [26, 27]. These patients benefit from early surgical intervention as the initial choice of treatment as outlined in Table 1, followed by postoperative pharmacologic therapy aimed at preventing postoperative recurrence [10–12]. Eberhardson et al. [28] described the findings of a population-based study with 1,856 CD patients who received anti-TNF therapy. The authors analyzed the incidence of bowel resection after initiation of anti-TNF agents from 2006 with up to 7 years

of follow-up. Overall, only 65% of patients remained on the same biologic agent after 12 months. Cumulative rates of surgery between years 1 and 7 after initiation of anti-TNF treatment were 7, 13, 17, 20, 23, 25, and 28%, respectively. Moreover, rates of surgery were similar between patients irrespective of the duration of anti-TNF use (<12 vs. >12 months, $p = 0.27$). Thus, it seems that despite efforts in using biologics precisely and timely, surgery can only be delayed in some patients with CD, as rates of the need for surgery continued to increase over the 7-year period of the study's follow-up.

Delays in surgery may lead to more difficult surgery, which can be associated with worse postoperative outcomes. Iesalnieks et al. [15] analyzed the relationship between time of clinical deterioration and postoperative complications in 197 patients with CD submitted to 231 surgical resections. The authors demonstrated that longer duration of clinical deterioration before surgery was associated with more drug combinations and more significant weight loss. Additionally, surgery was more complex and associated with a higher rate of postoperative infections, as a higher proportion of patients had involvement of >3 strictures in the inflammatory mass.

Kotze et al. [16] described the findings of a retrospective cohort study with 123 patients with CD submitted to elective abdominal surgery. Patients with surgery after >5 years of disease ($n = 77$) had higher rates of overall surgical complications, reoperations, surgical site infections, anastomotic dehiscence, abdominal abscesses, and overall medical complications. These data support the finding that although biologic therapy is an important component of the treatment armamentarium, their use can be associated with delays in surgery, more complex operations, lower use of minimally invasive laparoscopic techniques, and higher rates of postoperative complications if they are not introduced in a timely fashion.

The LIR!C trial has refined our thinking around the concept of early surgery in the era of biologics. The LIR!C trial was a randomized multicenter study in patients with active localized terminal ileal CD (<20 cm of extension) who did not respond to conventional therapies. Patients were randomized to ileocecal laparoscopic resection or infliximab [17]. This was a landmark study, as it was the first trial to prospectively compare surgical versus medical treatment in any scenario in IBD. Patients who had previous ileocecal resections, fibrotic stricturing disease, disease extension of >40 cm, or ASA class III and IV were excluded from the study. Overall, 143 patients were randomized, with 70 in the infliximab and 73 in the laparoscopic ileocolic resection groups, re-

spectively. The primary outcome was quality of life measured using the Inflammatory Bowel Disease Questionnaire (IBDQ) at 12 months. Secondary outcomes included general quality of life according to the Short Form-36 (SF-36) health survey and its physical and mental component subscales, days unable to participate in social life, days on sick leave, complications (including additional procedures and hospital admissions), body image, and cosmesis.

The mean IBDQ score at 1 year was 178.1 (95% CI: 171.1–185.0) in the laparoscopic surgery group versus 172.0 (164.3–179.6) in the IFX group (mean delta of 6.1 points, 95% CI: 4.2–16.4; $p = 0.25$). After a median follow-up of 4 (IQR 2–6) years, 26/70 (37%) patients initially randomized to infliximab were submitted to an ileocecal resection, whilst 19/73 (26%) patients randomized to the laparoscopic resection group received an anti-TNF agent. These results demonstrated that surgery, despite not being superior, was similar to infliximab therapy in terms of achieving quality of life outcomes and was not associated with more serious morbidity. The authors concluded that early laparoscopic resection, in this specific population, may be offered as an alternative to biological therapy in localized ileocecal CD, due to its potential advantages and durable disease control.

A second publication from the same group described the cost-effectiveness of both treatment strategies [18]. Overall, the mean CD-related total direct healthcare costs per patient after 12 months were lower in patients randomized to the laparoscopic resection group compared to the infliximab group (mean difference of –8,931 EUR; 95% CI: –12,087 to –5,097 EUR). Total societal costs in the surgery group were also lower as compared to patients randomized to infliximab, despite not being statistically significant (mean difference –5,729 EUR, 95% CI: –10,606 to 172 EUR). The study showed that total direct health CD-related costs per patient over the period of 1 year were lower in the initial resection group. Therefore, the authors concluded that laparoscopic resection and infliximab are comparable in terms of their effect on quality of life, and that resection was a more cost-effective alternative to early anti-TNF therapy in patients with localized ileocecal luminal CD.

More recently, the long-term results of the LIR!C trial were published [19]. The outcomes analyzed were the need for surgery among patients initially randomized to infliximab or re-resection or the need for anti-TNF therapy in the early resection group. Data were collected from 94% of the patients who initially participated in the LIR!C study, with 69 in the resection and 65 in the infliximab

Table 2. Possible advantages and disadvantages of early surgery in different phenotypes of CD

	Advantages	Disadvantages
Early surgery in luminal CD	Reset on inflammatory burden Durable remission Possibility of delaying the need for biologics over the long term Higher rates of laparoscopic resections (low conversion rates) Lower costs	Possibility of postoperative complications Need for stomas when specific complications such as anastomotic dehiscences and obstruction occur Bowel image and cosmesis
Early surgical intervention in stricturing and penetrating CD	Resection of nonfunctional damaged intestinal segments Avoidance of potential acute emergency situations (i.e., obstruction and abdominal abscess)	Increased risk of stomas Possibility of additional bowel injury leading to short bowel syndrome (extensive dissection of adhesions or inflammatory masses) Lower rates of laparoscopic resections (higher conversion rates)

CD, Crohn's disease.

groups, respectively. The average follow-up period was 63.5 months. In the resection group, only 18/69 (26%) patients needed to start an anti-TNF agent and none required a second resection. In the infliximab group, 31/65 (48%) patients underwent a CD-related ileocecal resection, and the remaining patients were kept on biological therapy. Duration of treatment effect was similar in the 2 groups, with a median time without additional CD-related treatment of 33.0 months (95% CI: 15.1–50.9) in the surgery group and 34.0 months (95% CI: 0.0–69.3) in the infliximab-treated patients (log-rank $p = 0.52$).

The results of the LIR!C trial demonstrated advantages of early surgery in patients with luminal localized ileocecal CD, as no re-resections were needed, and only one-quarter required anti-TNF therapy during follow-up due to disease recurrence. It is important to recognize that these results were achieved using minimally invasive surgical techniques, conducted primarily at tertiary care referral centers, with experienced IBD surgeons. Nevertheless, joint decision-making including surgeons, gastroenterologists, and patients may individualize who are the best candidates for this strategy.

Table 2 summarizes possible advantages and disadvantages of early surgery in luminal inflammatory disease and in patients with established bowel damage (stenotic and penetrating phenotypes) which can guide decision-making for the multidisciplinary approach. As seen, advantages in luminal disease are mostly related to early resection in luminal disease, with lessons learned from LIR!C.

Early Surgery versus Early Medical Therapy: An Individualized Choice

Even though the eponym of CD was initially derived from the description of a cohort of patients who had undergone surgical resection [29], the positioning of surgery for CD in 2021 has largely been relegated to the “treatment of last resort” after failure of medical options [10, 30]. As the number of advanced treatment options for managing moderate-to-severe CD has increased, there has also been a growing tendency for clinicians to try to exhaust all medical therapies prior to calling for surgical help, even in patients with refractory disease. However, is this truly the right approach? Answering this question requires careful consideration of several lessons learned from the past 20 years of the biologic era.

First, given the progressive bowel damaging nature of CD, there exists a window of opportunity during which early medical intervention may change the trajectory of the disease. The REACT trial demonstrated that an aggressive early combination immunosuppression approach including TNF antagonist initiation in combination with an immunomodulator has been shown to improve clinical outcomes, including avoidance of surgery, hospital admissions, and serious disease-related complications [5, 31]. Second, the efficacy of TNF antagonists appears to be higher in patients with early disease. Supporting evidence for this includes (1) higher rates of treatment success in both pivotal trials and observational studies of when remission is stratified according to disease duration, with better outcomes when therapy is initi-

ated within 2 years of diagnosis [32–34]; (2) higher rates of remission reported in landmark treatment strategy trials such as SONIC and CALM that enrolled primarily patients with early CD [3, 35]; and (3) generally higher rates of response observed in trials enrolling pediatric compared to adult populations [36]. Taken together, these findings suggest that early initiation of effective medical therapy is one of the most powerful tools in the gastroenterologist's armamentarium.

Would early surgery therefore delay the initiation of appropriate biologic treatment? We speculate that this is unlikely. Treatment paradigms for postoperative medical management of CD have evolved over the past decade, and early pharmacologic prophylaxis, especially in patients with risk factors for progressive disease, is now the standard of care and has been endorsed in clinical practice guidelines. For most patients with CD, prophylaxis will include a biologic therapy, as the efficacy of mesalamine and immunosuppressants is unclear, and there are substantive risks associated with long-term imidazole antibiotic exposure [37]. Data from the PREVENT trial demonstrated that treatment with IFX after surgery was associated with a nearly 30% absolute risk reduction in endoscopic recurrence compared to placebo (30.6 vs. 60.0%, $p < 0.001$), and De Cruz et al. [38] showed that an aggressive approach to monitoring for postoperative recurrence with early ileocolonoscopy to direct immunosuppression was associated with high rates of disease control. These pivotal trials have changed our approach to managing patients with CD after surgery, recognizing that for the vast majority, surgery does not mark the end of their disease journey, but rather a major steppingstone towards long-term disease control.

In patients who do undergo surgery, it remains unclear if biologics are more effective after the macroscopic burden of disease has been resected, with a so-called “fresh start,” when there is no residual disease elsewhere. On the one hand, surgical intervention may “reset” the immunologic response by reverting chronically active disease segments back to a more nascent, early inflammatory phenotype. Surgery reduces the burden of mesenteric creeping fat (which secretes cytokines, chemokines, and proinflammatory mediators including TNF, IL-6, and IL-1 β) [39], alters the fecal microbiota composition, and removes inflamed gut with poor intestinal permeability that promotes a chronic immunologic response [40, 41]. Reversing these factors may in fact promote a gut environment in which medical therapies may be more effective, although this remains an area of research priority. Evaluating the comparative efficacy of biologics before and af-

ter surgery is inherently challenging because the endpoints for treating active lesions versus preventing lesion recurrence are different. Stratifying results in existing trials by pre- versus postsurgical status may not be informative as patients are typically excluded if they have undergone recent surgery; patients are enrolled based on active inflammation at baseline, and in that situation, previous surgery is primarily a surrogate measure of overall disease severity.

Despite these uncertainties, there is clearly a patient population for whom early surgical intervention is the correct treatment decision. Moran et al. [42] evaluated factors associated with failure of medical therapy: patients with stricturing or penetrating disease phenotypes had >6- and 3-fold increased risks of failing medical therapy and requiring surgical intervention. Indeed, very little evidence supports the use of biologic agents for resolving internal penetrating disease or for “cold” fibrostenotic strictures [43, 44]. In these scenarios, as previously stated, delaying inevitable surgery by introducing a biologic agent may have detrimental consequences as it changes the benefit-risk proposition. It is challenging to assess the true effectiveness of the medical agents, potentially resulting in early treatment discontinuation and inadvertent drug immunization with anti-drug antibody formation. Furthermore, delays to surgery may result in progressive malnutrition or disease-related complications that require urgent intervention, both of which are known to contribute to poor surgical outcomes [45]. Therefore, no single dogma can rule the day: while early surgery may not be the right choice for every patient, the ultimate decision regarding whether surgical or medical therapy comes first in the treatment paradigm must be individualized for each patient based on the disease characteristics, phenotype, risk factors, and personal preferences.

Patient Perspectives

For early surgery to be effectively implemented as a treatment strategy in CD, it must be considered acceptable by patients. This is a considerable hurdle as fear of surgery remains one of the primary concerns among patients with CD, driven by anxieties around coping with a potential stoma, the risk of postoperative complications, and the possibility of disease recurrence after resection [46]. Acknowledging these concerns is paramount in the shared decision-making process. Surgical resection is associated with potentially significant adverse events, such

as bleeding, infection, and anastomotic leak, as well as a material risk of mortality: in a meta-analysis including 75,971 patients with CD undergoing surgery, Singh et al. [45] reported that the pooled risk of mortality ranged from 0.6% for elective procedures to 3.6% for emergency surgery. Interestingly, the long-term risk of requiring an ileostomy was lower in patients randomized to laparoscopic ileocecal resection compared to patients in the infliximab first arm of the LIR!C trial [17]; nevertheless, addressing cosmetic, social, sexual, and functional implications of a stoma is critical in helping patients understand their surgical risk. Finally, it must be acknowledged that surgery is a highly technical skill, and given the complexity of these surgeries, the success of any operation and the associated risks of morbidity are operator and technique dependent. Both referring physicians and patients should be aware of the expertise of the surgeon performing the operation and recognize that crude complication rates may not be reflective of surgical experience, as these are confounded by referral and selection bias for more complex cases.

Final Messages

Over the last decade, our understanding of the benefits of timely surgical intervention in the management of CD has evolved. This is largely due to the multidisciplinary dynamic approach in patient care, and the development of IBD surgery as a specialty where surgeons focused on IBD can guide the ideal positioning of early surgery. Clearly, there are significant limitations with the use of

biologics in stricturing and internal penetrating disease, where surgery remains the best treatment option. However, the benefits of early surgery in localized luminal ileocecal CD have been well demonstrated in the LIR!C trial. Therefore, although early surgery can be seen as a “hard sell” for some patients due to the fear of surgery, early resection should be part of the revolutionary new norm and should be part of our discussions with patients.

Conflict of Interest Statement

Christopher Ma has received consulting fees from Robarts Clinical Trials. Remo Panaccione has received consulting and speaker fees from AbbVie, Allergan, Celgene, Eli Lilly, Ferring, Gil-ead, Janssen, Shire, and Takeda; served as a Scientific Advisory Board member for AbbVie, Allergan, Celgene, Eli Lilly, Janssen, and Takeda; and received research grants from AbbVie, Janssen, and Takeda. Paulo Kotze has received consulting and speaker fees from AbbVie, Janssen, Pfizer, Takeda, and UCB. Beatriz Maruyama has no conflicts of interest.

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Author Contributions

R.P. and P.K. designed the review. B.M., C.M., R.P., and P.K. did literature review and equally wrote the manuscript. All authors contributed to intellectual content and reviewed and approved the final version.

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