

PAULO GUSTAVO KOTZE, MD



Paulo Gustavo Kotze is Adjunct Senior Professor of Surgery of the Colorectal Surgery Unit at Cajuru University Hospital of the Catholic University in Curitiba, Paraná, Brazil. He received his medical degree at the Federal University of Paraná in 1997 and completed his General Surgery training at the Evangelical University Hospital in Curitiba (2000). He also completed his senior Fellowship in Colorectal Surgery at the Clinics Hospital from the Federal University of Parana (2002). Dr. Kotze achieved his Masters' Degree on Surgery at the Catholic University in 2008 and joined the faculty of medicine at the same university in 2011, as assistant professor of surgery. He achieved his PhD degree studying the influence of biological therapy on surgical outcomes in Crohn's disease, in the University of Campinas, in São Paulo, Brazil (UNICAMP) in 2015. Dr. Kotze was also an IBD advanced visiting fellow in the IBD unit at the University of Calgary (Cumming school of medicine), Canada, for the period of 2017-2018. Currently, he is Professor of the Postgraduate Health Sciences Program at the Catholic University of Paraná. Dr. Kotze is an experienced academic IBD surgeon and author of 3 books, more than 200 PubMed peer-reviewed articles and multiple book chapters focused on Crohn's disease and ulcerative colitis. He has special interest in the fields of surgery, biological therapy and epidemiology in IBD. He actively participates on the directory board of the Brazilian Study group for IBD (GEDIIB) and is currently co-editor of the Journal of Coloproctology (periodical of the Brazilian society of colorectal surgeons) and participates as an international editorial board member of the Lancet Gastroenterology and Hepatology, Journal of Crohn's and Colitis, Colorectal Disease, Intestinal Research, Therapeutic Advances in Gastroenterology, Techniques in Coloproctology and the British Journal of Surgery. He is also a reviewer for several international journals such as Gut, Alimentary Pharmacology and Therapeutics, Clinical Gastroenterology and Hepatology, Gastroenterology, among others. Dr. Kotze was formerly a committee member of S-ECCO (surgeons of ECCO) from 2015-2018 and a member of the ECCO EduCOM (educational committee), from 2018-2022. In 2020, he was selected as a full active member of IOIBD (International Organization for the Study of Inflammatory Bowel Disease). He is also a senior researcher of the Brazilian National Research Council (CNPq).

Affiliations: Professor, Health Sciences Postgraduate Program, Catholic University of Paraná (PUCPR), Curitiba, Brazil

THE ROLE OF UPFRONT SURGERY IN THE MANAGEMENT OF ILEAL CROHN'S DISEASE

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder characterized by transmural inflammation that can affect any part of the gastrointestinal tract. Among the various phenotypes of CD, involvement of the terminal ileum, known as ileal CD, poses unique challenges in management due to its potential for complications such as strictures, fistulas, and abscesses.¹ While medical therapy remains a cornerstone in the management of CD, the role of surgery, particularly upfront surgical intervention (early resection), has garnered increasing attention in recent years.²

The decision to pursue surgical intervention at the outset of disease management, rather than relying solely on medical therapy, is a subject of ongoing debate in the field. Upfront surgery (prior to advanced medical therapies) may offer benefits such as rapid resolution of symptoms, avoidance of long-term immunosuppressive therapy and prevention of

disease progression. However, concerns regarding the postoperative morbidity and potential for recurrence associated with surgical intervention warrant careful consideration.³

Recent studies have provided valuable insights into the efficacy and safety of upfront surgery in ileal CD. The PREDICT study, conducted by Agrawal et al., demonstrated favourable outcomes with early surgical intervention in a cohort of patients with ileocecal CD, highlighting the potential for improved clinical outcomes and reduced healthcare utilization compared to medical management with anti-tumor necrosis factor (TNF) agents. More importantly, approximately half of patients did not need medical therapy after 5 years of follow-up, which demonstrates the durability of surgically-induced remission in early stage CD.⁴ Additionally, the landmark LIRIC (Laparoscopic Ileocecal Resection versus Conventional Medical Management for Patients with Luminal Crohn's Disease) trial evaluated the role of laparoscopic ileocecal resection (LICR) versus

infliximab in patients with uncomplicated localized ileocecal CD, further informing the debate surrounding upfront surgery in this patient population.⁵ The trial demonstrated that after 5 years of follow-up, 48% of patients using infliximab needed a surgical resection, implying that medical therapy does not prevent a surgical resection in all patients, but may delay surgery in many.⁶

In this narrative review, we aim to critically evaluate the existing literature on upfront surgery in ileal CD. Additionally, we seek to elucidate the optimal surgical management approach for patients with ileal CD and provide guidance for clinical decision-making in this challenging disease entity. Last, we discuss surgical approaches used in association with this strategy.

Rationale for Earlier Surgery in Terminal Ileum Crohn's Disease

While medical therapy remains a mainstay in the management of luminal CD, the limitations of pharmacological interventions, including the risk of adverse effects and the development of treatment refractoriness, underscore the importance of considering surgical intervention early in the disease course.⁷ Currently, with optimal strategies using advanced therapies, mucosal healing is achieved in a limited proportion of patients. As an example, data from the CALM trial, using tight monitoring and early use of adalimumab, demonstrated that mucosal healing occurred in only 48% of patients.⁸ As there is a lack of predictors of response to medical therapy, patient selection for advanced therapy or surgical resection occurs as a result of detailed discussion with patients

around their objectives and expectations for their future disease course.

A compelling rationale for early surgical intervention in luminal terminal ileal CD lies in the potential for reducing disease-related morbidity and improving long-term outcomes. Kotze et al. conducted a retrospective cohort study evaluating postoperative morbidity in elective surgery for CD, highlighting a significantly lower rate of medical and surgical postoperative complications in patients with less than 5 years of disease duration.⁹ Surgery after 5 years from diagnosis was associated with a higher risk of the need for a stoma (OR: 3.203; 95% CI: 1.011-10.151; P=0.048). Additionally, Avellaneda et al. reported favourable outcomes with earlier surgical intervention, demonstrating a reduction in the incidence of postoperative complications in patients with the luminal phenotype vs those with complicated disease, with fibrotic stenosis and penetrating complications.¹⁰

Potential advances and disadvantages of upfront surgery in ileal CD are detailed in **Table 1**. Earlier surgical intervention offers the advantage of addressing underlying pathology promptly, thereby mitigating the risk of disease progression and the development of irreversible complications such as stenosis or penetrating complications. Early surgery may prevent the need for repeated hospitalizations, invasive procedures and the long-term use of immunosuppressive medications, ultimately improving patient quality of life and reducing healthcare resource utilization.¹¹ Thus, the limited efficacy associated with optimized medical strategies, the reduced morbidity of surgery in the luminal phenotype, and the possibility of full disease control with no medications comprise the rationale of potential advantages of earlier surgical resection in localized terminal ileal luminal CD.

Early surgery in localized luminal ileal CD	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Reset of inflammatory burden (no residual disease) • Durable remission • Possible avoidance of advanced therapies in the long term • Higher rates of minimally invasive procedures (laparoscopic, robotics) with low conversion rates • Lower direct and indirect costs 	<ul style="list-style-type: none"> • Possibility of postoperative complications • Need for stomas when specific complications such as anastomotic leaks and obstruction occur • Body image and cosmesis

Table 1. Potential advantages and disadvantages of upfront surgery in luminal ileal CD; courtesy of Paulo Gustavo Kotze, MD.

Available Evidence in Favour of Earlier Surgery

The LIRIC trial, conducted by Ponsien et al., compared the efficacy of LICR with conventional medical management in patients with luminal CD.⁵ The long-term evaluation of 134 (94%) of the 143 patients included in the LIRIC trial, of whom 69 were in the resection group and 65 were in the infliximab group, was described.⁶ Median follow-up was 63.5 months (IQR 39.0-94.5). In patients who underwent surgery, 18 (26%) of 69 patients were initiated on anti-TNF therapy and none required a second resection. A total of 29 (42%) patients in the resection group did not require additional CD-related medication, although 14 (48%) of these patients were given prophylactic immunomodulators. In the infliximab group, 31 (48%) of 65 patients had a CD-related resection, and the remaining 34 patients maintained, switched or escalated their anti-TNF therapy. These results position early laparoscopic resection as an effective and durable therapy in patients with limited ileal CD.

The PREDICT study, conducted by Agrawal et al., prospectively evaluated the outcomes of early surgical intervention vs anti-TNF agents as primary therapy in Danish patients with CD, after one year of diagnosis.⁴ A total of 1279 patients were included. Of these, 45.4% underwent ileocolic resection and 54.6% received anti-TNFs. The composite outcome (defined as at least one of the following criteria: perianal CD, need for steroids, hospitalizations or re-resection) occurred in 273 individuals (incidence rate, 110/1000 person-years) in the surgery cohort and in 318 individuals (incidence rate, 202/1000 person-years) who used anti-TNFs. The risk of the composite

outcome was 33% lower with surgery compared with anti-TNFs (adjusted hazard ratio, 0.67; 95% confidence interval, 0.54-0.83). Surgery was associated with a reduced risk of need for steroids and (additional) CD-related surgery. The proportion of individuals on no medical therapy 5 years after surgery was 49.7%, demonstrating the durable effect of surgery as primary therapy, with consistent disease control over time.

The SURGICROHN-LATAM consortium described postoperative morbidity after ileocecal resections comparing outcomes in patients who underwent earlier resection (luminal phenotype) with those with complicated disease (stenotic or penetrating phenotypes).¹⁰ A total of 337 patients were included in the analysis, with 60 (17.80%) in the luminal phenotype. Patients with complicated disease had increased requirement of urgent surgery (26.71 vs 15%, $P=0.056$), longer operative time (164.25 vs 90.53 min, $P<0.01$), lower rates of primary anastomosis (90.23 vs 100%, $P=0.012$), an increased incidence of overall postoperative complications (33.21 vs 16.67%, $P=0.013$), more re-operations (13.36 vs 3.33%, $P=0.026$), higher rates of major anastomotic leaks, and longer hospital stays. These findings demonstrate the reduced morbidity associated with surgery in luminal CD vs complicated disease, positioning surgery as a safer procedure if performed in expert hands before disease progression occurs. The increased complication rates in patients with delayed surgery are possibly associated with inadequate nutritional status, use of steroids, larger inflammatory masses, and intraoperative difficulties due to extensive disease. **Figure 1** describes in detail comparisons in different variables of upfront surgery with delayed procedures.

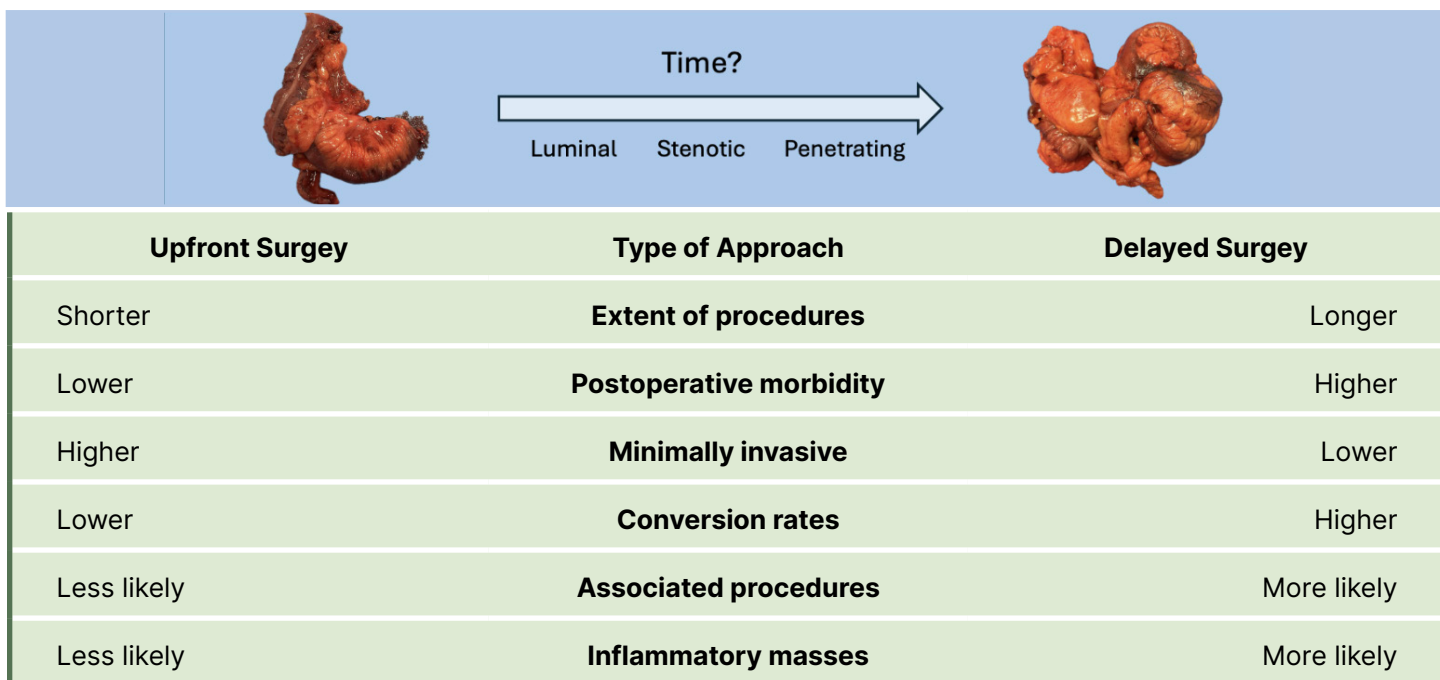


Figure 1. Surgical characteristics of upfront (earlier) surgery vs delayed procedures in ileal CD; courtesy of Paulo Gustavo Kotze, MD.

Surgical Options in Upfront Surgery in Ileal Crohn's Disease

In the luminal phenotype, minimally invasive procedures with multiport laparoscopy, single-port or robotic platforms comprise the mainstay of the surgical approach.¹² The need for conversion to open surgery is reduced due to the preserved anatomy of the disease, in the absence of inflammatory masses or penetrating complications.

In most centres globally, multiport laparoscopy is the preferential method for ileocecal resections.¹³ Typically, 4 ports are placed, followed by resection, releasing the terminal ileum, cecum, and proximal transverse colon from the retroperitoneal structures and omentum. The ileocolic vessels are ligated and resection can be accomplished. Anastomosis can be performed intra-corporeally (with endoscopic staplers and specimen withdrawal via a Pfannenstiel incision), or extra-corporeally (with small midline incisions to withdraw the specimen and perform the anastomosis with conventional linear staplers). Compared to conventional open surgery, laparoscopic procedures minimize surgical trauma, reduce postoperative pain, and accelerate recovery. Patients undergoing laparoscopic surgery experience shorter hospital stays and quicker return to normal activities, leading to improved patient satisfaction and quality of life. By avoiding large abdominal incisions and minimizing tissue manipulation, laparoscopy reduces the risk of wound complications, surgical site infections, and incisional hernias. Furthermore, the laparoscopic approach results in less intraoperative blood loss and lower rates of postoperative ileus, contributing to a smoother postoperative course and faster recovery.

Evidence supporting single-port surgery for ileocecal resection in CD continues to accumulate, demonstrating its feasibility, safety, and potential advantages over traditional multi-port laparoscopy.^{14,15} Recent studies have shown that single-port laparoscopic surgery offers comparable surgical outcomes to multiport laparoscopy while providing additional benefits such as reduced postoperative pain, shorter hospital stays, and improved cosmetic results. Patients undergoing single-port resections require lower doses of analgesics compared to those undergoing multi-port laparoscopy, highlighting the potential for enhanced postoperative recovery with the use of single-port surgery. Furthermore, single-port surgery offers the advantage of a single, less conspicuous incision, resulting in improved cosmesis and patient satisfaction, which may be particularly relevant for younger patients or those with aesthetic concerns.

Robotic-assisted surgery has emerged as a promising option for ileocecal resections in CD, offering several potential advantages over traditional laparoscopic approaches. Studies investigating the use of robotic surgery, in CD have demonstrated its feasibility, safety and efficacy in achieving surgical

goals.¹⁵ Robotic platforms provide surgeons with enhanced dexterity, precision, and three-dimensional visualization, allowing for meticulous dissection and suturing in confined anatomical spaces. This can be particularly advantageous in complex cases of CD with dense adhesions, fistulas, or involvement of adjacent structures, where precise tissue manipulation is critical to minimize intraoperative complications and achieve optimal outcomes. Recent evidence suggests that robotic ileocecal resection in CD may lead to improved short-term outcomes compared to conventional laparoscopic techniques.¹⁶ Studies have reported shorter operative times, reduced blood loss, and lower rates of conversion to open surgery with robotic-assisted approaches. Furthermore, robotic surgery offers the potential for faster postoperative recovery, shorter hospital stays, and decreased postoperative pain compared to traditional laparoscopy. These findings highlight the potential benefits of robotic-assisted surgery in optimizing perioperative outcomes and enhancing patient recovery following ileocecal resection for CD.

Personal Commentary on the Role of Upfront Surgery in Ileal Crohn's Disease

Burrill Crohn's seminal paper from 1932 included an initial case series of 14 patients, all of whom underwent ileocecal resections as part of disease treatment.¹⁷ Currently, more than 90 years after this initial description, available data suggest that in localized terminal ileal CD, surgical resection still plays a significant role in multidisciplinary management.

Clearly, surgery performed in tertiary centres by experienced surgeons, with a minimally invasive approach, is safe and associated with reduced rates of postoperative complications. Therefore, it is important to at least discuss the surgical option with patients at the same level of advanced medical therapies, to highlight the potential advantages and disadvantages of each strategy. Still, the safety of medical therapies remains important in decision-making. Additionally, in modern everyday life where young individuals prefer to spend time working or enjoying themselves instead of going to infusion clinics, the practicality of surgery to potentially avoid medical therapy for some time may represent a preferred option for some patients. It is also extremely important to emphasize that despite the reduced risk of an anastomotic leak (approximately 3.5%), if that complication occurs a temporary ileostomy may be needed and patients' quality of life can be affected. Another point to be discussed in shared decision-making is that upfront surgery does not avoid the need for continuous tight monitoring with biomarkers, imaging, and endoscopic tests targeting early detection of recurrence, where medical therapy will be essential.

Therefore, in a discussion of the ideal multidisciplinary therapeutic strategy for luminal ileal CD, upfront surgery plays a solid role as a safe

and durable option, if performed by experienced inflammatory bowel disease (IBD) surgeons. The current challenge in clinical practice is that there are no validated biomarkers that can predict response to medical therapy. If one could precisely predict which patients have less likelihood of response to optimized medical therapy and direct them straight to upfront surgery, this could represent a more trustworthy algorithm to avoid medical undertreatment and surgical overtreatment. While a biomarker-driven strategy is still not available, individualized multidisciplinary discussions with clinicians including gastroenterologists, IBD surgeons, and patients with their families comprise the best approach to the treatment of luminal ileal CD at this point.

Correspondence:

Paulo Gustavo Kotze, MD
Email: pgkotze@hotmail.com

Financial Disclosures:

Consultancy/Speaking honorarium: Abbvie, Celltrion, Janssen, Pfizer and Takeda; **Scientific Grants:** Pfizer, Takeda

References:

1. Roda G, Chien Ng S, et al. Crohn's disease. *Nat Rev Dis Prim.* 2020 Dec 1;6(1).
2. Yamamoto T, Lightner AL, Spinelli A, et al. Perioperative management of ileocecal Crohn's disease in the current era. *Expert Rev Gastroenterol Hepatol.* 2020 Sep 1 [cited 2024 May 27];14(9):843-55.
3. Avellaneda N, Kotze PG. Author's reply: "Early surgery for Crohn's disease—An appeal for a reassessment of biologics." *Dig Liver Dis.* 2023 Dec 1;55(12):1777-8.
4. Agrawal M, Ebert AC, Poulsen G, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared with anti-tumor necrosis factor therapy: a population-based cohort study.. *Gastroenterol.* 2023 Oct 1;165(4):976-985.e3.
5. Ponsioen CY, de Groof EJ, Eshuis EJ, A, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol.* 2017 Nov 1;2(11):785-92.
6. Stevens TW, Haasnoot ML, D'Haens GR, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIRIC trial. *Lancet Gastroenterol Hepatol.* 2020 Oct 1;5(10):900-7.
7. Vieujean S, Kotze PG, Netter P, et al. Stemming the tide with ileocecal Crohn's disease: when is pharmacotherapy enough? *Expert Opin Pharmacother.* 2023;24(14):1595-607.
8. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet.* 2017 Dec 23;390(10114):2779-89.
9. Kotze PG, Magro DO, Martinez CAR, et al. Long Time from Diagnosis to Surgery May Increase Postoperative Complication Rates in Elective CD Intestinal Resections: An Observational Study. *Gastroenterol Res Pract.* 2018 Apr 23;2018:4703281.
10. Avellaneda N, Coy CSR, Fillmann HS, et al. Earlier surgery is associated to reduced postoperative morbidity in ileocaecal Crohn's disease: Results from SURGICROHN - LATAM study. *Dig Liver Dis.* 2023 May 1;55(5):589-94.
11. Maruyama BY, Ma C, Panaccione R, Kotze PG. Early Laparoscopic

ileal resection for localized ileocecal Crohn's disease: hard sell or a revolutionary new norm? *Inflamm Intest Dis.* 2021 Jan 19;7(1):13-20.

12. Avellaneda N, Maroli A, Tottrup A, et al. Short and long-term outcomes of surgery for inflammatory (uncomplicated) ileocecal Crohn's disease: Multicentric retrospective analysis of 211 patients. *Dig Liver Dis.* 2024 May 1;56(5):730-6.
13. Maggiori L, Panis Y. Laparoscopy in Crohn's disease. *Best Pract Res Clin Gastroenterol.* 2014;28(1):183-94.
14. Bhattacharya P, Hussain MI, Zaman S, et al. Single-incision versus multi-port laparoscopic ileocolic resections for Crohn's disease: Systematic review and meta-analysis. *J Minim Access Surg.* 2023 Oct 1 [;19(4):518-28.
15. Gardenbroek TJ, Verlaan T, Tanis PJ, et al. Single-port versus multiport laparoscopic ileocecal resection for Crohn's disease. *J Crohns Colitis.* 2013 Nov 1;7(10)e443-8.
16. Zaman S, Mohamedahmed AYY, Abdelrahman W, et al. Minimally invasive surgery for Inflammatory Bowel Disease: a systematic review and meta-analysis of robotic versus laparoscopic surgical techniques. *J Crohns Colitis.* 2024 Mar 11; epub ahead of print.
17. Crohn BB, Ginzburg L, Oppenheimer GD. Landmark article Oct 15, 1984. Regional ileitis. A pathological and clinical entity. *JAMA.* 1984 Jan 6;251(1):73-9.