

Title:

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First-Line Surgery in Crohn's Disease: Who Benefits and When?

Proposal for First-Line Surgery in Crohn's Disease

| Criterion | Details |
|---|--|
| Age | ≥ 16 years |
| Surgical risk | Low surgical risk |
| Location and extent | Ileal or ileocecal location with short extension |
| Disease phenotype | Inflammatory or non-complicated stricturing phenotype |
| Surgical history | No previous intestinal surgeries |
| Patient preference | Wishes to avoid long-term medical therapy or its side effects |
| Contraindication to anti-TNF | Present |
| Absolute or relative contraindications to immunosuppression | History of active or recent malignancy, uncontrolled HIV infection, or primary immunodeficiency disorders. |
| Reluctance to adverse effects of medical therapy | Patient reluctant to immunosuppressive or biologic therapy |
| Multidisciplinary assessment | Approved by treating multidisciplinary team |
| Exclusion factors | Active smoker, fistulizing or penetrating phenotype, extensive disease, prior surgery |

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First-line surgery in Crohn's disease: who benefits and when?

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Abstract

Crohn's disease (CD) patients often require surgery due to complications such as strictures or fistulas. While historically reserved as a last resort, emerging data suggest that early ileocecal resection (EICR) may provide long-term benefits in selected patients, including reduced need for biologics and lower relapse rates. Identifying which patients

are ideal candidates for first-line surgery remains a clinical challenge, but recent studies point toward improved outcomes when surgery is performed in early, localized disease.

Key words: Crohn's disease. Surgery. Primary ileocecal resection.

Introduction

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), can affect any segment of the gastrointestinal tract, although the ileocecal region (L3 disease) is the most involved site (1). Approximately one-third of patients present with disease limited to the ileocecal area. The clinical course of CD is highly variable, frequently progressing to stenosing and penetrating complications, which increases the need for surgical interventions and significantly impacts patients' quality of life (QoL) (1). Surgical resection is often inevitable during the disease course. While earlier studies reported that 20–40% of patients required surgery within the first year after diagnosis and 30–70% within ten years (2), more recent population-based data indicate a decreasing trend in surgical rates over time, likely reflecting the impact of modern therapeutic strategies (3). However, surgery remains common and necessary in many cases, particularly for stricturing or penetrating complications, as highlighted in the Spanish Epidemiology cohort (4).

Although surgery has traditionally been considered a last resort in CD management, it is not inherently negative. Emerging evidence from studies such as LIRIC (Laparoscopic Ileocecal Resection vs Infliximab for Terminal Ileitis in Crohn's Disease) (5) and Agrawal et al. (6) suggests that early ileocecal resection (EICR) in appropriately selected patients with localized distal ileal (L1) or ileocecal (L3) disease (Figure 1) may lead to improved long-term outcomes, reduce the risk of disease-related complications, and decrease the cumulative burden of medical therapy (5,6).

However, implementing early surgical intervention in clinical practice remains a challenge. Patient reluctance to undergo surgery during the early stages of Crohn's disease is common, often due to concerns about invasiveness and long-term outcomes. Furthermore, there is still no clear consensus or reliable predictive markers to accurately identify which patients are most likely to benefit from early surgical treatment.

Methodology

This narrative review aims to synthesize the existing evidence on the role of early ileocecal resection (EICR) as first-line treatment for localized ileocecal Crohn's disease. A non-systematic search was conducted in PubMed, Scopus, and Google Scholar databases until May 2025. Search terms included "Crohn's disease," "early ileocecal resection," "EICR," "anti-TNF," "biologic therapy," and "initial medical therapy (IMT)." Original studies that directly compared early surgical strategy with initial medical treatment in ileal or ileocecal Crohn's disease were prioritized, including clinical trials, observational studies, meta-analyses, and systematic reviews. Articles were selected by consensus by the authors, considering their clinical relevance, potential impact on medical practice, and overall methodological quality. In addition, key studies evaluating economic aspects, quality of life, postoperative complications, and predictors of recurrence were included.

I. Therapeutic Strategies

I.a. Initial medical therapy (IMT)

Early and effective treatment of CD is essential to prevent disease progression and enhance long-term outcomes. Advances in IMT (IMT), particularly the use of immunosuppressants and biologics have fostered a conservative approach in managing CD. Anti-tumor necrosis factor (anti-TNF) therapy is central to treat moderate to severe

CD (7,8). SONIC trial demonstrated that early use of infliximab, particularly in combination with azathioprine, was more effective than either agent alone in inducing and maintaining remission in patients with moderate to severe CD (9). Currently, a "top-down" strategy utilizing biological therapy as the first line is preferred, yielding better remission rates and reducing steroid use (10).

However, although population-based data suggest that timely initiation of medical treatment may reduce surgical intervention rates, prolonged IMT may simply delay an inevitable surgery (2). Bouguen and Peyrin-Biroulet emphasized that biologics may reduce the rate but do not eliminate the need for surgery entirely (11). More recently, a large population-based study has shown that while the annual rate of bowel resections in CD has decreased in the biologics era, the proportion of surgeries performed for obstructive indications has increased significantly. This suggests that although IMT may delay surgery, its ability to prevent surgery, particularly for stricturing disease, remains limited (12).

I.b. Evidence Supporting Early Bowel Resection (EICR)

Traditionally, surgical treatment is advised for complicated CD cases (e.g., strictures, fistulas) or patients who are refractory to IMT. Nonetheless, interest in EICR has increased (13). Recent evidence suggests that early surgical intervention in Crohn's disease is safe, with low morbidity and mortality, particularly when minimally invasive techniques are employed. These advances, combined with perioperative protocols, have led to faster recovery and fewer complications. Furthermore, surgery performed at early stages reduces the risk of extensive resections and complications (14).

In the LIR!C randomized trial, laparoscopic ileocecal resection achieved quality-of-life improvements comparable to infliximab after one year in patients with limited and non-stricturing ileocecal Crohn's disease (5). In addition, a retrospective long-term follow-up (median 5 years) of LIR!C participants revealed that most patients in the surgical arm did

not require additional medical or surgical therapy, while 48% of those in the infliximab arm eventually underwent surgery and the rest continued on biologic treatment (15). The LIR!C trial has been criticized for limited generalizability due to methodological flaws, including lack of blinding, short follow-up, narrow patient selection, and minimal assessment of inflammatory control (16).

A meta-analysis by Ryan ÉJ et al., encompassing seven studies with 1,863 patients with ileocolonic CD, suggested that EICR might be associated with fewer relapses and a decreased need for biological therapy compared to IMT (17). Similarly, a meta-analysis by Husnood N. et al., involving eight studies with 1,867 patients with ileocolonic CD, demonstrated a reduced need for pharmacological treatment in the EICR group. Five-year intestinal resection rates were 7.8% in the EICR group versus 25.4% in the IMT group (OR = 0.32; 95% CI: 0.19–0.54; $p < 0.0001$). These results were consistent in subgroup analyses of patients with distal ileal or ileocecal CD (18). Limitations of these systematic reviews include the heterogeneity of the included studies and the predominance of observational studies, where EICR was sometimes conditioned by complicated disease phenotypes (stenosing-penetrating) and some studies included other disease locations (see Table 1).

Both American and European guidelines support considering early EICR as an alternative to IMT for localized CD, particularly in the terminal ileum-ileocecal area (19,20). The precise mechanism by which EICR promotes sustained remission is not yet fully understood, but it is hypothesized that resection of chronically inflamed bowel and associated mesenteric fat may alter disease trajectory, mitigating long-term intestinal damage (21). In this sense, EICR may function as an effective "top-down" therapeutic approach by eliminating the source of inflammation early in the disease course.

On the other hand, the impact of surgery on quality of life and psychosocial well-being, particularly among younger patients, must be carefully considered, including potential effects on body image, sexuality, and professional activity. These aspects should be discussed during shared decision-making.

I.c. Surgical Technique

Laparoscopic ileocecal resection is the preferred surgical approach in early Crohn's disease due to its association with reduced postoperative morbidity and faster recovery. Minimally invasive techniques, especially laparoscopy, have demonstrated benefits in terms of shorter hospital stays, lower complication rates, and improved cosmetic outcomes compared to open surgery (22). Following ileocecal resection for Crohn's disease, standard techniques include side-to-side, end-to-end, end-to-side, and Kono-S anastomosis. The SuPREMe-CD trial demonstrated medium- and long-term benefits of the Kono-S anastomosis compared with conventional side-to-side anastomosis (23). However, recent evidence has not shown significant differences between the two techniques (24, 25). Therefore, further studies are needed to consider switching from conventional side-to-side anastomosis (Figure 1).

II. Early Bowel Resection May Lower Health Care Costs?

Beyond clinical outcomes, economic analyses support the potential of EICR to lower overall healthcare expenditures. This is particularly relevant in systems where prolonged use of high-cost biologics poses sustainability challenges. However, comparative studies on the cost-effectiveness of EICR versus IMT in the context of biosimilars remain limited.

It is widely recognized that CD, as a chronic lifelong condition, incurs substantial healthcare costs, predominantly driven using biological therapies (26). There is evidence suggesting that early surgery may reduce long-term healthcare costs. A health economics analysis from the LIR!C trial demonstrated that patients undergoing early ileocecal resection had lower direct healthcare costs and gained more quality-adjusted life years (QALYs) compared to those receiving infliximab (27). Additionally, other

studies have corroborated that most postoperative costs are medication-related, suggesting that early surgical resection could be a more cost-effective strategy in well-selected patients (26). Nonetheless, additional research is needed to evaluate the cost-effectiveness of biosimilars to reach a definitive conclusion.

III. Long-Term Impact of EICR

Despite the evidence, the long-term impact of early resection for localized CD remains largely unexplored in real-world settings. In the study by Agrawal et al., utilizing a population-based cohort (1,279 patients), compared long-term outcomes of EICR (uncomplicated disease) versus anti-TNF therapy. The authors reported a 33% lower risk of a composite outcome (hospitalization, repeat CD-related surgery, corticosteroid exposure, and perianal CD) in the ileocecal resection group compared to primary anti-TNF therapy. Approximately half of the patients who underwent ileocecal resection did not require treatment five years post-surgery (6). Understanding the biological and clinical characteristics of these patients who remained treatment-free long-term is essential, as this could help identify those most likely to benefit from early surgical intervention and guide personalized therapeutic strategies.

In a multicenter retrospective study by Avellaneda et al. (LATAM study), postoperative outcomes following EICR were compared between patients with luminal CD (early strategy) and complicated CD (strictures-fistulas). The decision to perform EICR was based on a multidisciplinary evaluation, considering factors such as insufficient response to conventional medical treatment and patient preferences. Importantly, many of these patients had received prior medical therapies and the exact interval from diagnosis to surgery was not specified in this study. However, a longer disease duration before surgery was observed to be associated with worse postoperative outcomes (28). Recent evidence also highlights that surgical delay may increase early postoperative complication rates. A retrospective cohort study by Gómez Díez et al., showed that

prolonged disease duration prior to surgery was associated with higher recurrence and complication rates, reinforcing the value of timely intervention (29).

IV. Defining the Optimal Timing for Primary Surgery

Determining the optimal timing for primary surgery in patients with luminal ileocecal CD (inflammatory phenotype) remains challenging, as no universally accepted definition exists. Historically, surgery was considered “early” if performed within the first year of diagnosis. However, disease progression from luminal inflammation to stricturing or penetrating lesions does not occur uniformly among patients. Some may develop early complications requiring immediate surgical intervention, but not necessarily EICR (30).

Despite growing evidence supporting EICR as an alternative to medical treatment for distal ileal or ileocecal CD, its implementation in routine clinical practice remains a challenge. To address this discrepancy, Husnood et al. will conduct a multicenter study exploring the views of both patients and physicians on the use of bowel resection instead of conventional medical treatment. The results of this study could contribute to clarifying the gap between evidence and clinical practice, providing useful information for the design of future clinical trials (37). Table 2 presents a comparison between EICR and IMT.

Conclusion

In summary, increasing evidence supports EICR as a viable first-line alternative to biologics in patients with localized luminal Crohn’s disease. This strategy may provide long-term remission, reduce therapy burden, and possibly lower costs. In Table 3 we describe our proposal on which patients are eligible for first-line surgery in CD. The approach should be considered within a multidisciplinary framework, favoring young patients with inflammatory phenotype and no prior surgeries or contraindications. Future studies should aim to refine patient selection criteria and evaluate real-world

outcomes in diverse healthcare settings.

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Figure 1. Ileocecal resection in Crohn's disease

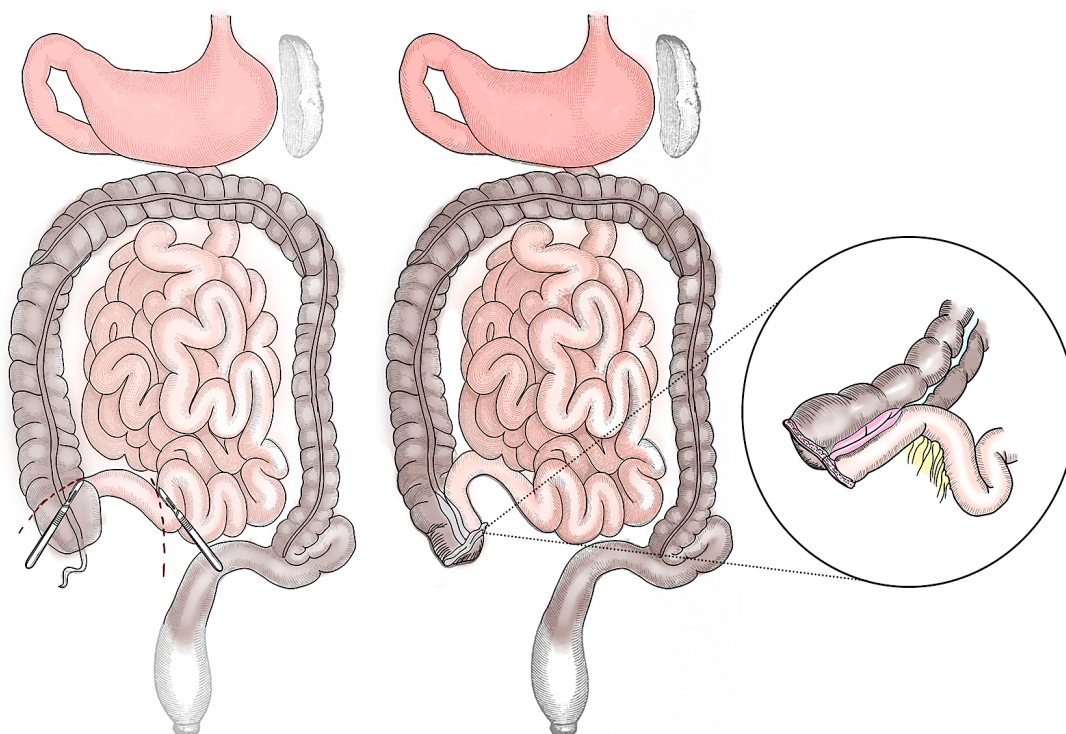


Table 1. Overview of comparative studies in ileocecal Crohn's disease

| Author (Year) | Study Type / Follow-up | Sample & Inclusion Criteria | EICR | Comparator | Key Outcomes | Outcomes data |
|----------------------|--------------------------------|-----------------------------|-------|---------------------|---|------------------------------------|
| Aratari (2007) (31) | Retrospective; median 147 mo | EICR patients | n=83 | Delayed ICR (n=124) | Recurrence, further surgery, immunosuppressants | Surgery-free survival: p=0.006 |
| Latella (2009) (32) | Retrospective; 1980–2005 | New CD dx; acute abdomen | n=115 | IMT (n=375) | Need for first resection, med therapy | Surgery rate: 29% vs. 53%, p<0.001 |
| Goloivcs (2013) (33) | Retrospective; median 11.4 yrs | New CD diagnosis | n=63 | IMT <1 yr (n=428) | Disease course, med exposure, repeat surgery | IMT exposure: 19% vs. 92%, p<0.001 |

| | | | | | | |
|------------------------|--------------------------------------|----------------------------------|-------|-----------------------------------|--|---|
| An (2016) (34) | Retrospective; median 67–97 mo | Ileal/ileocecal CD | n=62 | IMT / Delayed ICR (n=116) | Surgery recurrence, hospitalization, meds | Re- surgery: 6.4% vs. 24.1%, p=0.004 |
| Gerdin (2016) (35) | RCT; 1, 3, 5 yrs | CD <1 yr, med-naïve | n=18 | Infliximab + AZA (n=18) | CDAI, QoL (SF-36, VAS) | No significant QoL difference (p>0.05) |
| Ponsioen (2017) (5) | RCT; 12 mo | Active ileal CD, IMT ≥3 mo | n=73 | Infliximab (n=70) | QoL, surgery, cost/QALY | QoL SF-36 delta: 14 vs. 15 (NS); Cost/QALY: €13,160 vs. €17,579 |
| Stevens (2020) (15) | Retrospective; median 63.5 mo | Active ileal CD, IMT ≥3 mo | n=69 | Infliximab (n=74) | Re-surgery, biologic use, QoL | Re- surgery: 6% vs. 48%, p<0.01 |
| Kelm (2021) (36) | Retrospective; 2 yrs | EICR patients | n=29 | Delayed ICR post-IMT (n=29) | IMT use, time to re- surgery | Need for IMT: 27% vs. 72%, p=0.003 |
| Agrawal (2023) | Retrospective; | Ileal/ileocecal | n=581 | Anti-TNF | Composite (hospital, | Event-free |

| | | | | | | |
|-----|-------|----|--|---------|--------------------|--|
| (6) | 5 yrs | CD | | (n=698) | steroids, surgery) | survival: 62% vs. 54%, HR 0.75, p<0.01 |
|-----|-------|----|--|---------|--------------------|--|

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|-----------------------|-------------------------|-----------------------|--|---------------------|--|--|
| Agrawal (2023) (6) | Retrospective; 5 yrs | Ileal/ileocecal CD | | Anti-TNF (n=698) | Composite (hospital, steroids, surgery) | |
|-----------------------|-------------------------|-----------------------|--|---------------------|--|--|

Abbreviations: CD, Crohn's disease; EICR, Early Ileocecal Resection; ICR: Ileocecal Resection; IMT, Initial Medical Therapy; QALY, quality-adjusted life year; SF-36, SF, 36-item short form survey; CDAI, Crohn's Disease Activity Index; QoL, quality of life; RCT, randomized clinical trial, mo: months.

Table 2. Comparison of Early Ileocecal Resection vs. Initial Medical Therapy in Crohn's Disease

| Topic | EICR (Early Ileocecal Resection) | IMT (Initial Medical Therapy) |
|----------------------------|---|---|
| Clinical Remission | Higher rates in selected patients | Effective in many cases but may require optimization or switching |
| Risk of Complications | Lower risk if performed early; minimally invasive techniques reduce morbidity | Risk of infections, immunogenicity, and adverse events (e.g., lymphoma, TB) |
| Need for Ongoing Treatment | Often no further immunosuppressive therapy required post-surgery | Long-term maintenance often required, especially with biologics |
| Recurrence | Recurrence at anastomosis possible but often manageable | Risk of primary non-response or secondary loss of response |
| Quality of Life (QoL) | Comparable or improved (e.g. LIR!C trial) | Comparable if clinical remission achieved |
| Cost-Effectiveness | May be more cost-effective over time (saves on prolonged biologic use) | High cumulative cost of biologic therapy and monitoring. |
| Patient Acceptability | Often low due to surgery reluctance | Preferred by many patients |

| Criterion | Details |
|---|--|
| Age | ≥ 16 years |
| Surgical risk | Low surgical risk |
| Location and extent | Ileal or ileocecal location with short extension |
| Disease phenotype | Inflammatory or non-complicated stricturing phenotype |
| Surgical history | No previous intestinal surgeries |
| Patient preference | Wishes to avoid long-term medical therapy or its side effects |
| Contraindication to anti-TNF | Present |
| Absolute or relative contraindications to immunosuppression | History of active or recent malignancy, uncontrolled HIV infection, or primary immunodeficiency disorders. |
| Reluctance to adverse effects of medical therapy | Patient reluctant to immunosuppressive or biologic therapy |
| Multidisciplinary assessment | Approved by treating multidisciplinary team |
| Exclusion factors | Active smoker, fistulizing or penetrating phenotype, extensive disease, prior surgery |

Table 3. Proposal for First-Line Surgery in Crohn's Disease

Accepted Article