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REVIEW ARTICLE

# Advances in the surgical treatment of Crohn's disease

*Antonio Luberto[1,2], Annalisa Maroli[2], Michele Carvello[2], and Antonino Spinelli[1,2]**

*[1]Department of Biomedical Sciences, Humanitas University; [2]Division of Colon and Rectal Surgery, IRCCS Humanitas Research. Milan, Italy.*

## Abstract

*Despite the advances in medical treatment of Crohn's disease (CD), most of the patients require one or more surgical bowel resections during their life for complicated disease. Surgery for CD has gone through progressive technical refinement over time. Minimally invasive surgery and bowel-sparing techniques have been validated with regard to surgical trauma reduction, and their role has been clearly defined in the current guidelines. Nevertheless, continuous technology advancement has further expanded the surgical tools with single-access and robotic-assisted surgery. With the aim of further reducing the impact of surgery, the concept of "strategic surgery" has been explored. On the one hand, patients' optimization before surgery has the potential to reduce post-operative complications. On the other, early intervention for the uncomplicated disease before medical therapy escalation has been demonstrated equally reliable with respect to biologics in terms of quality of life and advantageous in terms of health-care costs. Ultimately, a better comprehension of the pathological mechanisms underlying the disease is the key to radically changing the surgical management of both abdominal and perianal CDs. In fact, novel surgical strategies aiming at reducing disease recurrence which take into account the anastomotic configuration and the role of the mesentery as an active player in the disease process have been pursued in the past decade. The purpose of this review is to describe the recent innovations in the surgical treatment of CD focusing on their potential impact on the short- and long-term outcomes.*

***Keywords:*** *Crohn's disease. Perianal Crohn's disease. Colorectal surgery.*

## Introduction

Crohn's disease (CD) is a chronic inflammatory disease with a prevalence of 300 per 100,000 persons[1] in the Western countries, characterized by skipping intestinal lesions interspersed with the normal mucosa, which may affect all the gastro-intestinal tract and, in particular, the terminal ileum, with possible formation of strictures, fistulae, and abscesses[2].

In the past years, the increasing use of biological and immunomodulating treatments has changed medical management of CD, significantly decreasing and delaying the need for surgery[3]. However, up to 80% of CD patients still require surgical intervention at least once in their life. Surgery is indicated to treat CD complications (stricture, fistulas, and abscess), but is not curative. In fact, post-operative CD recurrence is common and usually occurs at the anastomotic site, often leading to further surgical treatment[4].

Perianal fistulizing CD (PFCD) is a common manifestation of CD and it is associated with severe and disabling symptoms that significantly reduce patients' quality of life. Medical therapy combined with surgical management is the current approach to PFCD and provides an adequate healing rate[5].

In the past decades, several efforts have been made to improve the surgical approach to CD, minimally invasive surgery and bowel-sparing techniques have been validated concerning surgical trauma reduction, and their role has been clearly defined in the current guidelines.

***Correspondence:**
Antonino Spinelli
E-mail: antonino.spinelli@humanitas.it

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To further reduce the impact of surgery, the concept of "strategic surgery" has been explored. On the one hand, patients' optimization before surgery has the potential to reduce postoperative complications. On the other, early intervention for uncomplicated disease before medical therapy escalation has been demonstrated equally reliable with respect to biologics in terms of quality of life and advantageous in terms of health-care costs. Ultimately, a better comprehension of the pathological mechanisms underlying the disease is the key to radically changing the surgical management of both abdominal and perianal CDs. In fact, novel surgical strategies aiming at reducing disease recurrence which take into account the role of the mesentery as an active player in the disease process have been pursued in the past decade.

The purpose of this review is to describe the recent innovations in the surgical treatment of CD for ileocolic and perianal disease focusing on their potential impact on the short- and long-term outcomes.

## Upper gastrointestinal (UGI) CD

CD of the UGI tract is referred to esophagus, stomach, duodenum, and jejunum involvement. Typically, the lesions are aphthae, erosions/ulcers, fistulas, and strictures that could be diagnosed during endoscopic evaluation. Lesions' rate of UGI tract has been reported with great range variation (6.5-75%). However, only a small number of patients with endoscopically detected UGI-CD have symptoms[6]. Esophageal CD has an incidence of 6.5% in pediatric patients, while it is less common in adults (approximately 1%). Mild and distal part of the esophagus are the sites where lesions most frequently occur. Endoscopic dilatation is an effective treatment with a high rate of short-term outcomes and low rate of complications in case of gastroduodenal strictures, this procedure allows a redilatation for relapse[7]. Gastroduodenal CD is a rare site of disease with a total rate of 1-4% of patients[8]. Surgery should be performed in case of dysplasia or cancer or complicated disease (symptomatic fistulas or stenosis). However, surgical techniques are not well established due to the lack of data in the literature. ECCO guidelines[9] consider effective options: partial gastric resection, strictureplasty, and Roux-en-Y bypass in case of gastric antrum or duodenal bulb involvement, avoiding routine vagotomy. The second and third part of duodenum could be treated with strictureplasty, while more demolitive interventions are only indicated as a last resort[9].

## Ileal and ileocolic CD

Nearly 80% of ileocolic CD patients require a surgical resection within 10 years from the diagnosis[6]. In the past decades, several efforts have been made to improve the surgical management of ileocolic CD patients, with the main purpose of reducing the impact of surgical trauma, the rate of post-operative complications, ameliorating post-operative outcomes, and shortening the length of hospital stay.

## Predominantly inflammatory or predominantly fibrotic strictures: surgical strategies

Inflammatory strictures could be treated with medical therapy or surgery. Usually, surgical management is reserved for patients who do not respond to drug therapy.

The LIR!C trial proved laparoscopic ileocecal resection in patients with non-structuring ileocecal CD as a cost-effective treatment with similar results in quality of life when compared with infliximab therapy[10]. The long-term follow-up of LIR!C trial showed a high rate (74%) of patients who did not need additional biological treatment in the resection group, while half of the patients in the infliximab group had an ileocecal resection after a median follow-up time of 5 years[11]. Time of surgery could modify the post-operative course in CD. Early surgery in ileocecal CD reduces the risk of clinical recurrence and the rate of patients who need anti-TNF therapy when compared with patients that receive a late surgery, nevertheless, the likelihood of reoperation is not related to the time of surgery[12].

In predominantly fibrotic CD strictures, the likelihood of a good response to medical treatment is poor. Therefore, surgical resection or strictureplasty is required in these cases. The need for reducing postoperative complications and improving functional outcomes led to reconsider the use of extended bowel resections in CD. Indeed, extensive resection in CD is considered unnecessary because the recurrence rate is similar in patients treated with a wide resection compared with those underwent limited intestinal resection[13]. Therefore, ileocecal resection is usually preferred for limited small bowel disease, strictureplasty is recommended in case of multiple strictures, previous significant small bowel resection (> 100 cm), small bowel syndrome, or recurrent ileocolic anastomotic strictures[14]. Conventional

strictureplasty – Heineke-Mikulicz and Finney – may not be feasible in patients with multiple strictures in a short length of bowel or with a structure longer than 30 cm. Concern about Finney strictureplasty is related to the creation of a large non-functional diverticulum, resulting in bacterial overgrowth. While intestinal absorptive function is preserved in Heineke-Mikulicz strictureplasty, indeed patients rarely developed metabolic dysfunctions after this procedure[15]. In case of long strictures (more than 20 cm), the Michelassi strictureplasty – consisting in dividing the bowel in the middle part of the stricture and restoring the intestinal continuity with a side-to-side isoperistaltic strictureplasty, can be applied[16]. Long-term results showed that Michelassi strictureplasty is a safe, effective, and durable intestinal sparing procedure with a high range of patients which not developed recurrences after surgery[17]. A modified side-to-side isoperistaltic strictureplasty over the ileocecal valve was introduced in case of bowel length disease more than 20 cm which includes the ileocecal valve[18]. This technique is an alternative procedure to the ileocecal resection in extensive terminal ileitis in CD and it avoids the incorporation of healthy bowel length in the long strictureplasty. However, it is contraindicated in case of any septic complications, extensive fibrotic bowel wall, or mesenteric thickness. The authors reported post-operative ileus as a common complication related to this type of surgery, nevertheless, an endoscopic mucosal improvement was observed in 44.7% of patients at 6 months after surgery[19].

## Intra-abdominal fistulas and abscesses in CD

Intra-abdominal fistulas occurred in approximately 30% of CD patients and they are classified by indicating the bowel segment where they originate and followed by the non-diseased target organ (i.e., enteroenteric, enterocutaneus, enterosigmoid, and enterovescical)[20]. Usually, magnetic resonance imaging (MRI) is the most useful imaging method for the diagnosis of enteric fistulas and an evaluation with MRI and colonoscopy can direct the most appropriate treatment. Indeed, asymptomatic fistulas do not require surgical intervention, but it is important to monitor the effect of medication because the inflammation might result in a more complicated disease in the long run[9]. The data on the most appropriate surgical approach for enteric fistulas are scarce. However, in recent years, there has been a tendency to preserve non-disease target organs as much as possible from excessive surgical resections, which are reserved for the diseased organ. Active CD could be complicated by an intra-abdominal abscess. Abscesses should be treated initially with antibiotics and when larger than 3 cm with percutaneous drainage (PD). Indeed, ultrasonography or computed tomography PD placement is a relatively safe procedure with rare complications and it allows to delay surgery. In the time between PD placement and surgery, the patient should be optimized by starting parenteral nutrition and broad-spectrum antibiotic therapy and discontinuing biological therapy, delaying the surgical timing by a few weeks. Conversely, emergency surgery without optimization or sepsis control with PD and antibiotics significantly increases the risk of stoma and it is associated with higher rate of post-operative complications[21].

## Patient optimization

Nutritional deficiency is a common feature in patients with CD due to enteric fistulas, inflammation of the mucosa, and chronic diarrhea. A meta-analysis[22] has evaluated the impact of enteral and parenteral nutrition in a large cohort of patients with CD. Pre-operative enteral nutritional optimization reduced post-operative complications, especially decreased post-operative morbidity. Indeed, enteral feeding improves nutritional and immunological status with a lower risk of intra-abdominal infection or anastomotic leak after the surgery compared with undernourished patients[23]. A recent prospective study supported the aforementioned results with a 2-fold decrease rate of intra-abdominal septic complications and requirement for stoma in malnourished patients with a pre-operative enteral nutritional support compared with malnourished patients which underwent upfront ileocolonic resection for CD[24]. Latest ECCO guidelines[14] suggested enteral optimization before the surgery and considered parenteral nutrition when enteral nutrition is not tolerated, though the duration of pre-operative nutritional support is not standardized.

## Reducing the surgical impact by a minimally invasive approach

*Laparoscopic ileocolic resection* has been increasingly used as a result of encouraging clinical studies demonstrating its superiority with regard to the open approach[25,26]. In fact, laparoscopic surgery provides reduced hospitalization, lower rates of post-operative complications, reoperations, and readmissions, and lower rates of incisional hernia compared with the open approach. Despite increased device-related costs, the reduced

indirect burden makes the laparoscopic approach more cost effective compared with the open approach[26]. In fact, has been included in the current guidelines as a standard of care for primary ileocolic resection[14].

*Single-port (SP) laparoscopic surgery,* introduced as an evolution of the laparoscopic approach, implies one single incision to perform the entire procedure and extract the specimen. The first comparative analysis of SP laparoscopy reported similar post-operative complication rates and reduced post-operative opioid analgesic requirement compared with multiport laparoscopy (MP)[27]. However, a more recent investigation[28] showed reduced post-operative pain and opioid analgesic consumption in the SP group compared with the multiport approach. These results were also confirmed by the study of Celentano et al.[29], which retrospectively compared SP with MP laparoscopy and open surgery. In that study, the open approach showed a 2-fold increase in post-operative complications compared with minimally invasive procedures and SP patients had a significantly shorter hospital stay compared with laparoscopy and open surgery. Despite the concerns on the use of SP in complex cases, preliminary data demonstrated its feasibility also for stenosing or fistulizing CD[30].

*The robotic-assisted approach* provides a potential benefit in abdominal surgery, allowing for a three-dimensional visualization, wristed instruments, and a stable camera platform. Few studies assessed the efficacy of robotic ileocolic resection compared with standard laparoscopy in CD. Overall, the current evidence consistently reports comparable postoperative complications rate and functional outcomes between the two approaches[31,32]. However, the increased costs limited the spread of robotic-assisted ileocecal resection for CD.

The use of *intraoperative near-infrared light and indocyanine green (ICG) fluorescence angiography* is largely used in colorectal surgery to identify the anastomotic level avoiding hypoperfused bowel and potentially reducing the AL rate[33]. The role of this technology in CD is not well investigated. Freund et al.[34] assessed in a retrospective study the role of intraoperative ICG during complex redo ileocolic resection among 12 patients compared with 24 patients who underwent redo ileocolic resection without ICG fluorescence evaluation. The authors did not find significant differences between the two groups in terms of post-operative complications. In addition, ICG perfusion assessment did not change the anastomotic site. The small number of patients and retrospective nature are important limitations of this study. However, further studies are necessary to evaluate the role of ICG fluorescence in CD[34].

## Surgical strategies to reduce surgical recurrence

Although the traditional role of surgical innovation consists in improving the immediate postoperative outcomes, increasing preclinical evidence on the pathological mechanisms of CD triggered the development of innovative surgical techniques to prevent the post-operative recurrence of CD, shifting the main interest of surgeons from the early outcomes to the long-term outcomes of the disease.

Different anastomotic configurations after ileocecal resection in CD were described for restoration of intestinal continuity to reduce the rate of post-operative complications and recurrence. Muñoz-Juárez et al. compared wide-lumen stapled anastomosis (side to side) and end-to-end anastomosis after surgery for ileocolic resection in CD to investigate the post-operative outcomes[35]. The side-to-side group had fewer post-operative complications (6% vs. 13%) and a lower incidence of recurrent CD symptoms (24% vs. 57%) when compared with end-to-end anastomosis. A systematic review and meta-analysis of 11 trials and a total of 1,113 patients showed a reduction in terms of post-operative recurrence and reoperation when stapled side-to-side anastomosis was performed rather than handsewn end-to-end anastomosis[36]. Thus, stapled side-to-side anastomosis is considered an optimal anastomotic technique after intestinal resection for CD.

In 2011, Kono et al.[37] described an antimesenteric functional end-to-end handsewn anastomosis (Kono-S anastomosis) to reduce surgical recurrence at the anastomotic site. Kono-S anastomosis involves three principles: (a) mesentery preservation with mesenteric section close to the intestinal wall; (b) stapled resections of the pathological bowel site and consecutive suture of both the stumps to create a supporting column to prevent anastomotic distortion; and (c) longitudinal enterotomies on the antimesenteric site of the two stumps and a handsewn anastomosis (Fig. 1)[37]. A recent meta-analysis[38] - including nine studies and 676 patients – compared the Kono-S with conventional side-to-side anastomosis and found a significant decrease in the rate of 5-year surgical recurrence. The pooled analysis failed to demonstrate a reduced rate of endoscopic recurrence in the Kono-S group, although Kono-S patients displayed a lower mean Rutgeerts score

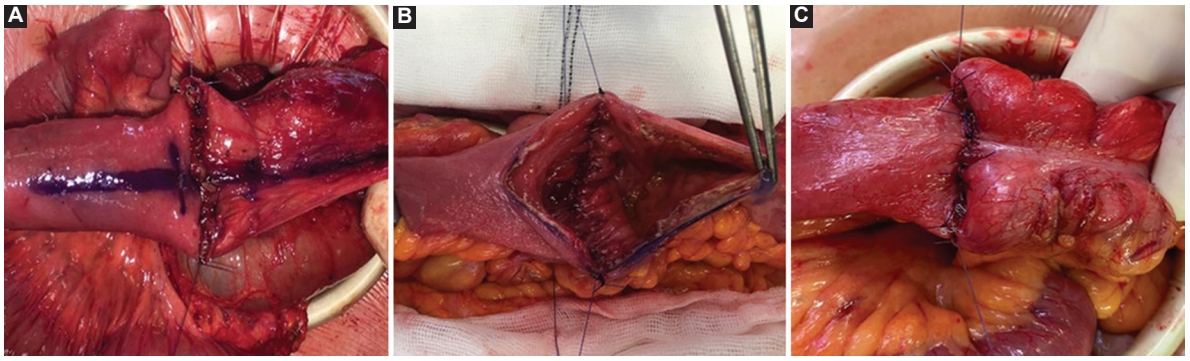


**Figure 1.** Kono-S anastomosis. **A:** stumps are sutured together to create the supporting column. **B:** longitudinal antimesenteric enterotomies 1 cm from the supporting column. **C:** handsewn anastomosis at the end of the procedure.

compared with the conventional anastomosis group. The rate of post-operative complications was comparable among the Kono-S and conventional anastomosis groups. Clinical recurrence was investigated only by the RCT from Luglio et al.[39], showing a significant reduction at 12 and 24 months. Kono-S anastomosis may reduce both clinical and endoscopic recurrence but further studies are needed to verify its feasibility and effectiveness: a multicenter randomized prospective trial promoted by the Weill Cornell Institute is currently ongoing and aims to compare Kono-S and standard side-to-side anastomosis (NCT03256240) (Table 1). In Kono-S technique, the mesentery – although manipulated – is preserved. However, recent studies pointed out the mesentery as a leading factor – rather than a mere target tissue – in the pathobiology of CD[40]. Mesenteric manifestations – including hypervascularization, fibrosis, thickness, and fat wrapping – correlate with CD activity and post-operative recurrence[40]. According to the classical model of CD pathogenesis, the mucosal damage is the primary event, which, in turn, provokes submucosal and mesenteric inflammation (outside-in model). In an alternative model, which emphasizes the role of the mesentery, the inflammatory process arises from the mesentery and the mesenteric nodes and the mucosal ulcerations are the terminal event (inside-out model)[41]. These observations led to hypothesize that a mesenteric resection close to the intestinal wall might provide reduced rates of clinical, endoscopic, and surgical recurrence compared with a partial excision[42]. The first study comparing mesentery resection versus mesentery sparing in ileocolic CD patients provided encouraging results with reduced rates of endoscopic and surgical recurrence – but the limited sample size prevented conclusive evidence[42]. These promising results were recently confirmed by a comparative analysis on CD patients undergoing colorectal resection: subjects receiving extensive mesenteric resection showed better surgical recurrence-free survival compared with those receiving limited mesenteric resection[43]. Due to technical difficulties and concerns regarding intraoperative bleeding[42], mesenteric excision is still underused but a growing number of randomized clinical trials has been initiated to further explore the safety, feasibility, and effectiveness of this technique, including one multicentric trial promoted by the University of Amsterdam (SPICY), one promoted by the Cleveland Clinic (SPARES), and one promoted by the Jinling Hospital in China (Table 2)[44]. In conclusion, despite recent progress in surgical procedures related to the role of the mesentery in CD, both mesentery excision and Kono-S anastomosis with mesentery manipulation and preservation have proved to be effective to reduce CD recurrence after bowel resection. The aforementioned findings question what is the best surgical approach in case of intestinal resection and bowel restoration, therefore, additional studies are necessary to better understand the pathogenesis of CD recurrence and to provide more effective surgical techniques in CD.

## Proctectomy in CD

Non-restorative proctectomy usually is performed in patients with severe CD proctitis refractory to medical treatments associated to perianal disease. Because of the benign nature of the disease, a complete lymph node harvest is not mandatory and a close rectal

**Table 1.** Summary of Kono-S ongoing studies

| Name of study | Type of study (country) | Primary aim | Study status (estimated completion date) | ClinicalTrials ID |
|---|---|---|---|---|
| "Study of the Kono-S Anastomosis Versus the Side-to-side Functional End Anastomosis" | RCT – Multicenter (Belgium, Finland, Germany, Italy, United States) | Post-operative recurrence of CD between Kono-S and side-to-side functional end anastomosis | Recruiting (December 2026) | NCT03256240 |
| "Surgical Prevention of Anastomotic Recurrence by Excluding Mesentery in Crohn's Disease (SuPREMeCD)" | RCT – Single center (Italy) | Post-operative outcomes between patients with Kono anastomosis and patients with stapled side-to-side anastomosis | Recruiting (November 2022) | NCT02631967 |

**Table 2.** Summary of extensive mesenteric excision versus limited mesenteric excision ongoing studies

| Name of study | Type of study (country) | Primary aim | Study status (estimated completion date) | ClinicalTrials ID |
|---|---|---|---|---|
| "The MESOCOLIC Trial: Mesenteric Excision Surgery or Conservative Limited Resection in Crohn's Disease"(38) | RCT – Multicenter (China, US, Ireland) | Rate of postoperative progression following extensive mesenteric excision (EME) and limited mesenteric excision (LME) in CD | Recruiting (January 2025) | NCT03769922 |
| "Mesenteric SParIng Versus Central mesenterectomY in Ileocolic Resection for Terminal Ileitis in Crohn's Disease (SPICY)" | RCT – Multicenter (Nederland) | Endoscopic recurrence following a mesenteric sparing VS a central mesenterectomy for CD | Recruiting (September 2022) | NCT04538638 |
| "MeSenteric SpAring Versus High Ligation Ileocolic Resection for the Prevention of REcurrent Crohn's DiseaSe (SPARES)" | RCT – Multicenter (Canada, Italy, United Kingdom, United States) | 6-month endoscopic recurrence between high ligation of ileocolic artery or mesenteric sparing for terminal ileal CD | Recruiting (December 2021) | NCT04578392 |

dissection – leaving mesorectum *in situ* – could be performed to reduce nerves lesions and to minimize post-operative pelvic empty space. However, a retrospective study has shown that proctectomy with total mesorectal excision in CD has significantly lower perineal complications and higher healing rates compared with close rectal dissection. These results are attributable to the pro-inflammatory role of the mesorectum in CD. Indeed, high presence of tumor necrosis factor α-producing CD14+ macrophages and less expression of wound-healing marker were funded in mesorectal tissue of CD patients[45]. Transanal approach might be feasible and has been demonstrated safe when performing proctectomy for CD[46]. Indeed, advantages of the transanal approach are mainly present in patients with a narrow pelvis. However, this approach for proctectomy in CD could be demanding due to the inflamed and bulky mesorectum causing difficult planes[46]. Restorative proctectomy and ileal pouch–anal anastomosis (IPAA) for refractory pancolonic CD could be considered in selected patients in the absence of small bowel and perianal disease, due to the high risk of pouch failure in CD patients[14]. Panis et al.[47] compared a cohort of CD-IPAA patients with a cohort of ulcerative colitis (UC)-IPAA patients. Short-term post-operative outcomes were similar between the two groups, but definitive ileostomy and pouch removal rates after 5-years were significantly higher in the CD group. The same results were shown in a large meta-analysis of 3103 patients[48]. CD-IPAA patients had a likelihood 6 times higher of pouch failures and poorer functional outcomes when they were

compared with UC-IPAA patients[48]. Several treatments for pouch failure have been proposed over the years (i.e., pouch strictureplasty and endoscopic balloon dilatation in case of strictures and infliximab treatment for active CD of the pouch)[49]. Although, rescue surgery is not indicated in this group of patients and defunctioning ileostomy or pouchectomy with definitive ileostomy is the only recommended surgery to reduce post-operative complications[9].

## Anorectal surgery for CD

PFCD manifests in up to 40% of CD patients[50]. Surgical management combined with anti-TNF treatment is the currently recommended approach for PFCD and allows for acceptable healing rates. The surgical approach to PFCD varies according to the anatomy and severity of the fistula: simple fistulas – either superficial, low, or with a single external opening – can be treated with a fistulotomy and – in selected cases – medical therapy may be avoided; complex fistulas – high, with single or multiple external openings, with or without rectovaginal involvement or proctitis – yield more challenging procedures. Complex fistulas often require multiple surgical interventions and have a lower rate of complete healing compared with simple fistulas. The first aim of the surgical intervention is to control the perianal sepsis. Once the acute infection is resolved, different surgical strategies may be applied to promote the healing, while preserving the sphincter function[5].

In recent years, new surgical strategies were developed to treat PFCD. However, a small subset of patients with refractory PFCD requires fecal diversion (FD) with a subsequent medical optimization. Singh et al. performed a meta-analysis among a total amount of 16 cohort studies including 556 patients to evaluate the effectiveness and long-term outcomes in patients treated with FD for PFCD[51]. More than half of the patients (63.8%) had an early clinical response after FD. Restoration of bowel continuity was attempted in 34.5% of patients and operation was precluded for the remaining patients due to the poor PFCD response or patient preference. Approximately 26% of patients who underwent bowel restoration required a rediversion for severe perianal disease relapse and 41.6% of patients required proctectomy due to the persistence of symptoms. Absence or improvement of rectal disease was the main factor associated with good outcomes after bowel restoration[51].

Indeed, active luminal disease and proctitis are related to low rate of PFCD healing and a higher proctectomy rate (29-77.6%)[52]. A global consensus of PFCD considered active luminal disease as an indication for aggressive medical treatment avoiding surgical procedures[52].

*Ligation of intersphincteric fistula tract (LIFT) procedure* was proposed to achieve fistula closure. In 2017, a retrospective evaluation assessed 23 patients with PFCD treated with LIFT[53]. Fistula healing was observed in 11 patients (48%) and the overall median time of LIFT failure was 8 months. LIFT may provide a low fistulae recurrence rate and with incontinence, but further studies are needed to demonstrate its effectiveness in PFCD.

*Fibrin glue* is a topical biological adhesive that mimics the physiological process of coagulation and takes advantage of the activation of thrombin to form a fibrin clot, thus inducing the mechanical sealing of the fistula tract. In a multicenter randomized trial comparing fibrin glue[54] with no treatment after seton removal, clinical remission was observed in almost 38% of patients treated with fibrin glue compared with 16% in the observation group. Despite its randomized design, this study had some relevant limitations: the small sample size and the use of an inactive comparator prevented a generalizable conclusion about the effectiveness of fibrin glue. Fibrin glue may be a simple, well-tolerated, and effective treatment for fistula in CD.

*Video-assisted anal fistula treatment (VAAFT)* is a sphincter-sparing approach, involving a diagnostic phase and an operative phase using a fistuloscope. The main advantage of the VAAFT procedure is the possibility of intraoperatively identify additional undetected fistula tracts, avoiding extensive perianal wounds[55]. However, VAAFT is a costly procedure, requiring a long learning curve to achieve proficiency.

In the past years, increasing evidence has focused on the feasibility and efficacy of *mesenchymal stem cells treatment (MSCs)* in perianal CD. MSCs can be obtained from cellular aspirate of human adipose or bone marrow tissue and differentiate in different types of cells, favoring the tissue regeneration and modulating the immune response[56]. ADMIRE-CD trial, a randomized double-blind placebo-controlled trial that assessed the effect of MSCs compared with placebo to treat PFCD, reported at 24 weeks a higher rate of complex PFCD healing in the MSCs group than in placebo (50% vs. 34%; $p = 0.024$)[57]. These results were confirmed in a second study after 52-week follow-up with a fistula healing in 56.3% in the MSCs group compared with 38.6% in the control group ($p = 0.01$)[58]. A second placebo-controlled trial to assess the efficacy and safety of darvadstrocel (Cx601) for the treatment of PFCD is underway (NCT03279081). The most recent meta-analysis[59] on the topic identified almost 24 randomized controlled trials and cohort studies comparing placebo (or fibrin glue injection) with

MSCs in both CD and cryptoglandular fistula, reporting a higher healing rate compared with conventional therapies. Interestingly, CX601 seemed more effective compared with homemade cultures, suggesting that a standardized systematic protocol for MSCs production plays a pivotal role in determining the therapeutic potential of MSCs[59]. In complex perianal fistula, MSCs treatment showed significantly higher healing rates compared with placebo administration, either alone or combined with fibrin glue injection. A subgroup analysis restricted to either autologous or allogeneic MSCs showed similar results with higher healing rates compared with placebo. A subgroup analysis on adipose-derived MSCs also showed more effective outcomes compared with placebo. Overall, MSC administration may be a safe and efficacious treatment to promote fistula healing in PFCD but – despite the encouraging results – a substantial heterogeneity exists among the several Phase I, II, and III clinical trials, using different MSCs donors (autologous or allogenic), source tissues (bone marrow or adipose tissue), administration timing, and doses. The high heterogeneity among the protocols and the inhomogeneous definition of fistula healing may prevent a conclusive recommendation in favor of MSCs treatment, particularly for complex CD fistula, and further studies – focusing on the biological mechanisms – are needed on the topic. Despite the comparable efficacy, allogenic adipose-derived MSCs are preferred with respect of bone marrow-derived MSCs, due to the easier isolation and higher yield. However, regardless of the origin source, the need for cultured expansion processes makes autologous and allogeneic MSCs production costly and time consuming. The possibility of obtaining adipose-derived MSCs from mechanically treated human adipose tissue – thus avoiding the cultured expansion step – has risen consistent interest in the past years. A recent prospective study[60] demonstrated – in a small number of patients – the feasibility and safety of local injection of autologous microfragmented adipose tissue to treat PFCD. Autologous harvested fat was processed using a marketed system (Lipogems system®) which provided microfragmented adipose tissue removing the pro-inflammatory residues. The results of the study – although very preliminary – suggest that microfragmented adipose tissue injection may be a valid treatment for PFCD.

## Conclusion

Surgery may be required in case of medically refractory patients or fibrostenosing and fistulizing disease. The main goal of the surgical treatment is to resolve the disease-related complications; however, several technical strategies may be implemented to improve the postoperative outcomes, reduce the post-operative complications, shorten the patients' recovery, and extend the disease remission. In the past years, significant steps forward have been made in the surgical management of CD but further research is needed to integrate these innovative strategies in the clinical practice.

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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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