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REVIEW ARTICLE

Can Surgery for Inflammatory Bowel Disease be Personalized?

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Abstract: ***Background*:** In the treatment of Inflammatory Bowel Diseases (IBD) despite advances in medical therapies, surgery has maintained a leading role in the management of complications of the disease, as well as in cases of failure of medical therapy.

***Objective*:** discuss the possible role for a personalization in debated fields of surgical treatment of Crohn's disease and ulcerative colitis.

***Conclusions*:** Surgery has become more and more minimally invasive, struggling for a difficult balance between guidelines and personalized treatment tailored on the single patient's need. There is no room for fixed management for surgery in IBD. A tailored approach is key to better outcome in each specific patient.

Keywords: Crohn's disease, inflammatory bowel disease, surgery, personalization, tailored surgery, ulcerative colitis.

1. INTRODUCTION

Surgery plays a significant role in the management of Inflammatory Bowel Disease (IBD), when medical treatment fails to provide adequate symptomatic relief or to avoid complications related to the disease. Even if surgical rates have been declining during the last three decades [1], more than 70% of all patients with Crohn's Disease (CD) will still require surgical treatment within 10 years of diagnosis [2] and up to 30% will require a further operation in case of recurrence [2-7]. Similarly, surgical management of Ulcerative Colitis (UC) is embraced in up to 30% of patients during the course of their disease [6].

Although the general indications for IBD surgery have not changed significantly over time, the approach and principles of surgical management are constantly evolving. This occurs due to the development of new biological therapies, imaging protocols, and minimally invasive surgical techniques, which are all designed to maximize patient's comfort, preserve healthy bowel, and minimize flares and treatment complications. Moreover, the goal of actual IBD management is to personalize therapy to the individual level, so that patients could receive the most effective and appropriate evaluation and therapy for their particular disease severity, with consequent positive effects on their quality of life.

The purpose of this article is to highlight which surgical aspects for the treatment of IBD should be personalized, and if so, a detailed discussion of the current options aims to be clarified.

2. CROHN´S DISEASE

CD may involve the entire gastrointestinal tract from the oral mucosa to the perianal area [8]. Except in the emergency setting, medical treatment is set up until it fails to improve symptoms, produces unacceptable adverse events, or a complication of the disease occurs. At this time, surgical therapy gains a crucial role in order to achieve the best possible control of the inflammatory disease with a satisfactory quality of life. However, any failure of medical treatment should be discussed on a case-by-case basis in multidisciplinary meetings since the care of CD is now primarily in the hands of gastroenterologists and surgery is mostly used after all medical attempts have failed [9, 10].

According to the European Crohn's and Colitis Organization (ECCO) [9] and the American College of Gastroenterology (ACG) [11] guidelines, indications for surgery in the elective setting for CD include several scenarios, that are described in details in Table **1**.

Acute complications in the emergency setting in patients with CD are infrequent. Most of them (as abdominal abscesses, for example) can be managed with medical therapy or radiological procedures resulting in decreased morbidity and mortality, and a delayed intestinal resection may be planned in the future, if necessary, in selected cases [11]. However, in cases of failure of conservative treatment these acute conditions may be life threatening and do require prompt surgical indication, without delay. The indications for surgical treatment in the emergent setting for CD are described in Table **2** [12].

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Table 1. Surgical indications for CD in the elective setting.

INDICATIONS FOR SURGERY IN THE ELECTIVE SETTING
1. Failure of optimal medical treatment (this includes dose optimisation of all medications used in combination)
2. Symptomatic localized ileal or ileo-caecal fibrotic stenosis, without any significant evidence of active inflammation
3. Refractory obstructive symptoms after initial medical treatment (steroids) in ileo-caecal CD
4. Symptomatic fistula complicating penetrating CD
5. Failure of medical therapy and percutaneous drainage management of active small bowel CD with a concomitant abdominal abscess
6. Failure of medical or endoscopic treatment of recurrence (*e.g.* anastomotic stenosis or short strictures submitted to previous dilatation)
7. Demonstrated or suspected malignant transformation.

Table 2. Surgical indications for CD in the emergency setting.

INDICATIONS FOR SURGERY IN THE EMERGENCY SETTING
1. Free perforation with consequent peritonitis
2. Intra-abdominal abscesses with sepsis, unresponsive to medical therapy or to percutaneous radiological drainage
3. Perianal abscesses
4. Massive bleeding refractory to embolization
5. Imminent obstruction refractory to medical treatment
6. Severe acute Crohn's colitis with significant complications (*e.g.* free or blocked perforation, massive bleeding or megacolon), as well as those refractory to second line medical treatment.

The proper surgical strategy is significantly important, since patients referred to surgery will have complicated disease and are likely to be at higher risk of septic complications [9, 13]. Irrespective of the type of the selected procedure, an extensive resection is no longer necessary (histologic disease at the surgical resection margins does not predict a greater risk of recurrence) [14, 15] and if performed, may potentially jeopardize patient's care (*e.g.* causing short bowel syndrome). Moreover, most patients with CD may require one or more operations in their lifetime, so that surgical efforts should be properly addressed to the part of the bowel mainly responsible for the symptoms. Usually the surgical strategy and approach con be decided before surgery thanks to a correct interpretation of preoperative imaging (*e.g.* magnetic resonance enterography) [16]. Even with adequate imaging studies before the operation, the surgical plan can be changed after macroscopic analysis of all intestinal segments during laparotomy or laparoscopy. Therefore, each patient may be targeted to the best strategy according to the disease location and complication status.

2.1. Laparoscopic Or Open Approach? How to Decide?

Laparoscopy has been used increasingly in the last decade in the management of CD and to date represents the most commonly adopted minimally invasive approach for this disease [17, 18]. Several articles had demonstrated the safety of laparoscopic ileocolic resection, with no increase in morbidity, reduced costs, shorter postoperative ileus, shorter hospital stay and decreased incidence of incisional hernias, when compared to the conventional approach [9, 18-20]. The laparoscopic approach might be a safe alternative to conventional surgery even in complex cases of CD, such as those with localized abscesses, fistulas, or recurrent disease with previous adhesions [20-24]. Furthermore, even in the emergency setting, if the disease involves only a short portion of the colon, a laparoscopic segmental resection seems to be a good and safe alternative to a more extensive procedure [25, 26].

CD patients are, theoretically, ideal candidates for minimally invasive surgery: they are often young and active and so may benefit from the advantages of laparoscopy in terms of cosmesis and enhanced postoperative recovery. Furthermore, the reduced intra-abdominal adhesions and abdominal wall trauma following laparoscopy, as compared to the conventional approach, might improve long terms results and facilitate the unfortunately frequently required reoperation in CD patients. Following this concept, optimal selection of patients and outcomes of laparoscopic approach continue to be under evaluation.

In an attempt to identify potential risk factors for conversion, Schmidt *et al.* [27] reported that intra-abdominal fistulas, smoking habit, preoperative steroid therapy, colonic disease apart from the cecum and preoperative malnutrition were associated with a higher risk of conversion. In another recent study [28, 70] consecutive patients who underwent a laparoscopic ileocaecal resection with an additional intestinal segment and intra-abdominal abscess or fistula were assessed

as independent risk factors for conversion after multivariate logistic regression. However, in experienced hands, a policy of starting most suitable cases laparoscopically may offer patients the potential benefit of a laparoscopic approach without increased morbidity.

Recently, single-port laparoscopic surgery (SPLS) has also been proposed for the surgical management of CD. Published experiences on small case series have reported SPLS feasibility and safety for ileocolic resection [29-32] and even in cases of complex and recurrent CD [33].

The decision of which should be the best approach for each patients needs to be individualized, in discussion with the gastroenterologists and the patients themselves. Clearly, patients without previous abdominal operations are good candidates for laparoscopy, and even those with lower Body Mass Index (BMI) can be submitted to single-port procedures. Those with several previous operations and with higher BMI are at risk for conversion and complications, and may benefit from laparoscopic techniques only in experienced hands. Therefore, the conventional approach for theses specific cases should be offered if no adequate minimally invasive expertise is available. To personalize the proper approach for each patient is sometimes challenging, and adequate preoperative counseling is therefore essential.

2.2. Resection Or Stricturoplasty in Small Bowel CD?

Stricturoplasties and jejunal or ileal resections represent two possible surgical options in case of small bowel CD. Stricturoplasty is considered the treatment of choice for patients with non-phlegmonous small bowel CD with fibrotic strictures that are responsible for symptomatic partial intestinal obstruction [9, 11]. Different techniques have been described so far (*e.g.* conventional Heineke–Mikulicz, Finney or Michelassi stricturoplasties [34, 35]) and the choice among these several methods should be done according to the number of strictures, length and relationship among strictures and potential intestinal segments selected for resection. Stricturoplasties should be considered for patients with a history of prior resections who are at increased risk for short bowel syndrome with additional resections [35] and they have been associated with excellent outcomes [34]. Therefore, bowel preserving techniques are usually offered when possible.

In cases of obstruction secondary to CD strictures, small bowel resection remains the standard of care. Segmental resections are indicated when a stricturoplasty is not recommended (*e.g.* phlegmon in the bowel wall, suspicious of carcinoma, active bleeding with mucosal disease, associated internal fistulas, generalized peritonitis, or bad nutritional status, due to the high risk of postoperative leakage [36]) and in cases of multiple strictures in a short segment where residual bowel length is sufficient to avoid short bowel syndrome [9].

Recent papers comparing small bowel segmental resections *versus* stricturoplasties [37, 38] have confirmed the safety and bowel-sparing potential of the latter technique for small bowel CD. Moreover, short and long-term results appeared to be similar between both surgical techniques. The risk of recurrent stricture formation between stricturoplasties and resections is at least comparable but still needs to be properly defined [9], considering that rarely recurrence appears at the stricturoplasty site but elsewhere [39].

Even if current guidelines suggest to perform a stricturoplasty in cases with strictures <10 cm in length [9], this technique can be safely adopted also in the presence of longer strictures (>30 cm) as other authors have already reported. Moreover, this procedure might be particularly indicated for the treatment of CD affecting patients with immunosuppression. Whether preservation of affected bowel increases the long-term risk of malignancy is yet to be determined, although case reports have documented adenocarcinomas arising from sites of previous stricturoplasties [40].

Indeed, a personalized approach in order to decide from which method the patients will benefit is essential. The criteria of the number of strictures, the length of the affected segment, the length of residual healthy small bowel and also the presence of complications associated to the stenosis need to be analyzed with caution in order to lead to the best decision as possible. No standardized approach can easily be proposed in this situation.

2.3. Segmental Or Total Colectomy?

The surgical strategy in cases of colorectal CD depends on the extent of the disease, the quality of the anorectal function, and the general condition of the patient [41]. In the elective situation and in the absence of a significant perineal involvement with anorectal incontinence, segmental resection or total colectomy (with ileorectal anastomosis) are the most commonly performed types of operations in this scenario.

When less than a third of the colon is involved, segmental or economic resection of the affected part is preferable [9, 11]. The majority of the available evidence [42-47] states that this strategy is associated with a higher rate of recurrence over total proctocolectomy, but it guarantees the avoidance of a (permanent) stoma with subsequent social and sexual impairment. Moreover, segmental resection, specially in patients with prior small bowel resections, is expected to be associated with fewer functional disturbances than can be experienced after total colectomy due to the preservation of the colonic absorptive capacity [45-48]. If the colon appears to be involved in two widely separated segments, in the two extreme portions of the large bowel, both segmental resections with two anastomoses and total colectomy with ileorectal anastomosis are acceptable options according to surgeon's preference and patient's status [9]. In case of rectal CD, in the absence of colonic involvement, the most conservative approach is a rectal abdomino-perineal resection, if possible with an intersphincteric approach. In comparison with a more extended approach, such as a total proctocolectomy, this operation allows a reduction of short-term morbidity and less functional disturbances, specially in those patients with previous ileal resection. Similarly to the considerations for colonic resection, this therapeutic choice is burdened by a higher recurrence rate in the large bowel preserved. There is still controversy if recurrence rates can be reduced in the era of biologicals, due to more effective prevention strategies with these agents. This concept still needs to be proved in prospective trials.

The decision to perform a segmental resection *versus* a subtotal colectomy *versus* a proctocolectomy in patients with colonic CD might be quite challenging in specific conditions (*e.g.* colonic involvement in two widely separated segments, presence of a particularly affected part of the colon among mild mucosal lesions in adjacent areas). If in one hand segmental colectomy is more limited and potentially associated to a reduced short-term morbidity, as compared to total colectomy, on the other hand it would result in higher long-term recurrence rates specially when a segmental resection is performed more than once in the patient's surgical history. An individualized approach, based on his current clinical scenario and past surgical procedures, may play a crucial role during the surgical planning.

3. ULCERATIVE COLITIS

As previously described for CD, the surgical treatment is also an important component of therapy in the management of UC. It alleviates symptoms, addresses serious complications, improves quality of life, and, in some settings, can be lifesaving [49, 50]. Moreover, it mostly represents the best long-term solution even if performed at the very early stage of the disease. If UC affects young patients, the disease seems to be more aggressive and the rates of colectomy can be higher. Conversely, older age at diagnosis has been associated with a lower risk of colectomy in several studies [51].

Indications for surgery are very specific, due to the nature of the disease. As a matter of fact, while CD can affect any segment of the gastrointestinal tract with skipped areas, UC is limited to the colon and rectum and its inflammation is homogeneous and continuous. In the elective setting, as well as in cases of "fulminant" colitis or drug refractory colitis, current guidelines [52] emphasize the importance of medical therapy. When a conservative treatment fails, a tailored surgical strategy should be addressed to improve the patient's symptoms and quality of life.

Apart from the urgent situation of acute severe colitis, failure of medical therapy, stenosis, dysplasia, or colorectal cancer are the main indications for elective procedures [53]. The main indications for surgery are listed in Table **3**, according to the ECCO guidelines [54]:

The onset of an acute fulminant colitis unresponsive to intensive medical treatment represents the main indication for surgery in UC in the emergency setting. This potentially life-threatening scenario can be triggered by massive bleeding, toxic megacolon or perforation. Another rare, but possible indication for urgent surgery is obstruction [55] after failure of medical treatment. The aim of the surgical procedure in the emergency setting for UC is to restore patient's health by removal of the inflamed colon. Hence, the main procedure in this situation is a subtotal colectomy with a temporary end ileostomy without removing the rectal stump [53] (the rectum can be managed as a mucous fistula, when severely inflamed and friable. Another option is to close the rectal stump and perform rectal washout with saline solution and place an intraluminal drain for 2 or 3 days). These options aim to reduce the risk of rectal stump fistulas. In the acute setting, restorative procedures should be avoided because of the high risk of pelvic bleeding, sepsis, and injury to pelvic nerves. After the patient had been fully recovered, including the nutritional status, subsequent proctectomy with pouch construction with diverting loop ileostomy or rectal preservation with ileorectal anastomosis can be carried out with a reduced risk of complications. This usually occurs 6 months after the first operation.

A proper timing for surgery is essential in the emergency setting [54, 55]. Indeed, if there is no improvement within 7 days of first (steroids) and second line (cyclosporine or infliximab) therapies, colectomy is recommended, in order to avoid an increase in postoperative morbidity [56]. In stable patients, laparoscopic colectomy for fulminant UC, if performed in experienced hands and in high-volume units, shows to be a safe and feasible alternative to open colectomy and offers some clinical benefits (shorter hospital stay and reduced postoperative infectious complications such as wound infections or deep abscess) [57-59]. Septic and unstable patients should have conventional open colectomy as a first option in order to have a reduced surgical time and rapid recovery in intensive care units. These individualized choices can be discussed with the patient and the family, in accordance with the surgeon's experience and the patient's condition.

Table 3. Indications for surgery in UC, in the emergency and elective settings.

MAIN INDICATIONS FOR SURGERY IN ULCERATIVE COLITIS:
1. Failure of optimal medical treatment, even significant and severe adverse events
2. Acute severe colitis/ fulminant colitis with no response to first and second line medical therapies
3. Colonic deformation (fibrosis or stenosis, with microcolon) or obstruction
4. Non compliance or non adherence to medical therapy
5. Extraintestinal manifestations (*e.g.* erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, arthritis, uveitis) refractory to medical therapy
6. Recurrent chronic or sub-acute bleeding
7. Growth retardation
8. Demonstrated or suspected malignant transformation.

Unlike CD, the surgical strategy in UC should consider some important aspects: a) most patients with UC are eligible for sphincter preserving operations; b) segmental resections are inappropriate for patients with UC because of the risk of recurrent active inflammation or cancer developing in the remaining colon; c) perianal disease associated to UC (haemorrhoids, anal fissures and fistulas) are rare conditions with an incidence of 7% [60] and should be treated as conservatively as possible; d) estorative proctocolectomy with Ileal Pouch Anal Anastomosis (IPAA) represents to date the standard of care in elective surgery, however it cannot be performed in all patients, as will be discussed further in this article.

3.1. Laparoscopic Or Open Approach?

According to the recently published ECCO guidelines [54], laparoscopic surgery is safe and feasible for the elective surgical treatment of UC. Current evidence shows that this approach can guarantee better short-term outcomes with the disadvantage of longer operative time and increased costs. Long-term advantages of laparoscopy are reduced adhesion formation and incidence of incisional hernias. Moreover, restorative proctocolectomy with IPAA is associated to decreased fertility [61], sexual dysfunction [62] and female fecundity [63], especially when performed with a conventional approach [64]. Due to these benefits, elective laparoscopic surgery is becoming the procedure of choice in high volume centers of IBD management, with surgical adequate expertise [65].

In emergency colectomies with stable patients, a laparoscopic approach results in shorter hospital stay and in reduction of postoperative complications (wound infections, deep abscess) so that in experienced hands and in high volume centers, it should therefore be the approach of choice [54].

Recently, experiences regarding single–port [29, 66-69] and robotic-assisted [70-72] proctocolectomy with IPAA have been published with promising outcomes. So far, the literature is limited to few case series demonstrating the feasibility and safety of both approaches with complication rates comparable to conventional multiport laparoscopy. These new techniques still need to pass to the proof of time in the IBD management, and can be offered only in centers with adequate experience.

3.2. When to Use Ileorectal Anastomosis?

Total colectomy with Ileorectal Anastomosis (IRA) could be considered for selected patients, as those with a relatively spared rectum (or a healed rectum under topical medical therapy), good rectal compliance and normal sphincter tone [54]. Other patients suitable for IRA are those who cannot undergo IPAA, those who refuse an ileostomy or those who have medical conditions in which a stoma is relatively contraindicated (*e.g.* portal hypertension or ascites). The operation may also be a good choice for patients in whom the diagnosis of CD cannot be excluded or for patients with colitis complicated by advanced colonic malignancy.

Acceptable quality of life and functional outcome comparable to those in patients with an IPAA have been reported [73, 74]. Some authors have advocated the operation in women of childbearing age with the aim to reduce the risk of infertility as an interim solution [75]. Indeed, while restorative proctocolectomy with IPAA is associated to decreased fertility [61], sexual dysfunction [62] and female fecundity [63], IRA is supposed to reduce or avoid potential sexual complications with the need of a mandatory surveillance of the residual rectum. For this reason, IRA might be considered a temporary option in young people and the surgical treatment can be personalized according to patient's desires. In elderly people with inadequate anal continence, but spared rectum, total colectomy with ileorectal anastomosis can also be indicated, mainly in women with multiple natural deliveries.

3.3. When to Indicate Total Proctocolectomy + Ileostomy?

Restorative proctocolectomy with IPAA is to date the standard of care in elective surgery for patients affected by UC. However, even if pouch reconstruction is theoretically the better solution in the majority of patients, it might be contraindicated in some cases. Patient's clinical status and preferences have to be considered during the decision-making process.

High-risk pouch failure conditions such as important immunosuppression, inadequate fecal continence or the concomitant diagnosis of low rectal cancer make patients unsuitable for an IPAA. In these situations, total proctocolectomy and end ileostomy are indicated. These are patients who will benefit from an end permanent ileostomy, no need for surveillance and medication, with cure of UC. In all patients unsuitable for a pouch procedure, a total proctocolectomy might be a valid alternative and can be carried out with a permanent ileostomy (Brooke ileostomy) or a continent Ileostomy (Kock's pouch) [76]. The Kock's pouch can be an alternative to conventional end ileostomy for patients with failed IPAA, for those who are not candidates for IPAA (sphincter injury *etc.*) and for those who have considerable problems with an ileostomy (leakage, skin problems, *etc.*). Even if quality of life with Kock's pouch seem superior to an end-ileostomy, it has been associated with higher reoperation rates [54]. Therefore, careful preoperative evaluation, multidisciplinary decision-making processes and individualized characteristics from the patients may help to select the ideal candidates for this operation.

CONCLUSION

Surgery for the treatment of IBD is constantly evolving due to solid advances in medical therapy and to the application of minimally invasive approaches on daily clinical practice. The best surgical treatment for CD and UC aim the maximum benefit of disease control with the least amount of adverse events and complications, in order to provide an increased quality of life. In this context, a personalized treatment plays a crucial role and should be applied to provide the most effective and appropriate surgical strategy. There is no room for standardized fixed strategies in the surgical IBD management for all patients. A tailored approach is mandatory, respecting individual characteristics from the patients and surgical experience, as well as previous training in minimally invasive procedures and available surgical devices.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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