Post-surgical recurrence of crohn's disease: situational analysis and future prospects

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Summary

Surgery retains a major role in the treatment of Crohn's disease, and the prevention of post-operative recurrence is an essential issue. In fact, despite the increasing use of biotherapies, almost all of the patients who undergo surgery will present with a recurrence, initially endoscopic and then clinical, eventually leading to a second intervention in 15 to 20% of cases. Certain risk factors for recurrence such as smoking, repeated and/or extensive resections, anoperineal involvement, myenteric plexitis, epithelioid granulomas, penetrating phenotype and lack of post-operative prophylactic treatment have been well established. Currently, measures to prevent post-operative recurrence are based mainly on smoking cessation in all patients and the prescription of anti-TNF medications for patients with a high risk of recurrence (at least two risk factors for recurrence). However, new surgical techniques have recently been described which could modify post-operative prevention strategies. Kono's lateral anti-mesenteric anastomosis could significantly reduce clinical and endoscopic recurrence compared to conventional anastomosis techniques. Long latero-lateral isoperistaltic stricturoplasties have been shown to be feasible and are associated with a low rate of long-term symptomatic recurrence requiring surgery. In a preliminary series, intestinal resections with extensive mesenteric resection reduced the rate of recurrence in comparison with patients operated on conventionally (3% *vs.* 40% at five years). If the results of these new surgical techniques are confirmed, the indications for post-operative immunomodulatory treatments could be down-graded in patients currently considered to be at high risk of recurrence.

Keywords: Crohn's disease, Recurrence, Ileocecal resection, Anastomosis

Essential points

• 30-50% of patients with Crohn's disease will require surgery during their lifetime in order to resolve obstructive symptoms in the more or less long term. However, almost all patients develop endoscopic recurrence post-operatively; its detection is essential since it precedes the development of clinical recurrence that may require surgery. Eventually, 15-20% of resected patients will require a new intestinal resection.

• Several risk factors have been implicated in post-operative recurrence: smoking, repeated and/or extensive resections (> 50 cm), anoperineal involvement, myenteric plexitis, epithelioid granulomas and lack of post-operative prophylactic treatment. The penetrating phenotype of Crohn's disease, classically recognized as promoting post-operative recurrence, has more recently been identified as a protective factor against recurrence.

• Currently, the prevention of recurrence requires the cessation of smoking in all cases and the prescription of anti-TNF to patients at high risk of recurrence (at least two risk factors). However, the effectiveness of anti-TNF agents is limited and diminishes over time.

• The consensus of ECCO (European Crohn's and Colitis Organization) favors a lateral stapled anastomosis for ileocecal resection and considers stricturoplasty as a valid alternative to resection for short or long strictures of the small intestine except for perforating disease where only resections are possible. Long stricturoplasty techniques for extensive strictures have provided encouraging results with regard to endoscopic healing and long-term surgical recurrence.

• The side-to-side Kono anastomosis and intestinal resections that include extensive mesenteric resection have shown promising results leading to decreased endoscopic, clinical and surgical recurrence. These new techniques could thus limit the need for post-operative prescription of immunomodulators in patients considered to be at high risk of recurrence.

1. Introduction

Surgery is an essential tool in the management of patients with Crohn's disease (CD). The percentage of patients requiring surgery varies in the literature and significant differences have been shown between population studies and data from reference centers. However, it is estimated that 30-50% of Crohn's patients will require at least one surgical resection during their lifetime (1). Biotherapies are still struggling to achieve a decrease in the overall rate of surgical interventions. Indeed, despite the increasing number of patients receiving biological treatments, the rates of ileo-colic resection (ICR) and right hemi-colectomy and the extensiveness of resections has remained stable over time (2). An increased resection rate has even been observed for perforating forms of CD (3). Surgery has the advantage of eliminating all macroscopic lesions with immediate relief of obstructive symptoms and improved quality of life, with low morbidity and zero mortality. Its economic impact on society is lower than that of immunomodulatory biotherapies (4,5). Nevertheless, a large majority of patients will develop an endoscopic recurrence within the first post-operative year (6). It is also known that endoscopic recurrence precedes clinical recurrence that may lead to further surgery. Thus, prevention, screening and management of endoscopic recurrence are essential since the latter heralds a new surgical resection in 15 to 20% of patients (7).

Some risk factors for post-operative recurrence have been well identified. These include active smoking, iterative and/or extensive resections (> 50 cm), anoperineal involvement, myenteric plexitis, epithelioid granulomas in the operative specimen, and the absence of post-operative prophylactic treatment. (8). The penetrating CD phenotype was initially thought to be associated with a higher post-operative recurrence rate compared to the stenosing or inflammatory phenotype (8), but a recent cohort study found contradictory results (9). In addition, the literature has reported solid data on the role of fecal flow and the intestinal microbiota on post-operative recurrence, and more recent data have underscored the role of the mesentery in recurrence (10–12).

The aim of this work was to review the literature in order to update knowledge on the medical and surgical management of post-operative recurrence of CD.

2. Influence of tobacco on post-operative recurrence

Tobacco plays a deleterious role in the progression of CD, a fact that was first highlighted in 1984 and has been confirmed in more recent studies (13). Smoking increases the risk of clinical and endoscopic recurrence after surgery (14). Smoking cessation significantly reduced the rate of clinical and endoscopic recurrence in prospective multicenter studies (15). Smoking cessation after ICR resulted in a four-fold reduction in the rate of surgical recurrence (10 *vs.* 38%, p = 0.02) (16).
Tobacco's mechanisms of injury on the digestive tract are still imperfectly understood and may involve an alteration of the immune system and/or gut microbiota, as well as the modification of intestinal permeability and mobility (17).

3. Role of fecal flow and intestinal flora on post-operative recurrence

Fecal flow has been implicated and widely emphasized in the physiologic pathogenesis of CD-associated inflammatory lesions . Isolation of an involved intestinal segment by stomal diversion of the fecal flow has indeed allowed rapid improvement of both clinical symptoms but also of mucosal lesions (11). In clinical practice, we have found that some patients are unwilling to have restoration of digestive continuity for fear of clinical deterioration. However, the long-term results of intestinal diversions through an ostomy have been disappointing for 20-40% of patients who eventually required intestinal resection for recurrent or progressive lesions upstream or downstream from the stoma (18,19).
The reintroduction of autologous intestinal flora downstream from a bypass stoma resulted in mucosal inflammation as early as day 8 (12). While intestinal bypass may therefore allow partial improvement in inflammatory lesions associated with CD, healing is not complete, and restoration of digestive continuity results in recurrence of lesions in the vast majority of cases (20).
In addition, fecal reflux into the upstream small intestine after ICR, linked in part to the loss of the ileo-cecal valve, is thought to be a cause of pre-anastomotic recurrence (21). Bacteria from the colonic flora colonize the lining of the upstream small intestine and thus promote recurrence of the lesions. To limit this risk, techniques to construct an anti-reflux valve after ICR have been evaluated with interesting results on both endoscopic and surgical recurrence (respectively, 46% at three years and 16% at five years) (22).

Pathophysiologically, there are profound alterations in the intestinal flora in CD with a reduction in biodiversity. This dysbiosis results in a decrease in anti-inflammatory bacteria and/or an increase in pro-inflammatory bacteria and could result in CD onset and recurrence (23). For example, the decrease of the anti-inflammatory bacteria Faecalibacterium prausnitzii in the intestinal flora has been associated with an increase in endoscopic recurrence at six months (24). Conversely, a particular form of Escherichia coli that has the capacity to invade the intestinal mucosa (adherent and invasive E. coli or AIEC) and then to replicate in macrophages and induce the production of TNFα has been implicated in post-operative recurrence (25). Recently, the presence of AIEC in the ileal mucosa has been correlated with the severity of endoscopic recurrence at six months (26).

4. Influence of surgical techniques on post-operative recurrence

a. Type of intervention

The frequency of post-operative recurrence varies depending on the location of the initial digestive involvement, although results vary depending on the study and the time period. In 1975, Greenstein *et al.* (suggested that there was a greater risk of recurrence after ICR than after colonic resection (53% vs. 11%), although the difference was not significant (27). Onali *et al.*, in a study of 537 patients operated on between 2001 and 2007, reported that ICR had a higher risk of endoscopic recurrence but a lower risk of clinical recurrence than other types of resection over an average follow-up period of eight years (28). Very recently, a study suggested that ICR had a significantly lower risk of surgical recurrence at five years compared to enterectomy and colonic resections (29). There is no current recommendation on prophylactic treatment based on the initial location of the disease or the procedure performed.

b. Type of anastomosis

i. Conventional anastomosis

The anastomotic morphology is likely to modify the rate of post-operative recurrence by acting on various factors: it would influence fecal stasis and local microbial overgrowth, fecal reflux into the upstream intestinal loops, and intestinal vascularization (30,31). The ideal anastomosis should be as large as possible and should limit reflux to the upstream small intestine while avoiding long-term ischemic

stenosis. However, publications assessing post-operative recurrence rates for different types of anastomosis have had varied and conflicting results.
In a prospective randomized study of ileo-colic, entero-enteric and colo-colic anastomoses, the rate of recurrence was lower for stapled anastomoses compared to hand-sewn anastomoses (30). In a 2007 meta-analysis, Simillis *et al.* concluded that side-to-side anastomoses and stapled anastomoses were less often complicated (immediate global complications and anastomotic leak) than hand-sewn end-to-end anastomoses, and had comparable post-operative recurrence rates (31). Mechanical stapling, by reducing tissue manipulation and providing uniform spacing between staples, appears to decrease the rate of anastomotic leak. Indeed, a 2011 Cochrane systematic review of prospective studies on ICR for cancerous and non-cancerous etiologies comparing stapled side-to-side anastomoses *vs.* hand-sewn end-to-end anastomoses found a lower rate of post-operative complications for mechanical anastomoses (32). In this study, the subgroup analysis of patients with CD did not show any statistically significant difference between the two types of anastomosis. The same results were reported in a prospective multicenter randomized study in which the rates of post-operative complications and recurrences were identical for stapled or hand-sewn anastomoses (33). In a retrospective study of 141 ICR for CD, the rate of recurrence after hand-sewn side-to-side anastomosis was lower than after end-to-side stapled anastomosis (34). A 2013 meta-analysis of side-to-side anastomosis *vs.* end-to-end anastomosis for CD did not show any statistically significant difference in terms of complications and recurrences (35). A 2014 meta-analysis of ICR for CD reported conflicting results, in which side-to-side stapled anastomoses were associated with a lower risk of complications and clinical and surgical recurrence compared to hand-sewn end-to-end anastomoses (36). More recently, a meta-analysis of CD surgery concluded that side-to-side stapled anastomosis was superior to end-to-end hand-sewn anastomosis with fewer clinical recurrences (OR: 0.32, 95% CI [0.13- 0.77]) and surgical recurrences (OR: 0.22, 95% CI [0.05-0.95]) regardless of the type of bowel resection (37).
Thus, there seems to be a consensus in favor of stapled side-to-side ileocolic and small bowel anastomosis for CD (8,38). To our knowledge, no recommendations regarding type of anastomosis have been published for colo-colic and ileorectal anastomoses.

ii. Kono's anastomosis (Figure 1).

In 2011, a Japanese team described a new type of anastomosis and introduced the notion of mechanical torsion as a factor in post-operative recurrence. A hand-sewn side-to-side (functional end-to-end antimesenteric handsewn anastomosis) was carried out after creating a "supportive column" by abutting the two stapled intestinal transection lines. In fact, the intestinal segments were divided using a linear stapler in an axis perpendicular to the plane of the mesentery. After reinforcing the intestinal corner with sutures, the two transection lines were abutted by five to seven separate stitches to create the supportive column. The small intestine and colon were then opened longitudinally for seven cm and eight cm respectively, starting the opening one cm from the transection staple line. The anastomosis was then performed transversely using interrupted sutures and the mesenteric breach was then closed with interrupted sutures (39).

Several elements might explain the interest of this anastomotic technique: the support column would help maintain the anastomotic diameter and prevent torsion and stenosis of the anastomosis. The authors have highlighted a larger anastomotic diameter compared to stapled side-to-side or end-to-end anastomoses (8 cm *vs.* 6 cm and 2 cm, respectively) (39). In addition, the placement of the supportive column behind the anastomosis could act as an interposed barrier protecting against recurrence of the disease proceeding from the mesentery (*cf*. Role of the mesentery) (39,40). The placement of the side-to-side anastomosis on the anti-mesenteric borders would have the theoretical advantage of preserving the intestinal vascularization and innervation and would make it possible to avoid the always difficult suturing of the mesenteric intestinal edges as is the case for end-to-end anastomoses. Finally, unlike stapled anastomosis, the manual suture line would retain some flexibility and promote the feasibility of future endoscopic dilations in the event of stenosis.

In 2011, Kono *et al.* reported the results of a retrospective multicentric study of 69 CD patients with ileo-colic, entero-enteric or colo-colic anastomoses by the Kono technique comparing them to a historical series of 73 patients with side-to-side or end-to-end anastomosis, hand-sewn or stapled (39). Endoscopic inspections at six months and one year post-operatively were performed by a gastroenterologist blinded to the surgical technique. The Rutgeerts score at one year and the surgical recurrence rate were statistically significantly reduced in the Kono anastomosis group (2.6 *vs.* 3.4; $p = 0.008$, and 0% *vs.* 15%; $p = 0.0013$ respectively). Another prospective multicenter study (one American and four Japanese hospitals) carried

out by the same team reported the results of the Kono anastomosis on 187 patients. With a mean follow-up of 65 months, the surgical recurrence rate was 1% (41). Very recently, a team from Naples reported the results of Kono anastomosis after ICR in a prospective randomized study of 79 patients. Thirty-six patients undergoing anastomosis by the Kono technique were compared with 43 patients who had a stapled side-to-side anastomosis. The rates of endoscopic recurrence at six months, clinical recurrence, and surgical recurrence at two years were lower in the patients who underwent Kono anastomosis (respectively , 22.6 *vs.* 62.8%,; p <0.001, 18 *vs.* 30.2%; p = 0.004, and 0% *vs.* 4.6%; p = 0.3) (42). However, certain methodological biases limited the conclusions of this study. Indeed, the monocentric nature of the study, the high rate of patients operated by laparotomy (48%) and undergoing surgery for recurrence (59.5%) emphasize the need to confirm these results. At present, the Kono anastomosis is not recommended in current practice standards. The results of the main studies of Kono anastomosis are shown in Table 1.

iii. Stricturoplasty

Intestinal resection for CD is the most common etiology of short bowel syndrome other than enterectomy for acute intestinal ischemia. The gradual development of stricturoplasty techniques, first for short strictures and then for longer strictures (> 20 cm) (44), has aimed to minimize lengthy enteric resections. The feasibility of these “enlargement plasties” was well demonstrated in a meta-analysis on 1112 patients that included 3259 stricturoplasties (81% of the Heineke-Mikulicz type, 10% of the Finney type, 5% lateral isoperistaltic) with a 13% rate of post-operative complications, 4% septic complications (anastomotic leaks and abscesses), and zero mortality (38); duodenal, jejunal, mid-small intestinal or terminal ileal sites of stenosis were candidates for treatment by stricturoplasty. In 2016, a Belgian team from Louvain reported the results of a "modified" long isoperistaltic stricturoplasty in 36 patients, by sectioning the diseased ileum in its middle part and performing a lateral isoperistaltic anastomosis including the ileocecal valve. With a median follow-up of 19 months, 14 patients developed clinical recurrence, one patient was re-operated at 63 months, but no stricturoplasty had to be resected (45). The same team updated their results in 2020 on 52 patients, with zero mortality and low morbidity (7.7% anastomotic leak). With a median follow-up time of six years, the clinical and surgical recurrence rates were 40% and 13% at five years, respectively, with complete

endoscopic and clinical remission in 26% of patients. No cases of cancer were detected in the long term (45).
Thus, the ECCO consensus considered conventional stricturoplasties (Heineke-Mickulicz, Finney) and long lateral-lateral isoperistaltic Michelassi-type stricturoplasties as a possible alternative to resection for patients with extensive involvement of the small intestine, with better results in terms of surgical recurrence (38). Colonic stricturoplasties are not currently recommended and the perforating form of CD (presence of abscesses, phlegmon or complex fistulas) remains a classic contraindication for small intestinal stricturoplasties (38,45).

c. Role of the mesentery in post-operative recurrence

Mesenteric thickening and wrapping of the intestine by fatty hypertrophy (fat-wrapping) is almost pathognomonic of CD. Patients with CD show an accumulation of intra-abdominal fat and this “mesenteric obesity” is present even in patients with a normal body mass index (BMI) and with no metabolic syndrome (46). For a long time, description of CD was focused on intestinal lesions (penetrating, stenosing forms) without considering the associated mesenteric changes, which were considered to be secondary to intestinal inflammation. Surgical modalities were adapted to the characteristics of benign disease with resection limited to the macroscopic intestinal lesions with minimal margins and without removal of the adjacent mesentery (as opposed to the wide resections recommended for oncologic surgery). However, there are now several indications that CD begins in the mesentery and that digestive involvement is only a consequence of the progression of inflammation towards the mesenteric edge of the intestine. Intestinal lesions are precisely aligned with this mesenteric hypertrophy with a corresponding transitional zone between the mesentery and the digestive tract (47). Mucosal lesions in CD can be circumferential but they predominate on the mesenteric border (63).
Microscopically, the same adipocyte hyperplasia and connective tissue thickening are observed in the mesentery and the adjacent intestinal submucosa (10).
In 2018, Coffey *et al.* evaluated the results of performing ICR with extensive mesenteric resection in 34 patients, comparing them to a historical series of 30 patients in which ICR was performed flush with the digestive tract without mesenteric resection (48). Mesenteric resection was associated with a statistically significant

reduction in surgical recurrence rate (2.9 vs 40%; p = 0.003). The length of bowel resection and the rate of positive resection margins were also lower with mesenteric resection. The mesentery therefore seems to play an important role in the pathophysiology and in the post-operative recurrence of CD. The authors also devised a mesenteric activity score based on the appearance of the mesentery (thickness of the mesentery and extent of fat-wrapping) and correlated it with the risk of surgical recurrence. A retrospective cohort study on the mesorectum of patients with rectal CD undergoing proctectomies showed similar results (49). The rate of perineal complications (pelvic abscess, persistent perineal sinus, pelvic hemorrhage) was lower in the case of total resection of the mesorectum compared to patients in whom proctectomy had been performed in contact with the rectum (17.6% *vs.* 59.5%; p = 0.007) with a statistically significant higher rate of perineal healing at six months (51.4% *vs.* 88.2%; p = 0.014). Pro-inflammatory markers (CD14 + TNFα-producing macrophages) isolated in the mesorectum could explain the improved results in patients undergoing total mesorectal resection. An international multicenter randomized study comparing extensive mesenteric resection with conventional ICR for CD is currently underway with the main objective of studying surgical recurrence (50). But at this time, there is no formal recommendation on the need for extensive resection of the mesentery.

d. Role of lymphatic circulation on postoperative recurrence

A 2008 study by Van Kruiningen *et al.* in 2008 reiterated the role of obstruction of mesenteric lymphatic channels in the pathophysiology of CD (51), but long before this, the first pathologists who examined fresh CD colectomy specimens described mesenteric lymphatic channel obstruction as a fundamental lesion common to all patients with CD. The study of fresh intestinal specimens resected for CD from patients who had not undergone treatment with antibiotics, corticosteroids or immunomodulators revealed chronic lymphangitis with lymphatic obstruction by lymphocytes and granulomas. On the other hand, obstruction of the lymphatic channels in murine and porcine experimental models (52,53) reproduced identically the characteristic segmental intestinal lesions typical of CD: intestinal wall thickening, entero-enteral and entero-cutaneous fistulas. Lymphatic obstruction is believed to be the cause of adipocyte stimulation and cytokine production, thus explaining the associated immune disorders and the exacerbated inflammatory response seen in

CD (54). Thus, disruption of mesenteric lymphatic flow could be the cause of intestinal lesions in CD. Dividing the mesentery during surgical resections interrupts mesenteric lymphatic flow and is believed to promote recurrence of CD lesions. There is currently no treatment to restore circulation to blocked lymphatic ducts. An indirect way to restore lymphatic circulation after intestinal resection would be to interpose omentum, particularly rich in lymphatic vessels, into the mesenteric breach. In a series of 20 patients operated on for CD with trans-mesenteric epiplooplasty (TME), Del Gaudio reported the absence of clinical and CT recurrence at five years (55). The authors felt that the re-establishment of lymphatic circulation in the mesentery thanks to TME was at the origin of these good long-term results. This technique, however, is not recommended in current practice standards.

5. Other risk factors for recurrence

a. Histological factors that influence post-operative recurrence

The intestinal-sparing surgical strategy with narrow margins for CD sometimes leads to performance of an intestinal anastomosis in an area with microscopic evidence of inflammation. Studies have evaluated the influence on recurrence of the presence of different histological markers of inflammation within the surgical specimens and at the excision margins. Epithelioid granuloma, containing epithelioid cells, macrophages and lymphocytes, was the histologic lesion best correlated with the diagnosis of CD, although it was only found in 37 to 60% of patients (56). Its role as a risk factor for recurrence has long been debated. Two meta-analyses involving more than 2000 patients showed that epithelioid granuloma was associated with a higher rate of endoscopic recurrence (RR = 1.37; 95% CI [1-1.87]) and surgical recurrence (OR = 2.38, 95% CI [1.43-3.95], p = 0.001) (56,57).
Myenteric plexitis is defined by the presence of at least one chronic inflammatory cell contiguous to or within a ganglion or nerve bundle. It would promote post-operative recurrence by way of the ganglia and nerve bundles left in place (58), which would release pro-inflammatory mediators. Ferrante *et al.* in a study of 59 patients undergoing ICR concluded that the presence of myenteric plexitis at the proximal ileal resection margin was associated with a thirteen-fold increased risk of endoscopic recurrence at one year (95% CI [1.45-16.99]) and that the severity of this recurrence was significantly correlated with the severity of the plexitis and the

number of inflammatory nodes within the plexus (58). Decousus *et al.,* in a study of 75 patients, also concluded that myenteric plexitis at the proximal resection margin was associated with a significant increase in the risk of endoscopic recurrence at one year (RR = 8.83: 95% CI [1.45-16.99]) (59). A recent meta-analysis by Ryan *et al.* also confirmed the association of myenteric plexitis with endoscopic recurrence, although without correlation with surgical recurrence (59). In addition, myenteric plexitis could increase recurrence by increasing the rate of post-operative complications. Indeed, post-operative anastomotic leaks have been considered responsible for an increased rate of surgical recurrence (60). However, 50% of patients who develop anastomotic complications have involved intestinal margins on histology (granulomas, pathological mucous glands or the presence of myenteric plexitis) (61). Despite these data, however, frozen section examination of the intestinal resection margins is not recommended in current guidelines.

b. Intrinsic factors of post-operative recurrence

There is consensual agreement that the concomitant presence of ano-perineal lesions, previous history of intestinal resections, and/or the need for a resection exceeding 50 cm of small intestine are associated with a significant increase in the risk of clinical recurrence after surgery (8). The penetrating phenotype has been classically considered a risk factor for recurrence (8) but a recent cohort study of 346 patients undergoing ICR for CD showed conflicting results by identifying the penetrating phenotype as an independent predictor of protection from post-operative recurrence. (9).

6. Place of medical treatment

a. Medical treatments

- Treatments with probiotics have not been shown to be effective in preventing post-operative recurrence of CD and their use is not recommended in practice (8,38).
- Treatment with 5-aminosalicylic acid (5-ASA) without surgery has proved ineffective in inducing and maintaining remission in CD (62). ICR, which removes the majority of gross intestinal disease, is a particular clinical situation in CD. Eight randomized double-blind studies including more than 1100 CD patients have shown

that oral treatment with 5-ASA at doses of 2-4 gm/d is superior to placebo in the prevention of clinical recurrence within the 12 to 36 months following ICR surgery (OR 0.68, 95% CI [0.52-0.9]) (63). However, even if 5-ASA treatment is welltolerated without major adverse effects, its benefit in this situation was only modest with the need to treat 16 to 19 patients in order to avoid a single clinical recurrence (63). A more recent meta-analysis by Gjuladin-Hellon *et al.* demonstrated similar results with a 36% risk of clinical recurrence 12 to 72 months after surgery for patients treated with 5-ASA *vs.* 43% in the placebo group (64). In practice, the indication for prophylactic treatment with 5-ASA to decrease the risk of post-operative recurrence is limited to patients who are at low risk of recurrence and who wish to receive medical treatment during the 6 to 12 months prior to screening endoscopy.

- L**ong-term antibiotic treatment with imidazoles** (metronidazole and ornidazole) for three months to one year has shown its effectiveness in two randomized double-blind studies in prevention of endoscopic recurrence (OR: 0.31, 95% CI [0.10-0.94]) and clinical recurrence at one year (OR: 0.14, 95% CI [0.0037-0.546]) (65,66). Unfortunately, these good results were associated with frequent adverse effects and early discontinuation of treatment, which limited the indication of these antibiotics to patients with contraindications to immunomodulatory treatments and, in particular, to patients with post-operative infections. Some authors have also proposed the use of imidazoles immediately after surgery while awaiting treatment with anti-TNFα (67).

- **Local or systemic corticosteroids** are not effective in maintaining clinical remission of CD after ICR (8).

- **The use of thiopurine treatments** (azathioprine and 6-mercaptopurine) to prevent post-operative recurrence has been disappointing. Seven double-blind controlled trials as well as a Cochrane meta-analysis have shown only a modest effect of thiopurine treatments in the prevention of post-operative clinical recurrence, without statistically significant superiority over treatment with 5-ASA but with more serious adverse effects (68). The benefit/risk ratio of thiopurines was therefore low and leaves no room for these treatments in the prevention of post-operative recurrence, except perhaps in patients with contraindications to anti-TNFα treatment.

- **Anti-TNFα agents have been the most effective treatment** in preventing post-operative recurrence in CD (69). The majority of controlled studies carried out, particularly with infliximab started within four weeks after surgery, have shown efficacy in preventing post-operative endoscopic recurrence at one year overall, without increasing the risk of post-operative complications, in particular infectious

complications (69). The longer-term efficacy of anti-TNFα in preventing clinical recurrence at one and three years after surgery was low, however, with an identical Crohn's Disease Activity Score (CDAI) with or without anti-TNFα (70).

b. How can post-operative recurrence of CD be prevented in practice?

Given that diarrhea and abdominal pain occur frequently after ICR, even without any inflammatory activity due to CD, diagnosis of post-operative clinical recurrence of CD remains difficult. In practice, the main objective of medical treatment is to reduce the risk of endoscopic recurrence at six months to one year after surgery, since the risk of endoscopic recurrence correlates with that of clinical recurrence. The decision to treat and the choice of treatment must then depend on the patient's risk factors for recurrence, the benefit/risk ratio of each treatment and the patient's preference.

Smoking cessation is strongly recommended for all patients, as well as performance of a screening colonoscopy at six months to one year after the operation (8).

- For patients at low risk of recurrence systematic preventive medical treatment is not recommended prior to screening colonoscopy. Treatment with 5-ASA may be offered to anxious patients or to avoid losing the patient to follow-up.

- **For patients with one risk factor,** treatment with low-dose metronidazole (250mgX3 / day) for six months or with a thiopurine, especially for smokers who are unable to quit, or in conjunction with anti-TNFα may be proposed.

- **For patients at high risk of recurrence (two or more risk factors),** anti-TNFα should be the preferred treatment. For patients who are not primary responders to anti-TNFα or who have anti-TNFα antibodies, treatment with vedolizumab or ustekinumab may be discussed, although there is insufficient evidence of their effectiveness in this situation.

The methods of preventing post-operative recurrence are summarized in Figure 2.

7. Conclusions

Surgery retains a major role in the treatment of CD and the patient often experiences the post-operative period--with his lesions removed, without inflammatory activity and

without need for treatment-- as a honeymoon. That said, post-operative recurrence remains a major concern and even though the advent of biotherapies has reduced the rates of endoscopic recurrence, the rate of long-term clinical recurrence still remains high and a second surgical intervention is necessary for one out of five patients. Post-operative prophylactic treatments for patients at high risk of recurrence may no longer be systematic if the results of new surgical techniques in reducing recurrence are confirmed. Thus, Kono's anastomosis, extensive mesenteric resection or modified lateral isoperistaltic stricturoplasty may allow prophylactic treatment to be considered only in the event of endoscopic recurrence at six months or one year and could avoid blind treatment of patients at high risk of recurrence.

The authors declare that they have no links of interest.

Figure legends

Figure 1: The different stages of Kono anastomosis after ileocecal resection.
A: Ileocolic resection flush with the digestive tract. B: Digestive transection with linear stapler perpendicular to the plane of the mesentery. C: Reinforcement of intestinal angles. D: Creation of the support column by abutting the two section lines. E: Longitudinal anti-mesenteric opening of the small intestine and colon. F: Transverse anastomosis. G: Final aspect of the anastomosis.

Figure 2: Therapeutic strategy for the prevention of post-operative recurrence.
FdR: Risk factors, APL: Anoperineal lesions, AC: antibodies

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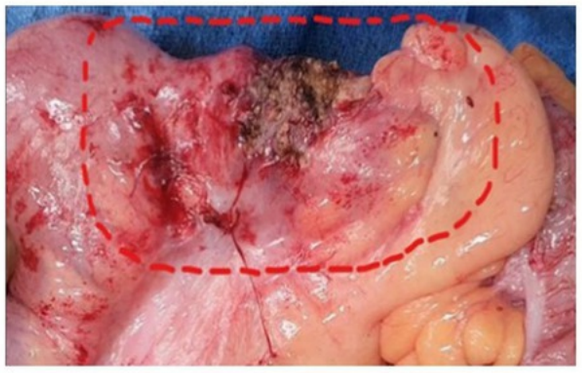
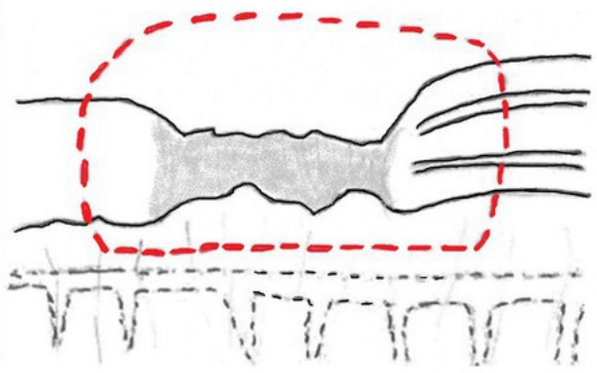
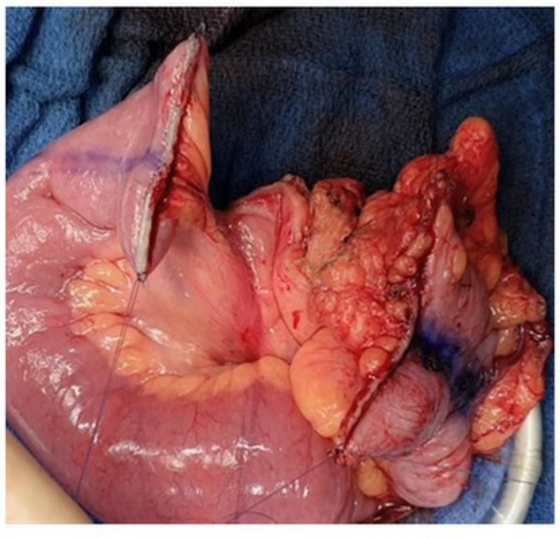
Table 1: Results of the Kono anastomosis in the literature on recurrent Crohn's Disease.

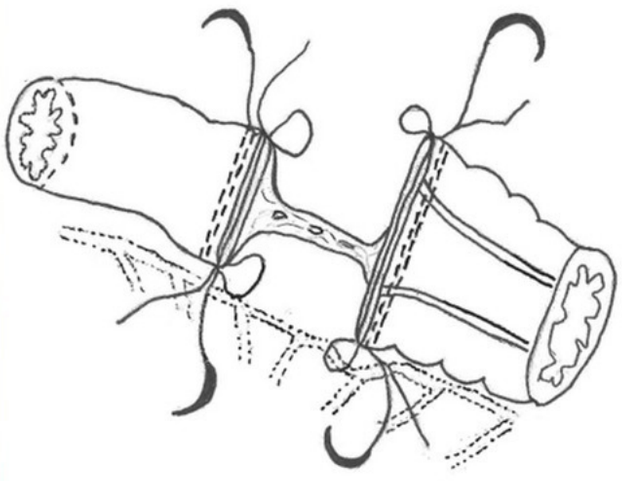
	Type d'étude	Inclusion dates	Number of patients		Endoscopic recurrence				Surgical recurrence			
			KA	CA	Measured at	KA (%)	CA(%)	p	Measured at	KA (%)	CA (%)	p
Kono et al., 2011 (39)	Rétrospective multicentrique	2003-2009	69	73	1 year	83	79	**NS**	5 yrs	0	15	**0.0013**
Katsuno et al., 2015 (43)	Prospective monocentrique	2009-2013	30	-	-	-	-	-	3 yrs	0	-	-
Kono et al., 2016 (41)	Prospective multicentrique	2003-2011										
• **Groupe Japon**			144	-	-	-	-	-	10 yrs	1.4	-	-
• **Groupe USA**			43	-	-	-	-	-	32 months	0	-	-
Shimada et al., 2019 (40)	Prospective monocentrique	2002-2016	117	98	-	-	-	-	4.5 yrs	3.4	24.4	**< 0.001**
Luglio et al., 2020 (42)	Prospective monocentrique randomisée	2015-2017	36	43	6 months	22.2	62.9	<**0.001**	2 yrs	0	4.6	0.37

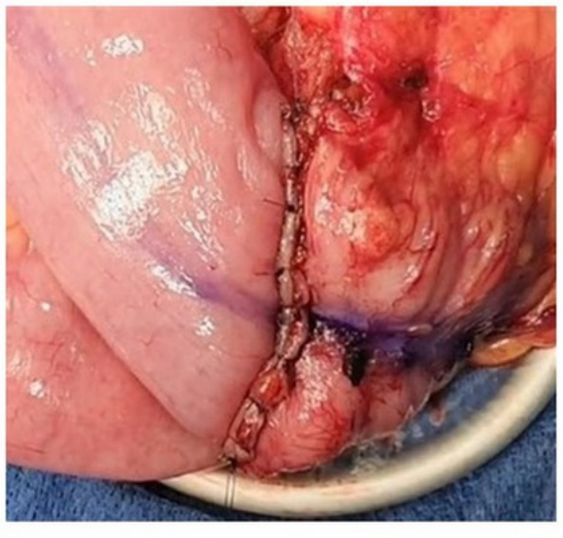
KA: Kono anastomosis; CA: Conventional anastomosis; NS: Non-significant

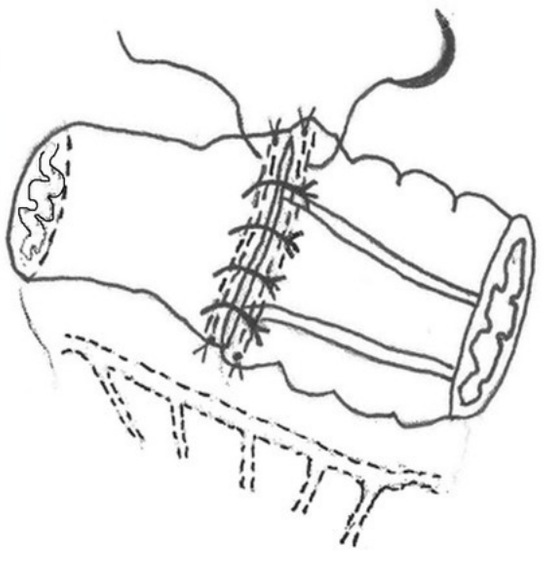


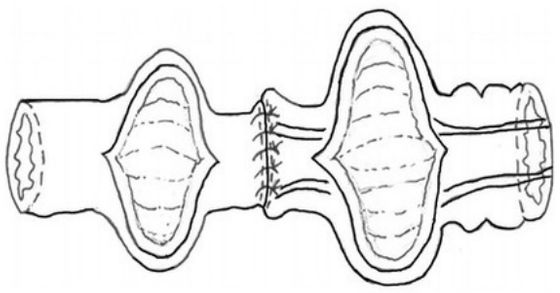


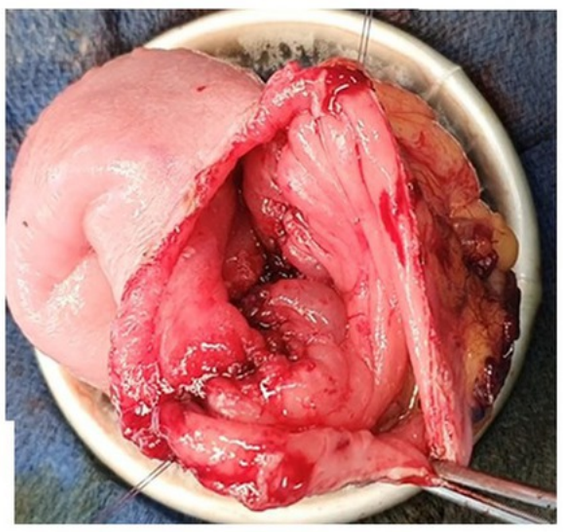


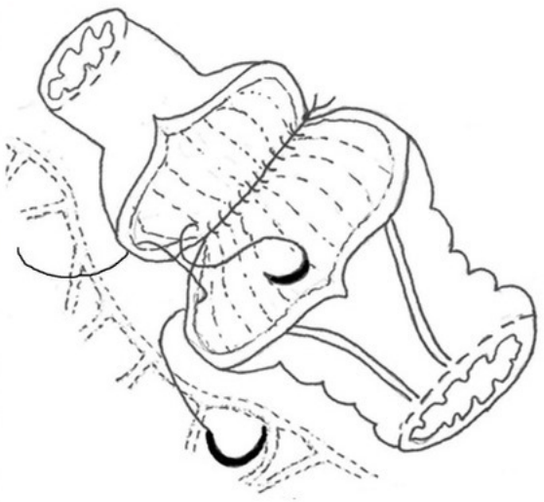


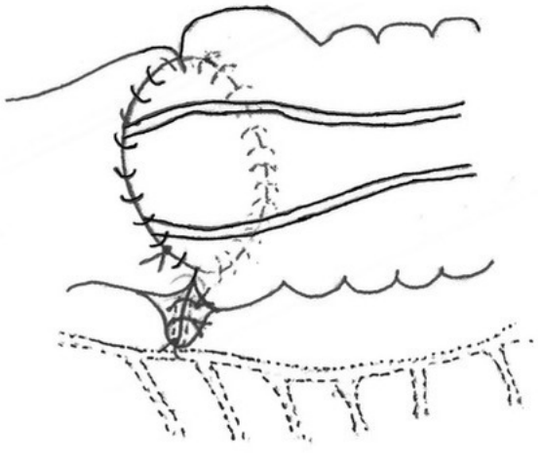


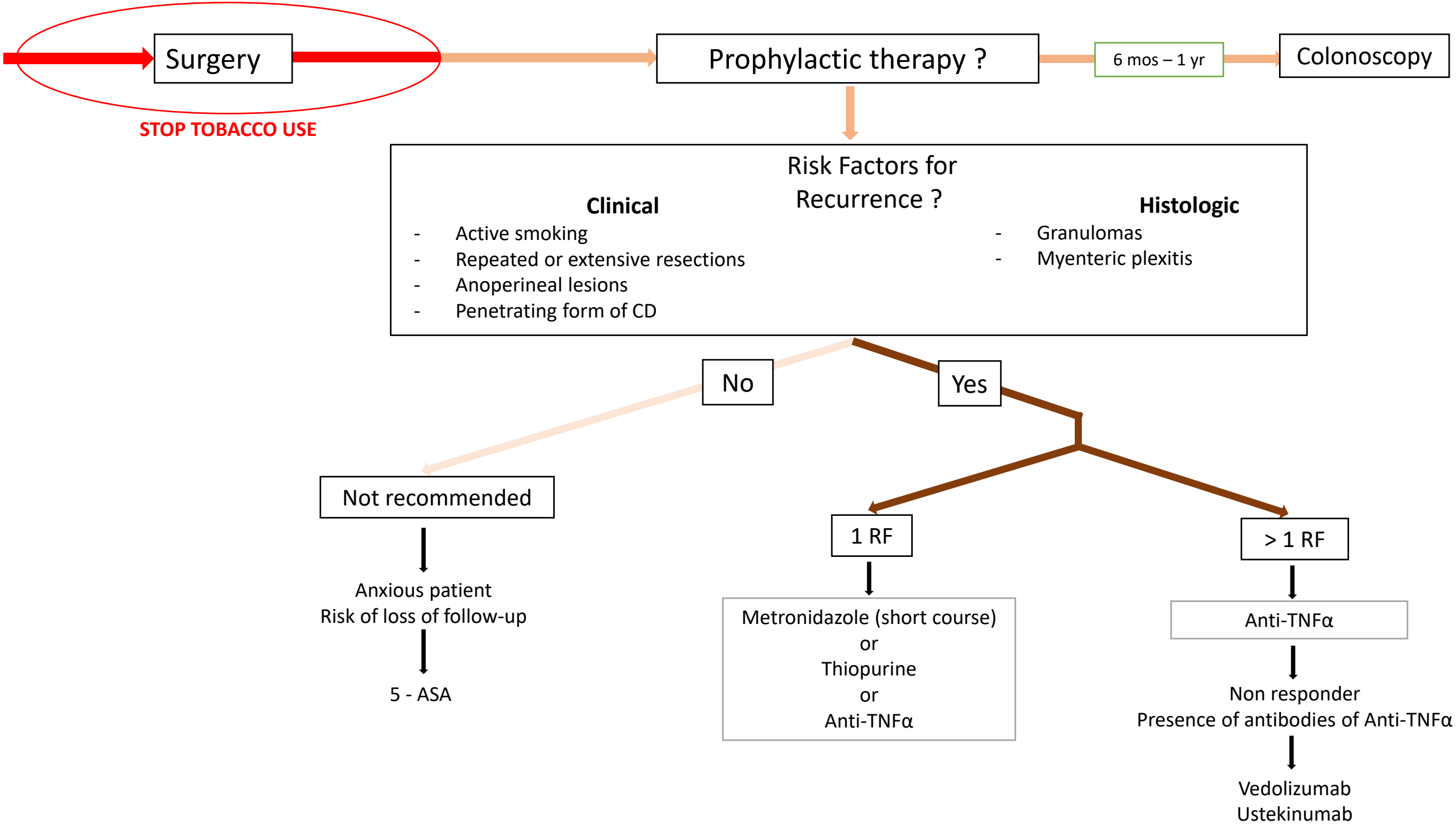











Surgery
STOP TOBACCO USE
Prophylactic therapy ?
6 mos – 1 yr
Colonoscopy
Risk Factors for Recurrence ?
Clinical
- Active smoking
- Repeated or extensive resections
- Anoperineal lesions
- Penetrating form of CD
Histologic
- Granulomas
- Myenteric plexitis
No
Yes
Not recommended
Anxious patient
Risk of loss of follow-up
5 - ASA
1 RF
Metronidazole (short course)
or
Thiopurine
or
Anti-TNFα
> 1 RF
Anti-TNFα
Non responder
Presence of antibodies of Anti-TNFα
Vedolizumab
Ustekinumab