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REVIEW



Endoscopy after surgery in inflammatory bowel disease: Crohn's disease recurrence and pouch surveillance

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ABSTRACT

Introduction: Crohn's disease (CD) and ulcerative colitis (UC) are immune-mediated disorders characterized by a chronic inflammation, with intermittent exacerbations of symptoms and inflammation. In both diseases, medical treatment has made revolutionary steps forward. Nevertheless, surgery is still required in many cases due to inefficacy of multiple medical therapies. It is not clear whether surgery rates in inflammatory bowel diseases (IBD) are currently decreasing despite all improvements.

Areas covered: Multidisciplinary management is critical in surgical patients to improve long-term outcomes. Endoscopy plays a crucial role, both before and after surgery, in planning therapeutic strategies and stratifying risk of recurrence. Aim of this review is to provide a deeper insight into the central role of endoscopy in the postoperative management of IBD patients, focusing on recent research advances, future challenges and unresolved questions.

Expert opinion: Both UC and CD surgical patients need endoscopy to define the correct therapeutic choice, predict subsequent disease course and adopt the correct surveillance strategy. In the next future, newer endoscopic techniques could be systematically applied in IBD patients after surgery, to assess early postoperative inflammation, response to treatment, or, regarding UC, to provide enhanced pouch surveillance, allowing for early detection of inflammation and dysplasia.

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1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are immune-mediated disorders characterized by a chronic inflammation. CD can potentially affect any part of the gastrointestinal tract, most frequently manifesting in the terminal ileum. Its main feature is the transmural involvement of the intestinal wall. The progressive inflammatory process often leads to a medically irreversible damage, with the development of strictures, fistulas and abscesses in about 50% of patients [1]. In UC, the inflammation affects the rectum extending proximally, with the potential involvement of the entire colon: the continuous inflammation pattern is a landmark feature of UC, but cases with rectal sparing or patchy distribution are also reported, especially in treated patients and children [2]. Intermittent exacerbations of symptoms and inflammation are typical. The anatomical extent of mucosal inflammation is an important predictor of the future course and the chance of colectomy [3]. In both diseases, medical treatment has made revolutionary steps forward, moving from conventional drugs to highly effective biological therapies and recently small molecules [4]. Several of these have been approved over the past decades and there are more currently in the pipeline.

Nevertheless, surgery is still required in many cases: this could be due to either a refractoriness to all therapies available or the high rates of complications, which, as described above, are still burdensome (especially in CD) and cannot be

prevented. Furthermore, it is not clear whether surgical resection rates for CD and UC are currently decreasing. Encouraging data are reported in the literature, with a significant decrease over the last decades [5]. A recent Canadian population-based study showed that at least in CD the surgical rates are declining at 8.4% each year [6]. Whether this is due to an increased use of biological therapies or because of other general factors such as earlier diagnosis, decreasing smoking trends or better patient education, still needs to be demonstrated.

In CD, it is reported that nearly 75% of patients will undergo surgery during their lifetime, with a 10-year risk that can exceed 50% [5–7]. A second intestinal resection is estimated to occur in about 35% of patients, even if a decreasing trend had been shown among those recently diagnosed [8]. In UC this risk is lower, but far from being negligible: according to the largest population-based studies available to date, the 1-year, 5-year, and 10-year risk of requiring colectomy lies around 3%, 7%, and 10%, respectively [9,10].

Current figures largely come from evidence accumulated in the past decades. It is reasonable to believe that, thanks to continuous improvements in IBD management, actual rates are lower than shown above, and will probably continue to decrease in the years to come.

What is clear, however, is that a significant number of patients are referred for surgery: related complications may

Article highlights

- Despite newer and highly efficient medical treatments, surgery is performed in a high percentage of IBD patients during their lifetime
- Endoscopy is a cornerstone in pre- and postoperative decision-making and in the multidisciplinary care of surgical patients, both in Crohn's disease (CD) and ulcerative colitis (UC).
- Rutgeerts' score (RS) was developed to predict the risk of clinical recurrence after ileocecal resection according to endoscopic findings at the anastomosis.
- The significance of some features of the RS, such as the subclassification of i2 grade and the finding of anastomotic and ileal blind-end ulcers, is uncertain and yet to be prospectively studied.
- Endoscopic surveillance of the pouch after ileal pouch-anal anastomosis (IPAA) in UC is under debate as long-term data regarding malignancy risk are contradictory.
- Screening pouchoscopy at 1 year for all UC-IPAA patients, followed by an algorithm of subsequent evaluation which takes into account risk factors for neoplasia and severity of endoscopic signs of inflammation, might improve long-term outcomes.
- Newer and increasingly used endoscopic techniques, such as video-capsule endoscopy and virtual chromoendoscopy, could play a role in postoperative evaluation and risk stratification of postoperative patients.

have a deep impact on subsequent quality of life. Appropriate multidisciplinary management is mandatory in order to improve long-term outcomes. Endoscopy plays a crucial role, before and after surgery, in planning therapeutic strategies, aiming to prevent future relapses and complications.

The aim of this narrative review is to give a deeper insight on the central role of endoscopy in the postoperative management of IBD patients, focusing on recent technological advances, future challenges and unresolved research questions.

2. Surgery in CD: indications and techniques

Surgical treatment in CD can be indicated in the following settings:

- Perforation
- Abscesses, when refractory to non-operative management
- Symptomatic obstruction, especially if long (>5 cm) or not amenable to endoscopic approach
- Enteric fistulas
- Inflammation that is refractory to medical therapy
- Ileocecal limited disease
- Perineal disease (whose discussion lies beyond the aim of this review)

The type of surgical approach mainly depends on the disease extent and location. Since CD is often localized at the terminal ileum and at the cecum, the most common procedure is ileocecal resection (ICR). In a large, recently analyzed, Canadian cohort of 1627 CD patients referred for surgery, ICR was indeed performed in nearly 65% of the cases [6]. In the same cohort, the second most frequent surgical intervention was a small-bowel resection (15%); in 12% of patients,

a diverting end or loop ileostomy was created. The purpose of fecal diversion is to enhance distal bowel healing, especially when severe bowel inflammation, perforation and peritonitis have occurred or if pre-operative risks are too high, with the aim of ultimately improving the outlook for future reconstruction. However, in refractory CD, fecal diversion may not just represent a temporary approach, and a certain amount of patients (around 10% of all CD patients) will permanently live with a stoma [11]. In terms of surgical techniques, laparoscopic surgery performed by expert hands is currently the gold standard according to European guidelines, at least for limited small bowel and ileocecal resections [12].

While several bowel reconstruction techniques have been proposed over time, the current trend is that the wider the lumen of the anastomosis, the better. Considering that both small bowel and ileocolic resections are the most frequently performed procedures, the bulk of clinical experience and evidence has accumulated within these settings. There are three mainly used techniques:

- Side-to-side anastomosis
- End-to-side anastomosis
- End-to-end anastomosis

Two recent meta-analyses have compared the efficacy of each approach: the recommended one, at present, is a laparoscopic ileocecal resection, followed by a stapled side-to-side anastomosis [13,14].

A relatively newer technique, the Kono-S-anastomosis has been used for bowel reconstruction both in ileocolonic and in ileal resections [15]. A 'supporting column' obtained through reinforcement of the two intestinal stumps should warrant a wider anastomotic lumen and technically prevent deformations or functional constrictions: encouraging data in terms of efficacy and safety come from a recent systematic review [16]. Randomized trials comparing this approach to a side-to-side anastomosis are not yet available and are needed in order to draw reliable conclusions.

From the endoscopist's point of view, the existence of several bowel reconstruction methods must be considered, so that a proper evaluation of the area can be carried out: whereas in end-to-end and end-to-side anastomoses prompt access to the neo-terminal ileum is usually warranted (the angles of reconstruction are >90°), in the side-to-side anastomosis a full retroflexion is sometimes required to proceed further. Moreover, some blind spots may be missed if the evaluation is not thorough, such as the ileal blind end of a side-to-side anastomosis, as discussed below.

3. Postoperative course of CD

Although clinical remission is obtained immediately after surgery, most patients will eventually relapse. Disease recurrence can take place at several levels: histological, endoscopic, or clinical. Histological recurrence can occur as early as a few weeks after surgery [17]. Its significance is still not clearly understood, both because it can develop in a mucosa with a normal endoscopic appearance and given there are currently

no studies specifically investigating the occurrence. Endoscopic recurrence can occur in 65% to 90% of patients at 1 year, and in 80% to 100% at 3 years [18,19] if no post-operative treatment is administered. Clinical recurrence is estimated to occur in about 25% of patients at 1 year from surgery [20].

It is clear that histological modifications and endoscopic recurrence precede clinical manifestations. Symptoms might be due to an already advanced grade of intestinal damage or early complications, a scenario that must be strongly avoided. In addition, vague abdominal symptoms could also be related to non-inflammatory causes, such as bile salt malabsorption, irritable-bowel syndrome or adhesions, which are frequent in the postoperative course. Nevertheless, many patients that are completely asymptomatic will experience endoscopic recurrence. Given these considerations, clinical recurrence cannot be considered a reliable target when managing patients with postoperative CD recurrence, and endoscopic findings have become the mainstay for the diagnosis of recurrence, and accordingly identified as crucial endpoints of most clinical trials.

4. Endoscopy in postoperative CD

Conceptually, surgical treatment warrants the induction of remission, provided that all the involved segments are completely resected. Although CD can technically affect other bowel segments, recurrence will most probably occur at the surgical anastomosis. Thus, its endoscopic evaluation, when easily reachable by a scope, represents the most practical and efficient way to evaluate disease activity. While colonoscopy would be the procedure of choice for distal resections (terminal ileum – colonic), if surgery occurs higher up

(jejunum, proximal ileum) direct visualization of the anastomotic mucosa would not be possible with a standard colonoscope. In this case, video-capsule endoscopy (VCE) could be a valid alternative, as discussed below. Greater attention is being placed on noninvasive methods of disease monitoring, such as fecal calprotectin, or cross-sectional imaging such as magnetic resonance enterography (MRE) or bowel ultrasound (BUS). Recently these methods are being extensively used to assess bowel inflammation and provide a comparable diagnostic yield when compared to standard endoscopy [21]. A meta-analysis has investigated their role in the postoperative setting, concluding that both MRE and BUS are comparable to ileocolonoscopy in terms of sensitivity and specificity [22]. Noninvasive approaches however have several obvious and important limitations which include the inability of visualizing any existing initial mucosal modification (such as superficial anastomotic ulcers), the inability to extract biopsies for histological activity assessment and the risk it may not be possible to perform required therapeutic maneuvers such as stricture dilation.

4.1. Ileo-cecal resection

The postoperative setting in which endoscopy has most largely been investigated is following ileocecal resection. The most widely adopted system for the assessment of disease recurrence at the ileo-colonic anastomosis is the Rutgeerts' Score (Table 1), developed in a landmark prospective study [18].

The classical Rutgeerts' Score grades the severity of recurrent CD in the postoperative patient with focus on the mucosa of the neo-terminal ileum, immediately proximal to the anastomosis. Score ranges from an ileal endoscopic score of i0 to

Table 1. Modified Rutgeerts' score.

Grade	Endoscopic finding
i0	No lesions in the distal ileum
i1	< 5 aphthous ulcers in the terminal ileum
i2	> 5 aphthous lesions with normal mucosa between the lesions, skip areas of larger lesions or lesions confined to ileocolonic anastomosis
	i2a Lesions confined to the ileocolic anastomosis
	i2b > 5 aphthous ulcers or larger lesions with normal mucosa in between, in the neoterminal ileum
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa (< 50% lumen)
i4	Diffuse inflammation, with larger lesions (>50% lumen): large ulcers, nodules/cobble, narrowing/stenosis

i4, correlating with an increased inflammatory activity. A score of i0 indicates an endoscopically normal neo-terminal ileum whereas the presence of a limited number of aphthous ulcers (<5) in an otherwise healthy mucosa is the basis of the i1 score (Figure 1(a)). The most controversial score is the i2 (as discussed previously, a modified subclassification was later proposed, according to the localization of the lesions), which was originally defined as the finding of more than 5 aphthous ulcers either in the neo-terminal ileum, with normal intervening mucosa or in skip areas of larger lesions. Diffuse inflammation with several aphthous ulcers of the neo-terminal ileum is the main feature of the i3 score (ulcers involve <50% of the lumen, Figure 1(d)), whereas a score of i4 score is characterized by larger and deeper ulcers involving more than 50% of the lumen or by fibrotic evolution (narrowing that does not allow examination of the neo-terminal ileum), and represents the most severe grade of recurrence (Figure 1(e)).

In the landmark study, 89 patients underwent ileocolonic resection and subsequent ileocolonoscopy, performed at 1 year after surgery, to seek for factors associated with a worse postoperative course. A higher degree of endoscopic activity in the last 10 cm of ileum correlated with the risk of clinical recurrence. Patients with normal mucosa or mild inflammation (i0, i1) had a less than 10% risk of clinical recurrence over 5 years, whereas in those with advanced inflammation the risk of symptomatic recurrence was higher, spanning from about 25% in i2a grade, 60% in i3, up to 90–100% at 5 years in i4.

The benefits of assessing postoperative endoscopic activity to guide therapeutic decisions have been first described in the POCER study, where 174 patients were randomized into 2

arms following different strategies of endoscopic monitoring [23]. In the active care arm patients had an ileocolonoscopy at 6 months, with a step-up therapeutic approach if endoscopic recurrence was diagnosed (i2 or more). In the standard care arm, a 6-month interval routine ileocolonoscopy was not performed. In the active care approach, the assessment of endoscopic activity guiding therapeutic choices, was significantly better compared to the standard strategy due to a greater reduction in postoperative endoscopic recurrence at 18 months (49% vs. 67%, respectively; p 0.03).

Clinical algorithms of CD management after ileocolic resection are based on endoscopic findings at the surgical anastomosis. According to recent international guidelines, an ileocolonoscopy is recommended at 6–12 months from the ileocolic resection, postoperative recurrence is diagnosed if a i2 or higher score is found [24,25] and treatment is managed accordingly. Since proposing extensive medical prophylaxis would probably result in an over-treatment (though very likely, not all the patients will immediately relapse), risk factors for postoperative recurrence have been investigated and identified: smoking, previous surgeries, extensive small-bowel disease, penetrating and perianal disease. Therefore, a reasonable approach is to tailor postoperative management according to the patient risk profile [26]: if just one risk factor is present, prophylactic therapy about 4 weeks after surgery with a thiopurine (with or without additional metronidazole for 3 months) should be recommended. A more aggressive strategy is advocated if the patient carries two or more risk factors, where the early choice of an anti-TNF drug can be justified by the high likelihood of disease recurrence. A proposed algorithm is

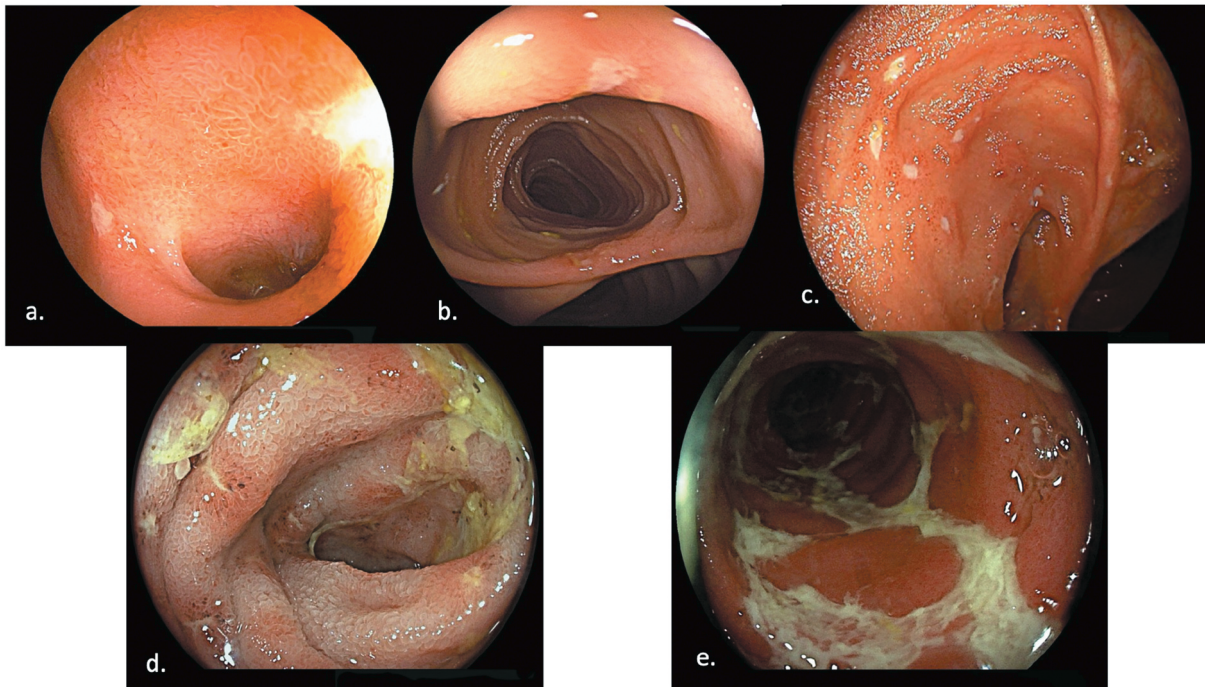


Figure 1. Rutgeerts' score; a. i1, b. i2a, c. i2b, d. i3, e. i4.

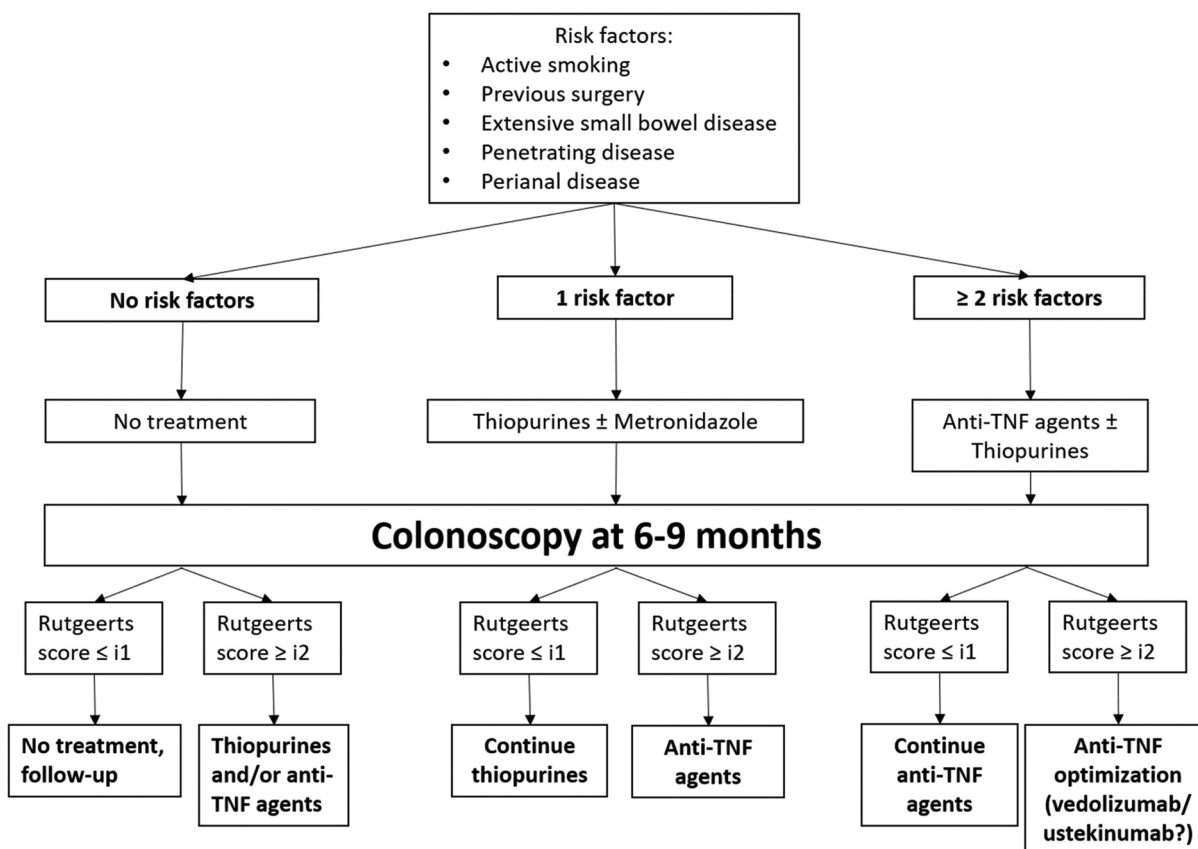


Figure 2. Proposed algorithm for postoperative management of CD. Adapted (with permission from EUREKA SCIENCE (FZC)) from; Argollo M, Kotze PG, Lamonaca L, et al. Prevention of postoperative recurrence in CD: tailoring treatment to patient profile. *Curr. Drug Targets.* 2019;20(13):1327-1338 [26].

shown below (Figure 2), demonstrating once again the central role of endoscopy in choosing the correct treatment pathway.

4.2. Rutgeerts i2 score and anastomotic lesions

Despite recommendations by major societies, some debate still remains about the significance of the i2 score, a stage in which it may also be reasonable to consider more an extended endoscopic monitoring rather than initiating treatment, especially in patients that, despite appropriate counseling about the risk of progressive (and often asymptomatic) intestinal damage, are more concerned about the adverse events of immunosuppressive therapies [24]. Considering the available evidence and in spite of common practice, a clinical validation of the Rutgeerts' score (in particular the i2 score) has never been carried out, hence the clear need for further research in this area.

Mucosal alterations of the anastomotic regions were indeed not taken into account in the original study by Rutgeerts et al. [18]. Classically, they were assimilated to i0 or i1, if not accompanied to any lesion in the pre-anastomotic region. However, there is an ongoing debate on the significance of lesions confined to the ileo-cecal anastomosis. It is not clear whether they represent an initial CD recurrence or postoperative benign modifications, most likely due to ischemic injury, which do not harbor a real risk of disease recurrence. Research has been conducted on this topic, and contradictory evidence is accumulating.

In a study by Domenech et al., for the first time a modified Rutgeerts' Score (mRS) has been proposed, dividing the grade i2 into two categories: lesions confined to the anastomosis (i2a grade) (Figure 1(b)) or >5 aphthous lesions in the neo-terminal ileum (i2b grade) (Figure 1(c)). Among the patients who only had anastomotic lesions (i2a), none of them progressed to clinical disease activity during the follow-up period, and a trend in lower risk of endoscopic progression to a higher RS grade was shown, when compared to the whole series (22% vs 40% at 3 years, p ns) [27].

More recently, a multicentric study by Bayart et al. evaluated the chance of clinical recurrence in 50 patients with mRS i2 grade (23 i2a, 27 i2b) [28]. Primary outcome was clinical recurrence (based on physician judgment, which exposed the study to a certain risk of bias), and no significant difference was found between the two groups (55% and 48% at 5 years). As secondary outcomes, no difference was observed in the rates of endoscopic recurrence, radiological recurrence, therapeutic optimization, or new surgical resection between the two groups of patients.

A similar trend was demonstrated in a larger population – 365 patients undergoing ileocecal resection (ICR) with a median follow-up time 79 months – by Riviere et al, where rates of clinical recurrence (defined as a composite of occurrence of CD-related symptoms associated to C-reactive protein >5 mg/L, endoscopic recurrence (i2a), or radiologic evidence of neo-terminal ileitis) and surgical recurrence (if the patient underwent endoscopic dilation or new surgery) were not

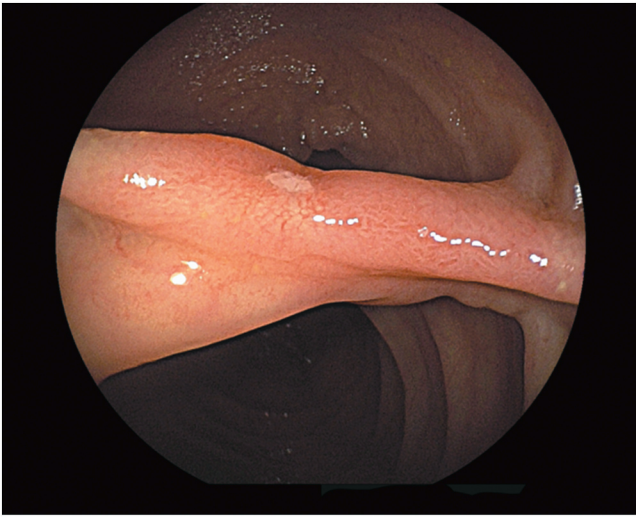


Figure 3. Anastomotic ulcer.

significantly different between 91 patients having i2a mRS and 89 patients having i2b mRS (clinical recurrence: 91.1% vs 90.7%, $p = 0.9$, at 1 year and 76.5% vs 69.4%, $p = 0.31$ at 3 years; surgical recurrence: 94.5% and 96.6%, $p = 0.45$ at 1 year and 86.2% and 94.3%, $p = 0.07$, at 3 years) [29]. These results question whether the subclassification of the i2a grade of RS into i2a and i2b plays a role in clinical decision-making.

Particular attention should be paid to anastomotic ulcers (Figure 3), as controversial results are coming from two recent studies. Hirten et al. investigated the topic in a retrospective cohort of 182 patients undergoing ICR [30]. Among them, 95 patients (52% of the total, which is a striking percentage) showed anastomotic ulcers at the first postoperative colonoscopy, and were analyzed independently from the other patients with i2a mRS grade: a composite endpoint of endoscopic recurrence (i2b or more at the next colonoscopy) or need for subsequent surgery occurred in 20 patients after a median follow-up time of 722 days. At a multivariable analysis, the presence of anastomotic ulcers was indeed associated with a higher risk of reaching the endpoint (aHR 3.64, CI 1.21–10.95; $P = 0.02$), suggesting that a more aggressive disease behavior may lie under the development of these lesions. Furthermore, according to their results, no perioperative factors (type of anastomosis, surgical complications) correlated with the development of anastomotic ulcers, thus discrediting their significance as a mere post-surgical injury.

Conflicting results were shown in another recent study [31]. In a retrospective analysis, 207 patients were followed-up for a median 3.9 years, and the rates of endoscopic progression of patients with i2a and i2b were compared to those of patients with i0 and i1 lesions. The risk of progression of i2a lesions was not significantly different from that of i0 or i1 (HR: 2.30; 95% CI, 0.80–6.66; $p = 0.12$), whereas significance was obtained when considering i2b lesions (HR: 6.22; 95% confidence interval [CI], 2.38–16.2; $p = 0.0008$). Similar results occurred when considering the risk of surgical recurrence in patients with i2a lesions (HR, 1.43; 95% CI, 0.35–5.77; $P = 0.62$) and in i2b (HR, 3.64; 95% CI, 1.10–12.1; $P = 0.034$) compared to the lower grades of RS. These results suggest that i2a lesions should

be assimilated to i1 lesions, which would justify a wait and see approach for such patients, rather than considering it a trigger to initiate or escalate therapy.

In conclusion, it must be considered that the discrimination of purely anastomotic lesions, unless they are only found on the anastomotic ring, from those affecting the neo-terminal ileum is not straightforward: the actual extension of the anastomotic area is rather unclear and liable to subjective interpretation by endoscopists, making the differentiation between i2a and i2b often very challenging. Moreover, results shown by the studies cited above should be interpreted with caution, as they share several limitations, such as the retrospective nature, the absence of uniformed postoperative medical management (who has been treated among patients graded i2 and who has not, which drugs have been administered, who received immediate postoperative prophylaxis) and the absence of a proper stratification according to the presence of risk factors for disease progression. Further studies with a prospective design avoiding such limitations are necessary to resolve this controversial issue.

4.3. Ulcerations at the anastomotic blind end

An area that is often overlooked when assessing ileocolonic anastomosis is the blind end of a side-to-side anastomosis. The occurrence of isolated ulcerations in this pocket is not uncommon; nevertheless, its significance has not been clearly deciphered (Figure 4). The reason for this common disregard is probably due to the past extensive use of end-to-end anastomosis. A recent study has helped shed light on their prevalence and nature [32]. In a retrospective review of 341 patients, the appearance of the blind loop was found to be described in only 125 of them (37%); ulcerations were reported in 43 patients (13%). Symptomatic recurrence occurred in nearly 75% of patients with ulcerations, and regardless of the postoperative medical management, endoscopic recurrence in the terminal ileum at 12 months (defined as RS i3 or i4) was found to occur in 4 out of 38 (11%); while in 5 patients (15%) additional surgery had to be performed to control symptoms. Some authors also report that, in their

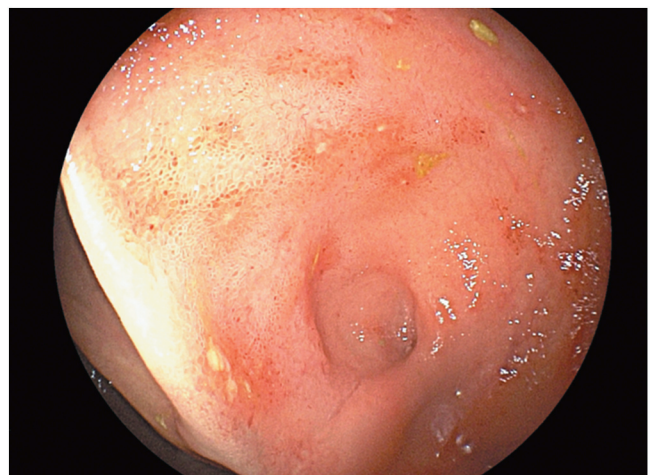


Figure 4. Ulcerations in the ileal blind end.

clinical practice, blind-end inflammation is considered to be associated with CD recurrence [33]. Whether they represent a harbinger of a future recurrence has yet to be investigated.

4.4. Video-capsule endoscopy

The diagnostic yield of VCE has been investigated in a postoperative setting: a recent meta-analysis of 5 studies showed that pooled sensitivity and specificity for the diagnosis of endoscopic recurrence were comparable to ileocolonoscopy, being 100% and 69% respectively, with an excellent AUC of 0.94 [22]. Some studies have also reported that VCE, when performed 6–12 months after surgery, can detect lesions not amenable to direct ileocolonoscopy visualization in more than 50% of postoperative patients, giving rise to some debate on their significance (since lesions lying out of the terminal ileum are not included in the Rutgeerts' classification) and possible impact on subsequent clinical management [34–36]. A recent retrospective study by Han et al compared the outcomes between low-risk patients undergoing ileocolonoscopy only (47) versus additional VCE (36), treatment was initiated if diagnosis of endoscopic recurrence was made by either method [37]: VCE found endoscopic lesions in all the patients diagnosed by colonoscopy and in 11 patients where lesions located in the proximal intestine would have been missed. At a control ileocolonoscopy at 18 months after surgery, endoscopic recurrence was significantly higher in patients who did not undergo additional VCE (43.5% vs 21.6%; $p = 0.036$), as well as clinical recurrence (21.7% vs 2.7%; $p = 0.019$), suggesting also that lesions that are out of colonoscopic sight could also be associated with a worse postoperative course.

It must be reminded that the risk for capsule retention is significant in CD, and that the use of a patency capsule or small-bowel imaging is recommended before performing VCE in order to minimize this risk [38]. Consequently, a certain number of patients will not result eligible for VCE, which eventually limits, as well as the impossibility to actively perform diagnostic or therapeutic maneuvers, its role as a first-step approach in the assessment of postoperative recurrence. A complementary use with ileocolonoscopy, especially in aggressive phenotypes of disease where intestinal damage is likely to occur throughout the small bowel, might represent a reasonable approach; yet the retrospective nature of all the studies investigating VCE in postoperative CD cannot bring firm conclusions.

4.5. Stoma monitoring in CD

It is estimated that nearly 10% of patients with CD will permanently live with a stoma, most frequently represented by an end ileostomy following a total proctocolectomy [11]. Subsequent management can be challenging: complications related to its construction, such as stricture, fistulas, prolapse, retraction or parastomal hernia, can occur in up to 30% of patients, often leading to a second surgical intervention; inflammation often occurs in the distal tract of the neo-small

intestine (NSI), and although it is often due to ischemic post-surgical damage, it can also represent an actual CD recurrence. However, recurrence rates seem to be lower than those in intestinal anastomosis. The most investigated setting is that after total proctocolectomy: Lopez et al. have shown that the rates of luminal recurrence in the NSI (defined as occurrence of symptoms combined to endoscopic or radiologic evidence of disease activity) are 8%, 16%, and 35% at 1, 2, and 5 years, respectively [39]. However, they did not specify which endoscopic lesions were defined as significant of disease recurrence. A meta-analysis showed that CD clinical recurrence in the NSI were 23.5% and 40% at 5- and 10-years [40]. Transstomal endoscopy is the procedure of choice in diagnosing endoscopic recurrence, since it is easy to perform and requires little bowel preparation. Biopsies can also be taken during examination for histological assessment. Nevertheless, no specific score grading the severity of endoscopic findings in the NSI has ever been validated. A single retrospective study has evaluated the role of applying the RS to the endoscopic findings in the NSI of an end ileostomy: patients with $RS \geq 1$ (25/73) were found to have significantly higher rates of clinical recurrence (92% vs 27%), need for endoscopic dilation (40% vs 10%), subsequent bowel surgery (68% vs 15%), disease-related hospitalizations (80% vs 23%) and escalation of CD medications (64% vs 25%) compared to those in the normal RS group [41].

5. Surgery in UC: ileo-anal pouch and endoscopic appearance

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) represents the procedure of choice for the elective surgery in UC, provided that anal sphincter function is preserved and no risk factors for postoperative complications are present. Avoiding the need for a permanent stoma, IPAA provides good quality of life and acceptable bowel functionality. Laparoscopic approach is recommended if enough expertise is available, though a meta-analysis found no differences in mortality and complications when compared to open surgery [42]. Several types of pouches can be constructed, with similar efficacy outcomes [43]:

- J-pouch
- S-pouch
- W-pouch

J pouch is the most used and endorsed approach, mainly because of its rapidity. It basically consists in a reservoir of two ileal limbs joint in a parallel fashion along their major axis. The typical endoscopic feature is the identification of blind limb and afferent limb, showing a typical double-lumen appearance (Figure 5(a)).

In the **S pouch**, three ileal loops are stapled to create a larger body than in the J pouch. An advantage may also be given by additional 2–3 cm of ileum that can be connected to the anal transition zone, with improvement in anastomotic tension and blood supply, especially in those with a short mesentery.

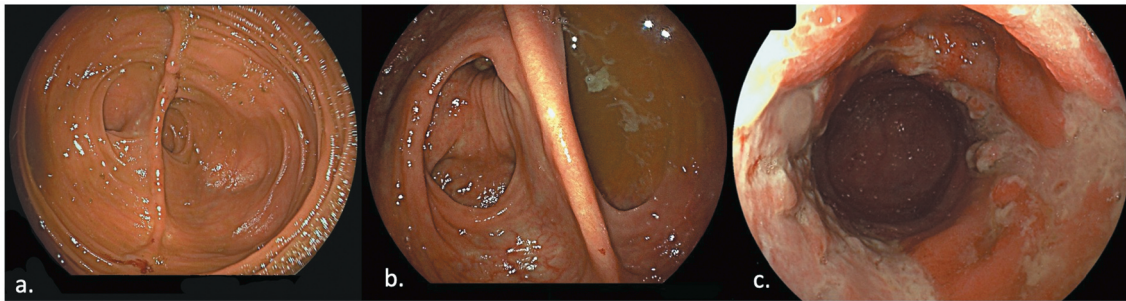


Figure 5. Pouch; a. J-pouch, b. S-pouch, c. Endoscopic appearance of severe pouchitis (endoscopic PDAI subscore = 6).

Endoscopic appearance is featured by a large single lumen, a pouch inlet area and a terminal ileum (Figure 5(b)).

W-pouch, a quadruplicated ileal reservoir, is by far a less common option.

6. Endoscopy in postoperative UC: pouchoscopy

Although surgery in UC can lead to permanent remission, a relapse can take place in the colonic remnant (the rectal cuff); moreover, postoperative course can be troublesome, as complications after IPAA are various and not rare. Endoscopy plays an important role in the postoperative management of pouch patients: if no improvement is registered after surgery, and symptoms such as increased bowel frequency, diarrhea, urgency or abdominal pain persist, pouchoscopy is indeed recommended, in order to assess the pouch and rule out complications [25].

Endoscopic evaluation of the pouch should be properly carried out. Four landmark areas must be identified and properly described in the endoscopic report: afferent limb, blind limb, pouch body and rectal cuff/anal transition zone. It is important to take biopsies from all the areas to assess histological modifications (dysplasia or inflammation), as will be discussed below. The evaluation of the pre-pouch ileum, to look for mucosal inflammation or ulcers, is also important to rule out a misdiagnosed CD.

In fact, thorough endoscopic evaluation of the pouch is a rather overlooked practical aspect, with significant variations in terms of endoscopic technique and surveillance intervals, even by clinicians of tertiary referral centers: in a recent retrospective analysis, it has been shown that a complete evaluation of the pouch, with a proper description of the four landmark areas, was reported in only 37% of the endoscopies [44].

6.1. Complications of the pouch

In the early postoperative period, surgical complications can often be diagnosed by endoscopic means: ischemia (sharp demarcation between inflamed and healthy mucosa), hemorrhage or anastomotic leaks. A variety of late pouch complications can also occur (irritable pouch syndrome, pouch sinus, afferent loop syndrome, or small-bowel obstruction, cuffitis), being of endoscopic interest mostly:

- Strictures, which can occur in about 10% of patients [45]; the diagnosis is readily made at endoscopic evaluation and it may be amenable to endoscopic dilation, shown to be an efficient and safe approach before considering surgical treatment [46].
- Fistulas, mostly developing from an underlying chronic pelvic sepsis, can originate from any part of the pouch, extending into pelvic organs (pouch-vaginal, pouch-vesical, pouch-anal) or into the skin. Pouch fistulas often require surgical treatment (seton placement in most cases, protecting ileostomy in refractory cases); endoscopic fistulotomy has recently been proposed as a surgical-sparing treatment, with resolution rates shown to be as high as 89% in a case series [47].

6.1.1. Pouchitis: an opportunity for a treat-to-target approach?

Pouchitis is the most burdensome long-term complication, occurring in up to 40% of patients in the first year after surgery [48]. Symptoms are typical of pouch dysfunction: increased stool frequency, rectal bleeding, urgency, abdominal pain. Most cases of acute pouchitis are inflammatory (primary idiopathic pouchitis): since dysbiosis is considered an important pathogenetic factor first-line recommended treatment is a 2-week course of antibiotics (ciprofloxacin, metronidazole). Pouchitis is defined as chronic if symptoms persist for more than 4 weeks, despite appropriate treatment; if no response is obtained, causes of secondary pouchitis must be excluded (*Citomegalovirus* or *Clostridium difficile* infections, nonsteroidal anti-inflammatory drugs use, ischemia, misdiagnosed CD, autoimmune or IgG4-related); if no other etiology is found, treatment should be escalated to antibiotic combination therapy, corticosteroids (oral budesonide or oral beclomethasone) up to biologics [49].

The most widely used score to stratify disease severity is the Pouchitis Disease Activity Index (PDAI) [50]: along with the clinical grading, a crucial role is played by endoscopic and histological assessment (Table 2, Figure 5(c)).

Whereas endoscopy of the pouch is widely considered a necessary diagnostic step when evaluating a patient with symptoms, some restraints to its execution in the asymptomatic patient seem to be present, with no specific recommendation issued in this regard. A 'treat-to-target' strategy is currently advocated as standard of care in IBD management,

Table 2. Pouchitis disease activity index.

Pouchitis disease activity index (PDAI)	
Clinical	
Stool frequency	0-2 (usual post-operative frequency, 1-2 stools more than baseline, >3 stools than baseline)
Rectal bleeding	0-1 (absent/rare, daily)
Urgency	0-2 (absent, occasional, usual)
Fever	0-1 (absent, T > 37.8°C)
Endoscopy	0-6 = 1 point each (oedema, granularity, friability, decreased/absent vascular pattern, exudates, ulcerations)
Histology	
Polymorphonuclear leucocyte infiltration	1-3 (1=mild, 2=moderate + crypt abscesses, 3=severe + crypt abscesses)
Ulceration (mean per LPF)	1-3 (1 =<25%, 2=25-50%, 3 =>50% ulceration)
<u>Range: 0-18; Pouchitis, total score ≥7 points; Remission, score ≤2 with endoscopic subscore ≤1</u>	

Adapted (with permission from Elsevier) from; Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis After Ileal Pouch-Anal Anastomosis: A Pouchitis Disease Activity Index. *Mayo Clin Proc.* 1994;69(5):409-415 [50].

but there is no exhaustive evidence to support the same approach in pouch patients. The possible correlation between endoscopic activity in asymptomatic patients and the risk of a later development of clinically active pouchitis has been studied by a recent retrospective study [51]. A total of 143 asymptomatic UC-IPAA patients underwent pouchoscopy and were then followed-up for a median of 3.03 years; advanced endoscopic activity, i.e. presence of ulcers and erosions, was found in a high percentage of patients (21.7%) and correlated with a higher risk of developing primary acute pouchitis (HR 2.39, 95% CI 1.23-4.67). However, no significant association with chronic pouchitis was demonstrated (HR 1.76, 95% CI 0.53-5.87). Primary sclerosing cholangitis (PSC) was the only other baseline factor associated with acute pouchitis risk (HR 3.8, 95% CI 1.34-10.74).

A management strategy could include an index endoscopy for all patients after surgery (in a similar fashion as recommended after ICR in CD), and treatment could be started if severe endoscopically active inflammation is found, even if the patient is asymptomatic. If such preliminary results were confirmed by prospective studies, a 'treat to target' approach could emerge as the standard of care in pouch patients.

6.2. Pouch surveillance

Although a definite neoplasia screening program exists for the intact colon, endoscopic surveillance of the pouch

appears to be a more controversial issue. Strikingly, a recent retrospective cohort study at five IBD referral centers showed that in a cohort of 272 patients analyzed, with a median duration of pouch follow-up of 10.5 [3.3-23.6] years, 35% had never undergone pouchoscopy for any indication and 70% had never undergone pouchoscopy with surveillance as the specific indication. In 30% of patients that underwent pouchoscopy with a surveillance intent, the majority were symptomatic. In the high-risk group, 12% patients had never undergone pouchoscopy. Two cases of adenocarcinoma were identified, occurring in the rectal cuff of low-risk patients. Curiously, patients under the care of surgeons appeared more likely to undergo surveillance, but 78% of them had an incomplete reporting, compared with 54% of patients followed by gastroenterologists (p 0.002) [44].

There are several reasons for such uncertainty regarding pouch surveillance, most probably due to the reported incidence of cancer in ileal pouch, which varies widely in the literature and is definitively lower than those observed with a colon in place. This is not surprising, since ileal mucosa is considerably less prone to malignant transformation compared to colonic mucosa; even so, the risk does not appear to be abolished. A Danish population-based study reported a rate of cancer that was 0.12% over a median follow-up of 12.9 years, arguably higher than the general population [52]. If both dysplasia and cancer are contemplated, a retrospective

cohort study showed cumulative incidences about 1%, 2%, and 5% at 5, 15, and 25 years from pouch formation, respectively [53].

In terms of location, data clearly show that most neoplasia originate from the rectal cuff/anal transition zone [44,53]: colonic residual epithelium of the rectal cuff, especially if chronic inflammation occurs, is indeed the most susceptible area to dysplastic modifications and cancerization. Over the past decades, risk factors for developing dysplasia or cancer have been identified: previous diagnosis of dysplasia or CRC [53], family history of CRC, type C ileal changes (severe pouchitis with rapid onset after pouch formation, with moderate to severe histological atrophy), long rectal cuff, and PSC [54].

Despite differences found between the available guidelines, it is currently accepted that enhanced surveillance must be carried out according to the patient's risk factors (Table 3): a yearly surveillance is generally recommended if at least one is present, particularly in patients with a history of neoplasia [55,56].

A reasonable approach should recommend a 'screening pouchoscopy' with biopsies at 1 year from surgery, to assess inflammation and histological activity of the pouch (Figure 6); an annual surveillance is then continuously recommended if severe pouchitis is endoscopically found [57]. A looser follow-up (3-yearly) can be considered if the only risk factor is PSC, less tightly associated with pouch cancer: supporting this approach, a study demonstrated that cumulative 5-year incidence of pouch neoplasia was only 5.6% in UC-IPAA patients with co-existing PSC [58]. However, pouch surveillance is debatable when no risk factors are present, as prospective data are not sufficient to support a specific strategy.

Nevertheless, though rarely, cancer has been reported in patients considered at low risk [44]. A 3- or 5-yearly pouchoscopy should be advised to patients with long standing disease (> 8–10 years) or a long rectal cuff, both conditions associated with chronic inflammation: such a loose surveillance schedule appears justified and would probably not be outweighed by any cost-effectiveness consideration.

7. Expert opinion

Endoscopic assessment, before and after surgery, is crucial for appropriate management of IBD patients. Both UC and CD resected patients need endoscopy after surgery, to define the correct therapeutic choice and, in some cases, to adopt the correct surveillance strategy. In the past, the target was limited to only clinical remission and endoscopy was considered optional; however, with the current focus on mucosal healing and the increasing attention given to histological changes, endoscopy has become indispensable to check therapeutic success.

In postoperative CD, there are still several hazy areas that should be clarified. Although widely accepted and adopted, limitations of a landmark endoscopic score such as Rutgeerts' are now undeniable (e.g. the fact that a single ulcer may preclude a patient from treatment initiation; the uncertain definition of anastomotic ulcers in the original score; the increasing use of side-to-side anastomoses, which had not been commonly introduced at the time of score development, and the consequent disregard of typical alterations as ulcerations of the ileal blind end). New postoperative endoscopic classifications are needed, with the aim to better stratify the

Table 3. Pouch surveillance strategies according to current guidelines.

Guideline	Reference	Year of publication	Risk categories	Surveillance
ASGE	[26]	2015	Highest risk: history of dysplasia or cancer	1-year surveillance recommended
			High risk: PSC, type C mucosa, refractory pouchitis	1-year surveillance may be considered
			Others	No recommendation
ECCO	[85]	2015	High risk: dysplasia/cancer at the time of surgery, PSC, type C mucosa, unremitting pouchitis	1-year surveillance
			No risk factors	No evidence
BSG	[79]	2019	High risk: dysplasia/cancer at the time of surgery, PSC, type C mucosa, unremitting pouchitis	Recommended but no evidence how frequently
			Low risk	No surveillance or 5-yearly

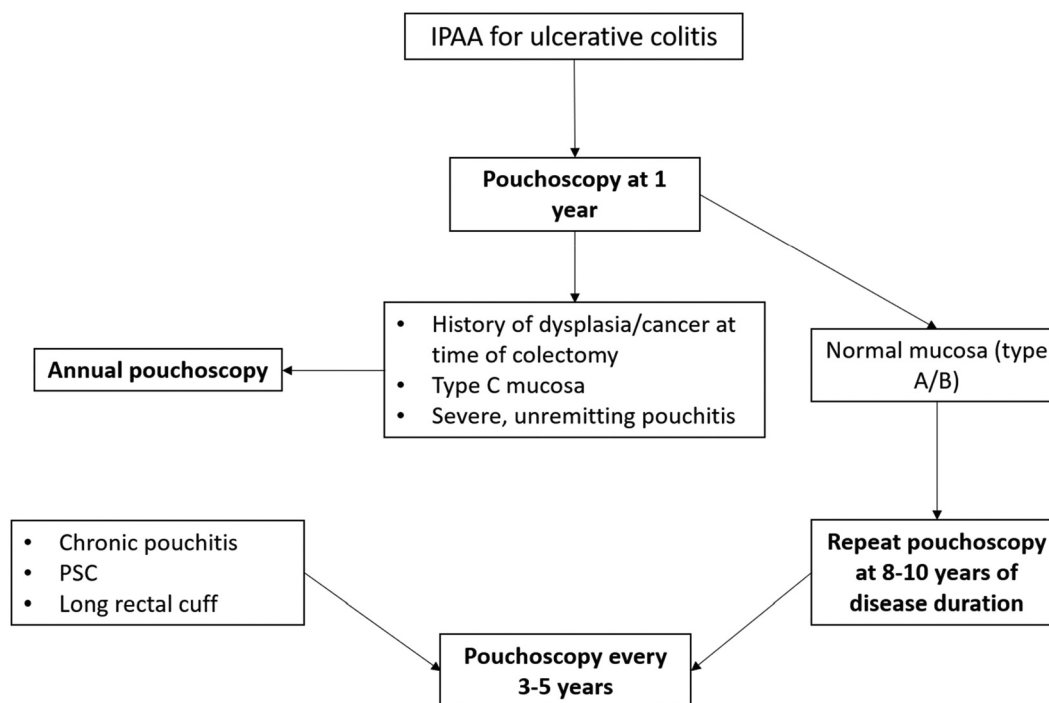


Figure 6. Proposed pouch surveillance algorithm. Adapted (with permission from John Wiley and sons) from; McLaughlin SD, Clark SK, Tekkis PP, et al. Review article: Restorative proctocolectomy, indications, management of complications and follow-up – A guide for gastroenterologists. *Aliment Pharmacol Ther* 2008;27(10):895–909 [57].

risk of recurrence and accordingly tailor medical treatment and follow-up. Increasing attention should be given to the differential evolutive potential of lesions located at the anastomosis or at the terminal ileum: with this regard, available evidence is rather heterogeneous and prospective studies are lacking. In the next years, a significant help in postoperative clinical decision-making could come from noninvasive biomarkers (fecal calprotectin) or assessment tools (BUS in particular is an extremely promising candidate, thanks to its rapidity, availability, and cost-effectiveness), which have already shown to be reliable surrogates of endoscopic activity. Such methods should not be used as alternative to endoscopy but merged in a patient-tailored approach. Cooperation between invasive and noninvasive assessment is now required more than ever, with the aim to increase diagnostic efficacy, take appropriate medical management decisions and reduce long-term complications.

As regards pouch surveillance, heterogeneity of currently available guidelines makes it still quite a controversial dilemma for the clinician, who might be tempted not to pay the required attention. Until newer and stronger evidence will not support a specific strategy, in patients with long-standing disease we recommend a cautious approach based on routine pouchoscopy (a minimally invasive, relatively well-tolerated procedure), even if no symptoms are reported.

Finally, in unoperated patients' endoscopic techniques are constantly evolving, especially in the field of surveillance. High definition images, virtual and dye chromoendoscopy, optical and digital enhancement allow for a better detection and characterization of endoscopic premalignant lesions, as well as defining mucosal inflammation and healing status. In

particular, such techniques made endoscopic images so detailed that they started to reflect histological changes (e.g., virtual-CE dysplasia detection), a scenario that just a decade ago could not have been predicted [59]. In the next future, these new techniques could be systematically applied in IBD patients after surgery, to assess early postoperative inflammation, response to treatment, or, with regard to UC, to provide enhanced pouch surveillance, allowing for early detection of inflammation and dysplasia. Ground-breaking research exploring the potential of these new endoscopic tools is warranted.

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