Endoscopic Assessment of Postoperative Recurrence in Crohn's Disease: Evolving Concepts

Partha Pal, MD, DNB, MRCP (UK), FASGE[a,*],
D. Nageshwar Reddy, MD, DM[a], Guduru Venkat Rao, MS, FRCS[b]

KEYWORDS

• Crohn's disease • Postoperative recurrence • Rutgeerts score
• Ileocolonic resection

KEY POINTS

- Postoperative endoscopic recurrence occurs in 70% to 90% patients with Crohn's disease after 1 year of ileocolonic resection in the absence prophylactic therapy.
- It is important for the gastroenterologists to know the severity grading of endoscopic recurrence based on the Rutgeerts score as it influences subsequent management.
- It is also essential for the endoscopists to have knowledge of the various postoperative anatomies (End-to-end, side to side, end-to-side) to appropriately grade endoscopic recurrence.
- It is crucial to identify various anatomic landmarks as ileal inlet/body and neo-terminal ileal lesions are related to recurrence whereas anastomotic/blind loop lesions could be related to surgery.
- Ileo-colonoscopy should be done within 6 to 12 months of resection irrespective of prophylactic therapy and risk of recurrence.
- Patients with high risk of recurrence may benefit from prophylactic treatment rather than endoscopy-driven expectant management.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease which can affect from the mouth to the anus. Uncontrolled inflammation can lead to tissue damage leading to stricturing and/or fistulizing complications in over one-third of the patients after initial 5 years of disease, and over 50% after 20 years.[1] In the absence of effective anti-fibrotic therapy, the risk of surgery based on a systematic review of population-based studies also goes hand in hand with the risk of CD complications: 33.3% at 5 years and 46.6% at 10

[a] Department of Medical Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, Telangana 500082, India; [b] Department of Surgical Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, Telangana 500082, India
* Corresponding author. 6-3-661, Somajiguda, Hyderabad, Telangana 50008, India.
E-mail address: partha1986@yahoo.com

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years.[2] Although the rates of first surgery are decreasing over the last few decades, the rate of second surgery has not changed over the last 3 decades despite introduction of advanced disease-modifying therapies.[3] Recurrent CD mimics evolution of disease from its inception with histologic followed by endoscopic recurrence preceding clinical and surgical recurrence.[4] Grading of endoscopic lesions at 1 year after resection is the best predictor of postoperative recurrence which is known as original Rutgeerts score (1990).[5] However over the last few decades, surgical techniques have evolved and the importance of the anatomic location/extent of endoscopic recurrence influencing future clinical course/management is increasingly recognized.[6] In this review, the authors discuss the evolving concepts of endoscopic recurrence in postoperative CD.

NATURAL HISTORY OF POSTOPERATIVE CROHN'S DISEASE

After curative ileocolonic resection (ICR), immunohistologic evidence of recurrence starts in the neo-terminal ileum as early as first few days of surgery (**Fig. 1**). This is evidenced by studies evaluating effects of infusion of intestinal luminal contents for more than a week into the excluded ileum after ICR which showed trans-endothelial lymphocyte recruitment and ultrastructural changes like dilation of endoplasmic reticulum and Golgi apparatus.[7] There is evidence to suggest that microscopic persistence of disease in resection margins, lymph nodes, neural plexus, and mesentery also predicted subsequent disease recurrence (see **Fig. 1**).[8,9] Pivotal study in post-operative recurrence (POR) by Rutgeerts and colleagues (1990) has shown that endoscopically visible lesion in the neo-terminal ileum at 1 year is seen in 73% patients although clinical recurrence was seen in only 20%.[5] Fecal biomarkers such as fecal calprotectin (FCP) is evaluated immediately post surgery which comes down to normal by 2 months. High FCP after 3 months of surgery indicates early POR.[10,11] Structural damage follows endoscopic recurrence leading to clinical recurrence which is seen in up to 30% to 60% after 3 to 5 years.[5,12–14] However, there is poor correlation between endoscopic recurrence and clinical symptoms (as evidenced by Crohn's disease activity index: CDAI) or biochemical markers (C-reactive protein: CRP) at 1 year after surgery.[15] Approximately a quarter of patients undergo second surgery within 5 years with up to 35% requiring

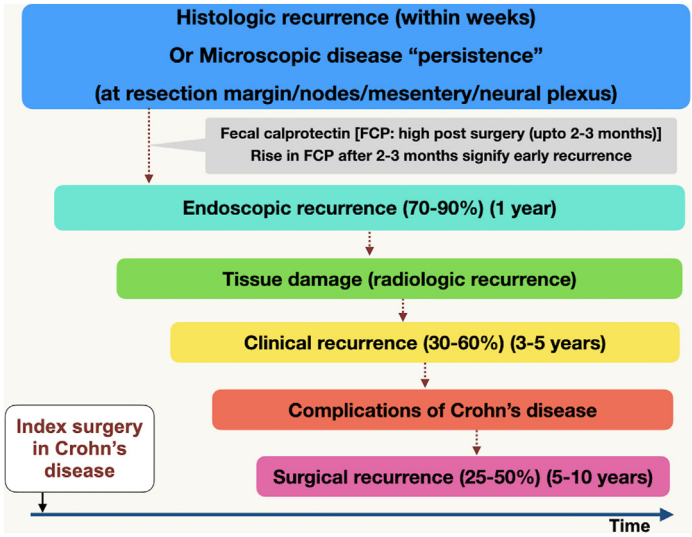

Fig. 1. Natural history of postoperative Crohn's disease. (Based on data from Refs.[5,7–14].)

second surgery by 10 years based on a systematic review. After 1980, there was a significant trend toward reduction in second surgery (45% to 33%) by 10 years.[2] On the contrary, a Swedish nationwide registry showed no significant decrease in 5 year resurgery rates in post biologic era (after 2000).[3]

HISTOLOGIC POSTOPERATIVE RECURRENCE OR MICROSCOPIC DISEASE PERSISTENCE POST SURGERY

Within a week after ICR, biopsies in the macroscopically normal neo-terminal ileum reveal evidence of histologic recurrence as evidenced by recruitment of inflammatory cells. This is driven by exposure of the mucosa of the neo-terminal ileum to fecal stream which triggers dysregulated mucosal immunity leading to inflammatory cell infiltration and differentiation of mononuclear cells to macrophages and epithelioid cells.[7,16] The significance of histologic activity in predicting POR in the absence of endoscopic and symptomatic recurrence is unknown and results are conflicting. Two conference abstracts from the same group showed contrasting results at different time points.[17,18] The most recent retrospective data showed that, histologic activity in the absence of endoscopic activity predicts future endoscopic and radiologic recurrence as compared to those with no histologic/endoscopic activity.[18]

Another important clinical application of histologic activity is to decide de-escalation of therapy in postoperative CD. It After 3 years of endoscopic remission without any histologic activity, de-escalation or discontinuation of postoperative prophylaxis can be considered. After stopping therapy, colonoscopy is repeated after 1 year to evaluate both endoscopic and histologic recurrence. Those with histologic recurrence but endoscopic remission pose clinical dilemma and the decision to continue therapy is based on individual risk of POR.[19]

There is also accumulating evidence suggesting microscopic disease persistence at the resection margins, lymph nodes, mesentery, and neural plexus which is shown to predict POR.[20] Several histologic parameters have been mentioned predicting POR including the proposal of the Crohn's primary site: granuloma, resection margin, infiltration depth, plexitis; N: nodes; M: Mesentery (CNM) classification.[8,9]

ENDOSCOPIC RECURRENCE

Endoscopic findings provide a practical target for the treating physicians to initiate, adjust, or stop therapy in postoperative CD and are also the primary focus in most of the clinical trials. The endoscopic scoring is based on the results of a prospective study by Rutgeerts and colleagues who followed 89 patients with ICR to study predictions of POR. Endoscopic activity in the neo-terminal ileum within 10 cm of anastomosis at 1 year after surgery was the strongest predictor of POR.[5,13] The Normal neo-terminal ileum was defined as i0 disease (**Fig. 2**A, B) and less than 5 aphthous ulcers in the neo-terminal ileum was defined as i1 disease (**Fig. 2**C, D). Those with i0 and i1 had less than 10% risk of clinical recurrence at 5 to 10 years. i2 was defined as more than 5 aphthous ulcers with normal intervening mucosa (**Fig. 3**A–C), skip areas of larger lesions, or lesions confined to anastomotic site (**Fig. 3**D–E). Severe lesions were i3 (diffuse aphthous ileitis/diffusely inflamed mucosa) (**Fig. 3**F) and i4 lesions (diffuse inflammation with larger lesions, nodules, and/or narrowing) (**Fig. 4**) (**Table 1**). In contrast to i0/i1, i3/i4 lesions were associated with 90% clinical recurrence at 5 to 10 years.[13]

Drawbacks of Original Rutgeerts Score

The Rutgeerts score (RS) has moderate inter-observer agreement (IOA) (kappa: 0.47) while differentiating <i2 from ≥i2, which can lead to inaccurate clinical decision-making

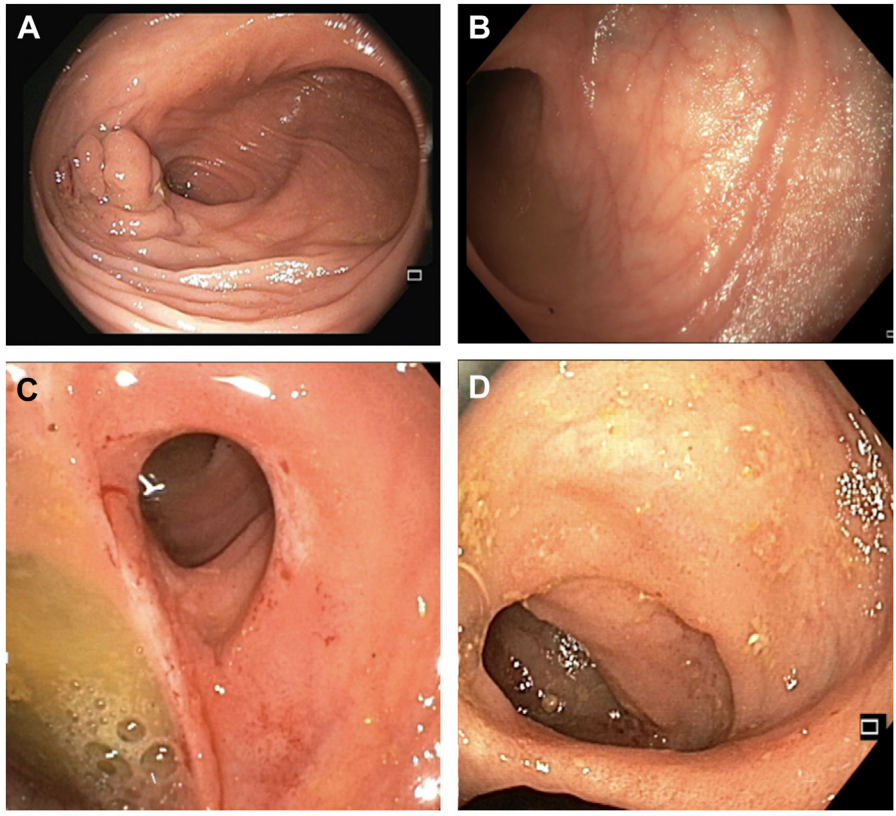

Fig. 2. Endoscopic recurrence in postoperative Crohn's disease: (*A*, *B*). Rutgeerts i0, (*A*): anastomosis, (*B*): neo-terminal ileum; (*C*, *D*). Rutgeerts i1, (*C*): anastomosis, (*D*): neo-terminal ileum: less than 5 aphthous ulcers.

in just more than 10% cases.[21] However, RS is simple and easy to use or adapt in clinical practice. Although the RS prognosticates future clinical or surgical recurrence, it is not validated to define remission or recurrence.[5,13] Nonetheless, the RS is used to define endoscopic remission (i0, i1) and endoscopic recurrence (i2–i4).

The difference between remission [i1 (<5 aphthous ulcers)] and recurrence [i2 (>5 aphthous ulcers)] could be only 2 aphthous ulcers. The importance of i1/i2 remains uncertain in case of more substantial separation between remission (i0) and relapse (i3/i4).

Moreover, i2 incorporates both anastomotic lesion and neo-terminal ileum lesions which are currently thought to be prognostically different as anastomotic lesions are thought to be related to post surgical ischemic changes.[22] However, recent studies have shown that anastomotic lesions involving more than half of the circumference could indicate future symptomatic recurrence.[23]

Modified Rutgeerts Score

Although it is acceptable that i0/i1 disease are associated with favorable outcomes as compared to i3/i4 with high risk of progression, there is ambiguity whether i2 lesions confined to anastomosis increases future risk of POR as they may represent postoperative ischemic changes. In a prospective study evaluating role of early azathioprine

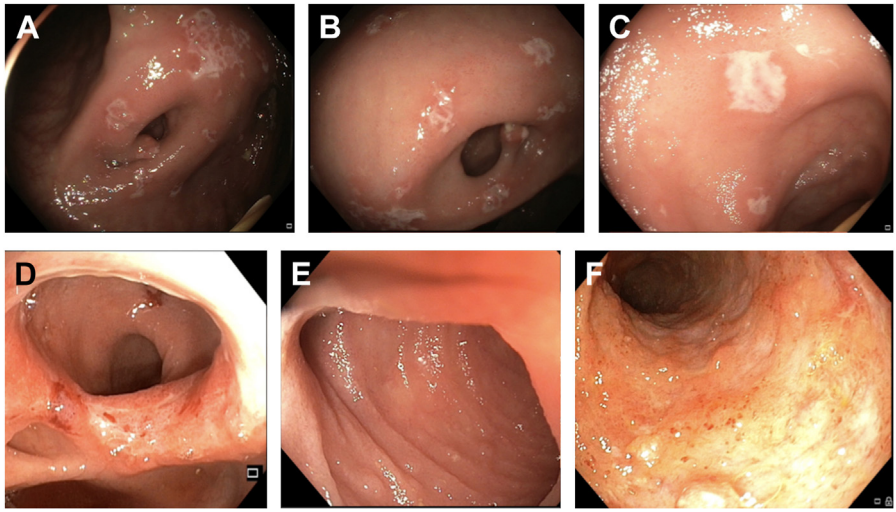

Fig. 3. Endoscopic recurrence in postoperative Crohn's disease. (*A-C*): Modified Rutgeerts i2b, (*A*, *B*): anastomosis, (*C*): neo-terminal ileum (>5 aphthous ulcers), (*D-E*). Rutgeerts i2a, (*D*). Anastomosis, (*E*). Neo-terminal ileum, (*F*). Diffuse ileitis (Rugeerts i3).

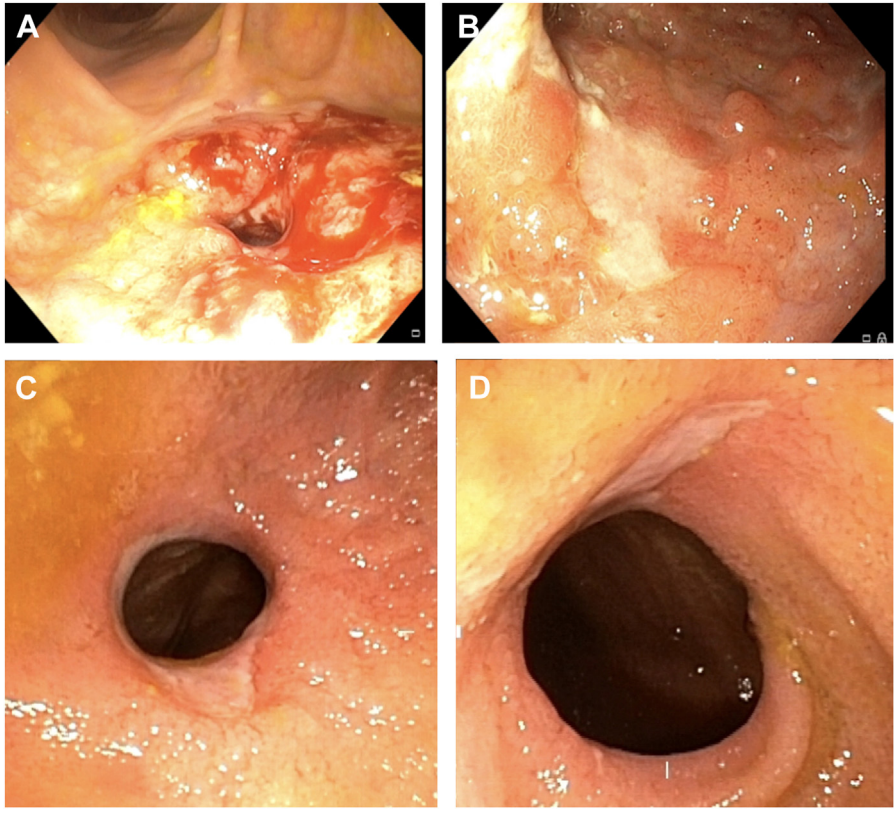

Fig. 4. Rutgeerts i4 recurrence. (*A*). Anastomotic ulcerated narrowing in ileo-transverse anastomosis, (*B*). Deep ulcers in diffusely inflamed ileum, (*C-D*). Ulcerated strictures in neo-terminal ileum.

Table 1
Endoscopic scores for assessing post-operative recurrence in Crohn's disease

Original Rutgeerts Score	Modified Rutgeerts Score	Updated Rutgeerts Score	REMIND Score		POCER Index	
			Neoterminal Ileum	Anastomosis	Anastomosis	
Scoing	Scoring	Scoring	Scoring	Scoring	Ulcer Depth	Circumference
i0 no lesions	i0 no lesions	i0 No lesions in the neoterminal ileum, anastomotic line, ileal inlet, or ileal body	i0 no lesions	A0 No lesions	0 None	None
i1 $\leq$ 5 aphthous lesions	i1 $\leq$ 5 aphthous lesions	i1 < 5 aphthous lesions in the neo-terminal ileum, ileal inlet, or ileal body with normal intervening mucosa	i1 $\leq$ 5 aphthous lesions	A1 ulcerations covering <50% of the anastomosis circumference	1 <2 mm	<25%
i2 >5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions, or lesions confined to ileocolonic anastomosis	i2a Lesions confined to the ileocolic anastomosis i2b > 5 aphthous ulcers with normal intervening mucosa or patchy areas of larger lesions	i2a Lesions confined to the ileocolic anastomotic line with or without < 5 aphthous lesions in the neo-terminal ileum, ileal inlet, or ileal body with normal intervening mucosa	i2 > 5 aphthous ulcers with normal intervening mucosa or patchy areas of larger lesions	A2 ulcerations covering >50% of the anastomosis circumference	2 <2 mm	$\geq$25%

				i2b	≥5 aphthous lesions or skip areas of larger ulcers in the neo-terminal ileum, ileal inlet, or ileal body with normal intervening mucosa with or without anastomotic line lesions						
i3	diffuse aphthous ileitis with diffusely inflamed mucosa	i3	diffuse aphthous ileitis with diffusely inflamed mucosa	i3	diffuse aphthous ileitis with diffusely inflamed mucosa in the neo-terminal ileum, ileal inlet, or ileal body	i3	> 5 aphthous lesions with diffusely inflamed mucosa in between	A3	anastomotic stenosis	3	Deep ulceration, at least 1 ulcer ≥2 mm	<25%
i4	diffuse inflammation with larger ulcers, nodules, and/or narrowing	i4	diffuse inflammation with larger ulcers, nodules, and/or narrowing	i4	diffuse inflammation with larger ulcers, nodules, and/or non-passable narrowing in the neo-terminal ileum, ileal inlet, or ileal body	i4	diffuse ileal inflammation with larger ulcers, nodules, and/or narrowing			4	Deep ulceration, at least 1 ulcer ≥2 mm	≥25%

Abbreviations: POCER, postoperative Crohn's endoscopic recurrence; REMIND, groupe de REcherche sur les Maladies INflammatoires Digestives.

to prevent POR, 40% of the patients with lesion confined to anastomosis had endoscopic progression but none of them developed clinical recurrence on follow-up. In this study, lesions confined to anastomosis were defined as i2a (see Fig. 3D–E). Rest of the lesions (>5 aphthous ulcers, larger lesions with skip areas) were defined as i2b (see Fig. 3A–C). This is the basis of modified Rutgeerts score (see Table 1).[24]

This finding was substantiated by a large (n = 207), retrospective, single center study which showed that i2a lesions had significantly lower risk of endoscopic progression (20.6% vs 55%) and re-surgery as compared to i2b lesion.[25] Modified RS has good inter-rater and intra-rater reliability.[26] Another retrospective multi-center study showed no difference in clinical recurrence or endoscopic/surgical intervention among i2a and i2b lesions.[27] In contrast, a multi-center, retrospective study showed that i2b was associated with higher risk of endoscopic progression although risk of surgical recurrence was not increased.[28] Individual patient data meta-analysis of 7 studies including 400 patients did not show any difference between i2a and i2b subcategories with regard to clinical and surgical postoperative recurrence.[29]

A more recent, large retrospective study with long-term follow-up (mean of 6.4 years) showed that modified RS lesions ≥i2b predict surgical recurrence whereas lesions ≥i1 predict clinical recurrence. Ileal lesions (i1 and i2b) but not anastomotic lesions (i2a) were associated with severe endoscopic recurrence (i2b-i4) highlighting the need for treatment escalation even in mild ileal lesions.[30]

Groupe de REcherche sur les Maladies INflammatoires Digestives (REMIND) Score

It was realized that some of the endoscopic evaluations are difficult using the modified RS especially in i1, i2a, and i2b lesions. A total of 30% of the i1 lesions (<5 aphthous ulcers) are confined to the anastomosis whereas 18% of i2b had mild ileal lesions (<5 aphthous ulcers with anastomotic ulceration).[31] Ileal i1 lesions were found to have m = higher clinical recurrence as compared to i0 lesions as shown in a prospective multi-center study (n = 225) by groupe de REcherche sur les Maladies INflammatoires Digestives (REMIND) study group (see Table 1). On the other hand, severe anastomotic lesions (involving >50% of circumference) had only a trend toward clinical recurrence with higher incidence of obstructive symptoms. Hence, the REMIND study group proposed evaluation of the anastomotic and ileal lesions separately. Anastomosis was scored as A0 (no lesions) (Fig. 5A), A1 (<50% circumference involved) (Fig. 5B, C), A2 (>50% circumference involved) (Fig. 5D, E), and A3 (stenosis) (Fig. 5F). Ileal lesions were defined as i0 (no lesions) (see Fig. 2B), i1 (<5 aphthous ulcers) (see Fig. 2D), i2 (>5 aphthous ulcers with skip areas or patchy areas of larger lesions) (see Fig. 3C), i3 (>5 aphthae with diffuse ileitis) (see Fig. 3F), and i4 (diffuse ileitis with larger ulcers [see Fig. 4A, B], nodules and/or narrowing [see Fig. 4C, D]). Clinical recurrence was significantly higher in all ileal lesions (i1–i4) compared to no ill lesions (i0). High-grade anastomotic lesions (A2/A3) developed higher rate of obstructive symptoms on follow-up independent of ileal lesions.[31]

Pivotal Postoperative Crohn's Endoscopic Recurrence Index

Pivotal postoperative Crohn's endoscopic recurrence (POCER) index developed from landmark POCER study evaluated anastomotic lesions based on depth and circumferential involvement (0- no ulcers, 1- superficial <2 mm ulcers, 2- superficial <2 mm ulcers with ≥25% circumference involvement, 3- deep ulceration, at least one ≥ 2 mm, <25% circumference involved, 4- deep ulceration, at least one ≥ 2 mm, ≥ 25% circumference involved) (see Table 1).[32,33] POCER index ≥2 at 6 months after colonoscopy was associated with 18 months risk of endoscopic recurrence but not the Rutgeerts score. This

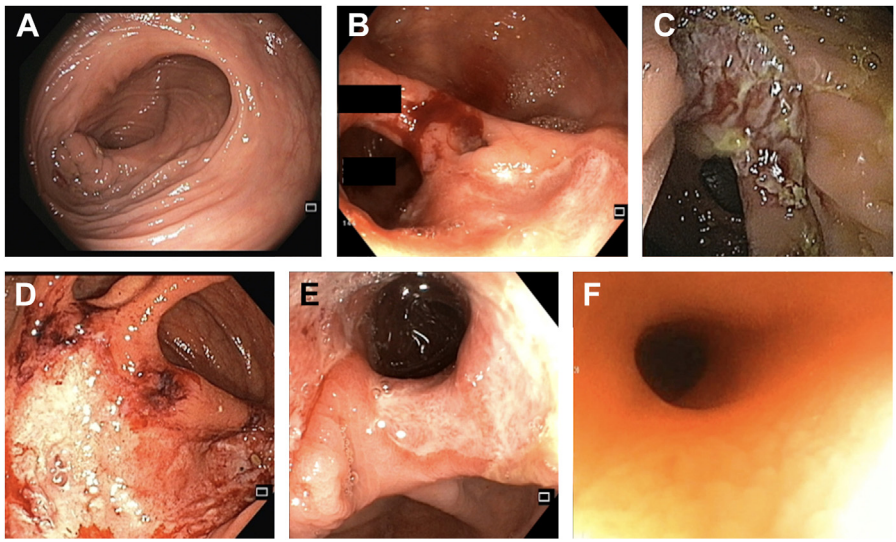

Fig. 5. Grading anastomotic recurrence according to REMIND score. (*A*). REMIND A0: No anastomotic lesions, (*B*, *C*). REMIND A1: Anastomotic ulcerations involving less than 50% of circumference, (*D*, *E*). REMIND A2: Anastomotic ulcerations involving greater than 50% of circumference, (*F*). A3: anastomotic stenosis.

score may help to risk stratify anastomotic lesions who need treatment escalation; however, it needs prospective validation.[33]

Caveats of Endoscopic Scoring in Anastomotic Lesions

In contrast to earlier studies, a retrospective study showed that anastomotic lesions are common (52%) and are persistent on follow-up colonoscopy (80%).[23,25] They were associated with more than 3-fold hazard of clinical recurrence.[23]

Understanding the wound healing after hand sewn or stapled anastomosis is important to understand anastomotic lesions. Longitudinal staple lines are usually causing serosa to serosa approximation and mucosa needs to re-epithelize over the staple line (Fig. 6A, B). On the other hand, cross-stapled lines are everted causing mucosa to mucosa approximation leading to primary wound healing (Fig. 6C). Hence, majority of inverted staple lines heal with ulceration in both CD (77%) and non-CD pathology (eg, colorectal cancer) (68%). Ulceration over everted staple line is uncommon (1.4% CD

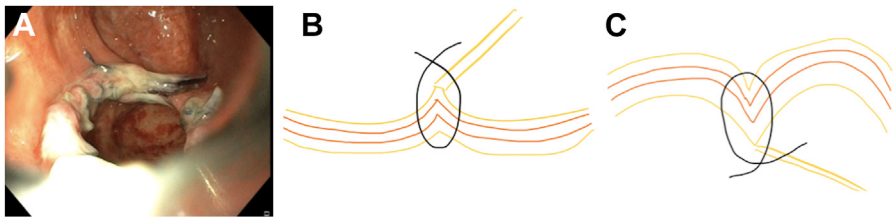

Fig. 6. Inverted and everted anastomosis. (*A*, *B*). Inverted anastomosis, (*A*): anastomotic site: suture material noted in inverted hand sewn anastomosis, (*B*). Schematic diagram: serosa to serosa approximation, mucosa needs to re-epithelize. (*C*). Schematic diagram: everted anastomosis: mucosa to mucosa approximation: primary wound healing.

and 0% non-CD). Hence, it was concluded that healing over invited staple line may interfere with endoscopic scoring in postoperative CD.[22]

A recent retrospective study showed that a neutrophil to lymphocyte ratio (NLR) greater than 2.45 in isolated anastomotic lesion predicted clinical recurrence.[34]

Technical Aspects of Endoscopic Scoring in the Anastomosis

There are basically 3 types of anastomosis after ileocolic resection: A. End-to-end anastomosis (conventional and Kono S), B. Side-to-side anastomosis (iso- or anti-peristaltic), C. Side-to-end or end-to-side anastomosis.

A. End-to-end anastomosis (conventional and Kono S)

End-to-end anastomosis is usually straight and scope can be passed from the colon to the neo-terminal ileum without manipulation. End-to-end anastomosis is usually hand sewn rather than stapled (**Fig. 7**A, B).

As mesentery is thought to promote recurrence, anti-mesenteric end-to-end anastomosis excluding mesentery (Kono-S anastomosis) is shown to prevent postoperative recurrence as compared to side-to-side anastomosis in a randomized controlled trial (RCT).[35]

Side-to-side (iso and anti-peristaltic) anastomosis

Side-to-side anastomosis results in wide luminal diameter with blind end of both the colon and ileum. The knowledge of anatomy is important as the blind end could be mistaken for the neo-terminal ileum (**Fig. 7**C, D). The original RS was based on

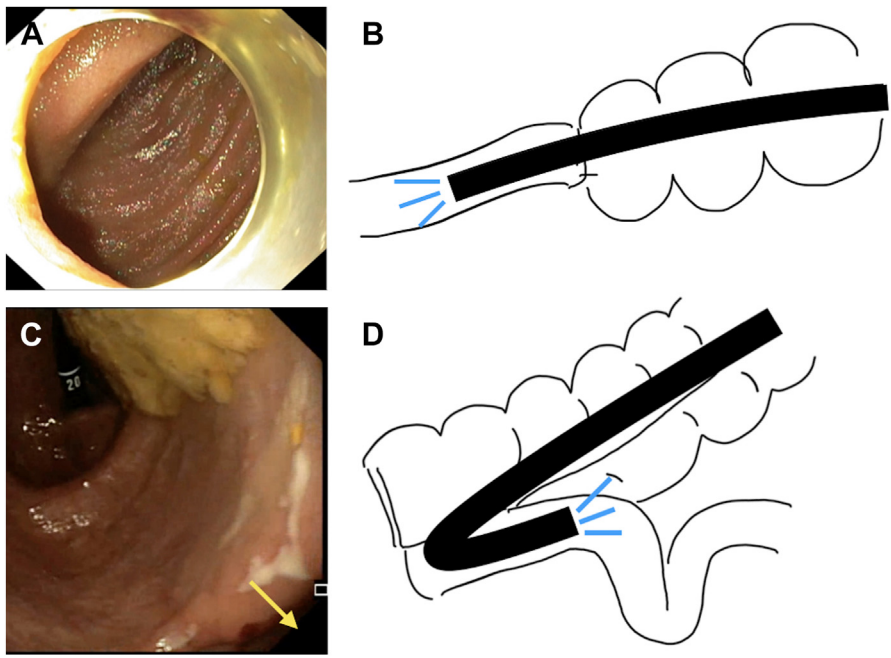

Fig. 7. End-to-end (*A*, *B*) and side-to-side anti-peristaltic anastomosis (*C*, *D*). (*A*). End-to-end anastomosis, colonoscope directly entering neo-terminal ileum, (*B*). Schematic diagram of End-to-end anastomosis. (*C*). Side-to-side anti-peristaltic anastomosis, colonoscope retroversion required to enter neo-terminal ileum (yellow *arrow*), (*D*). Schematic diagram of Side-to-side anti-peristaltic anastomosis.

endoscopy findings in patients with sutured, end-to-end anastomosis. Recently, wide lumen, stapled, side-to-side, or side-to-end anastomosis are more popular as they prevent fecal stasis/bacterial overgrowth with preservation of vascularity.[6] An RCT trial failed to demonstrate the benefit of side-to-side over end-to-end anastomosis in reducing recurrence possibly because the critical diameter at the inlet of the anastomosis is independent of the length of anastomotic staple line.[36] Another retrospective study showed that wide lumen side-to-side anastomosis led to lower endoscopic/surgical re-intervention than end-to end anastomosis on long-term follow-up although did not influence endoscopic/clinical recurrence.[37]

In side-to-side anti peristaltic anastomosis, scope should be retroverted to enter the terminal ileum (see **Fig. 7**C, D). On the other hand, in side-to-side iso-peristaltic anastomosis, scope can be introduced into the ileum with mild manipulation (**Fig. 8**C).

Side-to-end or end-to-side anastomosis

In end-to-side ileocolonic anastomosis, the terminal ileum is attached perpendicularly to the colon resulting in blind end of the colon (**Fig. 8**A, B). Less commonly side-to-end ileocolonic anastomosis is done by anastomosing the colon perpendicularly to the ileum resulting in blind end of the ileum (see **Fig. 8**D).

New Terminology Based on Anatomic Location of Endoscopic Involvement (Updated Rutgeerts Score)

The endoscopic recurrence can take into account 6 different anatomic locations in end-to-side and side-to-end anastomosis based on an expert recommendation taking

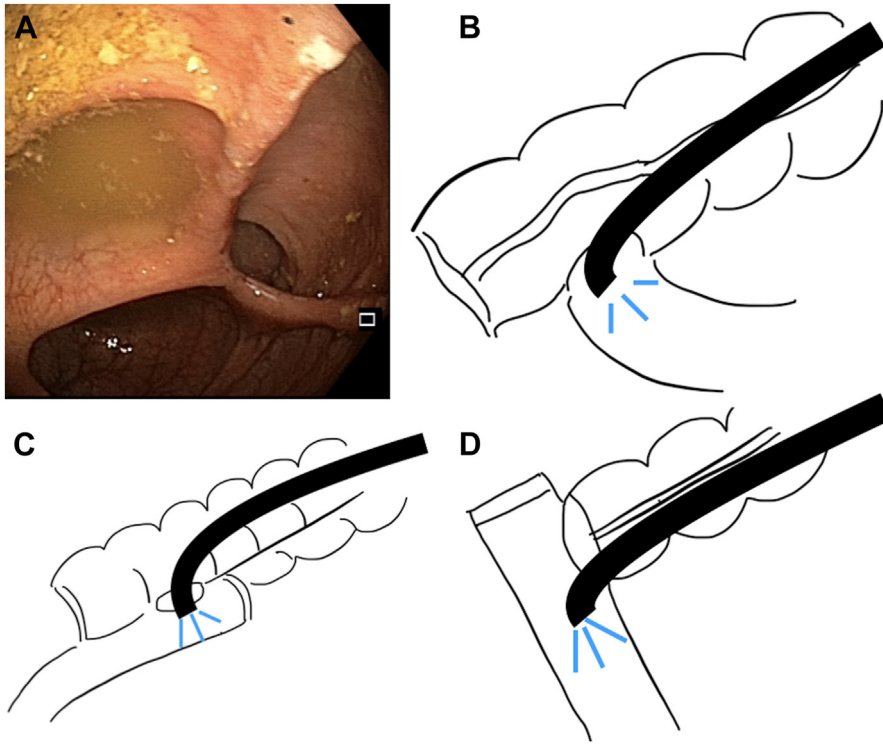

Fig. 8. End-to-side ileocolonic anastomosis (*A*, *B*), side-to-side iso-peristaltic anastomosis (*C*), and side-to-end ileocolonic anastomosis (*D*).

into account newer surgical techniques (Fig. 9).[6] "Anastomotic line" should be restricted to 1 cm above and below hand sewn or stapled anastomosis. The site of entry of the neo-terminal ileum represents the "ileal inlet" which is the critical site for postoperative recurrence. "Ileal body" is the area between the "anastomotic line" and the "ileal inlet." The part of the ileum opposite the inlet on the other side of the anastomosis is known as "ileal blind end." "Colonic blind end" can be seen in end-to-side and side-to-side ileocolonic anastomosis.[6] This classification can help to differentiate i2a and i2b lesions. Lesions confined to the anastomosis should be considered as i2a and can be considered as a result of surgical procedure. More than 5 aphthous ulcers with skip areas in the neo-terminal ileum, ileal inlet, and ileal body should be considered as i2b. Lesions in the ileal blind loop should not be considered part of the updated RS as they are not located at a critical place although they could be related to the surgical procedure.[6]

Inter-Observer Agreement of Different Endoscopic Scores

IOA for modified RS was substantial [kappa(k)- 0.67] while 71 videos were analyzed by 16 endoscopists. The IOA in updated RS was also substantial (k: 0.61–0.83, 0.61-ileal body/neo-terminal ileum, 0.63-ileal inlet, 0.68-ileal blind loop, and 0.83-colonic blind loop). For REMIND score, IOA was substantial for the neo-terminal ileum (0.73) but only moderate for anastomotic lesions (k-0.46).[38] Further improvement in agreement is warranted as therapeutic decisions are based on endoscopic scoring.

Endoscopic Surveillance

Timing

The pivotal postoperative Crohn's endoscopic recurrence (POCER) randomized controlled, double blind trial involving 17 centers across Australia and New Zealand showed that ileo-colonoscopy at 6 months post-surgery and adjusting treatment in case of endoscopic recurrence (≥i2) led to significantly lower endoscopic recurrence

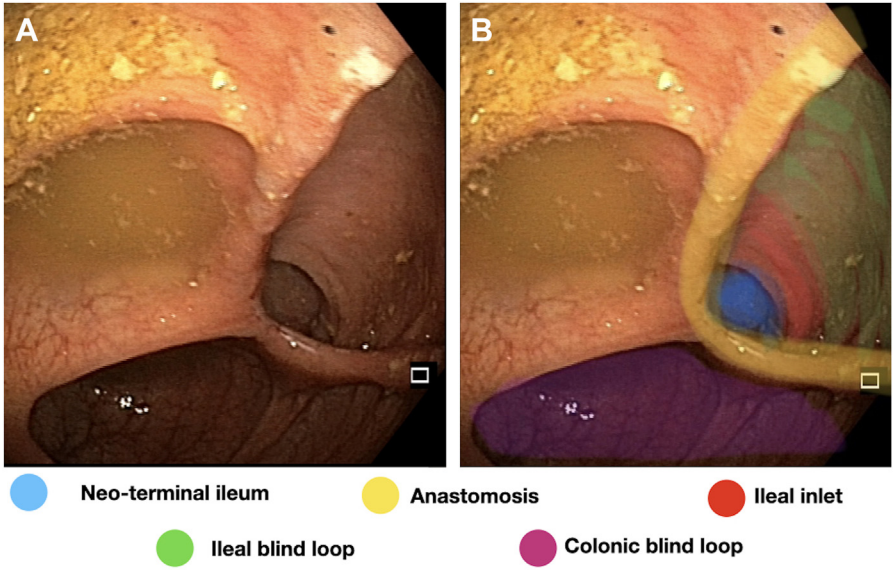

Fig. 9. End-to-side ileocolonic anastomosis (*A*) and anatomic locations in updated Rutgeerts score (*B*).

(49%) at 18 months when compared to the standard arm (67%) who underwent ileo-colonoscopy directly at 18 months. All patients received postoperative metronidazole for 3 months and high-risk patients (any 1 of active smoking, penetrating/B3 disease, previous resection) received azathioprine or adalimumab (previous thiopurine failure or intolerance).[32] The results of this study dictated current recommendations of early ileo-colonoscopy at 6 months irrespective of the risk of postoperative recurrence.[39]

A recent prospective observational study showed that ileo-colonoscopy within 1 month of surgery is safe and anastomotic scattered ulcers on 1 month ileo-colonoscopy predicted 12 month POR.[40] This suggests that future studies may focus on even earlier first colonoscopy to detect endoscopic recurrence.

Timing of repeat ileo-colonoscopy for those who have no endoscopic recurrence at 6 to 12 months ileo-colonoscopy should be based on standard surveillance guidelines (1–3 years).[19] More frequent ileo-colonoscopy may be required in those who chose to observe after mild endoscopic recurrence rather than starting treatment.[39] Ileo-colonoscopy for assessing mucosal healing after starting treatment can be done based on severity of initial recurrence at 6 to 12 months after initiating or adjusting therapy (**Fig. 10**).

Prophylactic versus endoscopy-driven treatment of post-operative recurrence

The risk of postoperative recurrence in high-risk group (age <30 years, active smoker, ≥2 prior surgeries for penetrating disease) at 18 months is very high (endoscopic recurrence 80%, clinical recurrence 50%) and hence may benefit from prophylactic pharmacologic prophylaxis with anti-tumor necrosis factor (anti-TNF) agents and/or azathioprine started within 8 weeks of surgery. On the other hand, for those with low clinical risk of POR, [age greater than 50 years, non-smoker, first surgery for

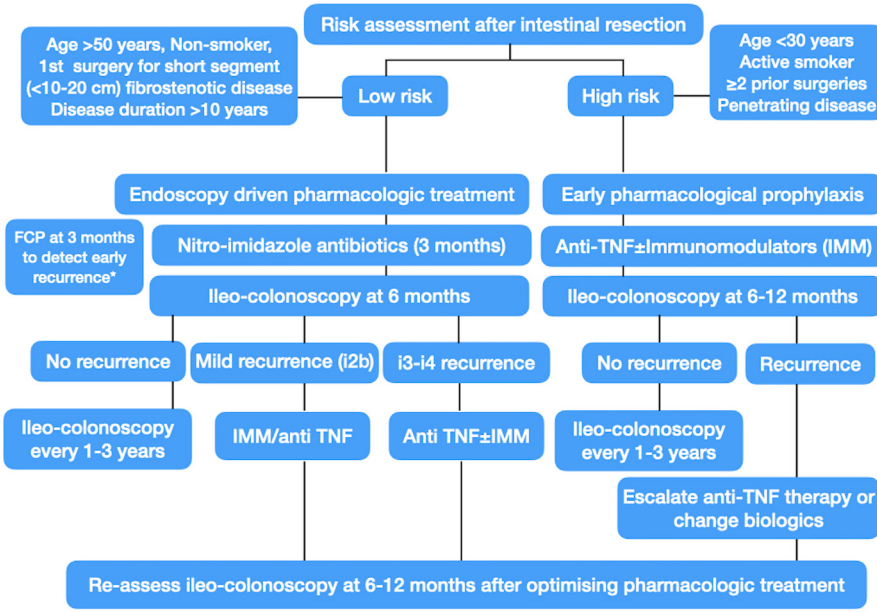

Fig. 10. Endoscopy-guided management strategy in postoperative Crohn's disease, TNF: tumor necrosis factor, FCP: fecal calprotectin, *in asymptomatic, low-risk patients and those who are on postoperative prophylaxis, FCP less than 50μg/g may obviate the need for a routine ileo-colonoscopy at 6 months after surgery. (*Data from* Refs.[5,10,11,13,19,32,39,41,48].)

short-segment (<10–20 cm) fibrostenotic disease, disease duration greater than 10 years] the decision for prophylactic versus endoscopy-driven treatment (at 6 months) could be individualized given relatively lower risk of POR at 18 months (clinical 20%, endoscopic 30%). Irrespective of prophylactic treatment, patients should undergo ileo-colonoscopy at 6 to 12 months and treatment adjusted based on endoscopic findings. For asymptomatic endoscopic recurrence, treatment should be started rather than continued monitoring especially in those with >i2 disease. i2 disease can be monitored off therapy; however, the patient should accept the risk of serial colonoscopy and disease progression. For asymptomatic recurrence on thiopurine therapy, treatment should be escalated to anti-TNF or combination therapy.[39]

A retrospective, multi-centric, European study comparing prophylactic versus endoscopy-driven treatment (PORCSE Study) showed that after first ICR, prophylactic treatment has lower rate of endoscopic POR over endoscopy-driven expectant therapy. Clinical recurrence was also lower but not statistically significant in prophylactic treatment arm whereas there was a trend toward lower surgical recurrence with proactive treatment.[41]

Endoscopic Scores Capturing Colonic Disease Recurrence

The afore-mentioned endoscopic scores in postoperative CD only take into account anastomotic or neo-terminal ileal disease recurrence. However, colonic disease recurrence is not captured in these scores. Post-hoc analysis of clinical trial data from Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence (PREVENT) study have shown that simple endoscopic score in Crohn's disease (SES-CD) and modified multiplied SES-CD (MM-SES-CD) can predict POR similar to RS and can capture colonic disease recurrence as well.[42]

Role of Capsule Endoscopy in Postoperative Recurrence

Capsule endoscopy (CE) can help identify residual lesions after surgery in CD as evidenced by studies in which CE was done within 3 months of surgery. Clinical recurrence was higher in those with high third tertile score signifying distal small bowel residual lesions predict clinical recurrence.[43] Similarly in another prospective study, CE was done within 3 months and repeated thereafter to identify residual and recurrent lesions which helped identify recurrence in pre-clinical stage. Treatment adjustments based on CE had better clinical outcomes (lower hospitalization or surgery).[44] Another prospective study evaluated modified Rutgeerts score based on panintestinal CE using colon capsule endoscopy at 4 to 8 weeks and 4 to 8 months after surgery. At 4 to 8 weeks, 19% had endoscopic recurrence whereas at 4 to 8 months, 50% had endoscopic recurrence based on CE as compared to 33% with ileocolonoscopy (at 4–8 months).[45] Inspite of the exciting results and ease of use, the barriers of using capsule endoscopy (CE) instead of ileo-colonoscopy in postoperative settings are lower accuracy in neo-terminal the ileum, inability to perform CE in those with positive patency capsule testing, risk of retention, poor correlation VCE activity, and clinical recurrence.[46]

BIOMARKER RECURRENCE

Fecal calprotectin (FCP) is one of the most sensitive stool biomarker to assess early POR. Initial study by Sorrentino and colleagues showed that although FCP can be high up to 2 months post surgery due to surgical trauma, FCP progressively decreases after surgery in those with no recurrence and after starting infliximab in responders

being persistently high in non-responders.[10] After that, several studies assessed the role of FCP in assessing postoperative recurrence and a systematic review showed that the cutoff of 150 μg/g has the highest accuracy (pooled sensitivity 70% and specificity 69%) to detect POR. Serial FCP evaluation may help to defer colonoscopy in up to 70% of postoperative CD patients.[47] Recent guidelines from American Gastroenterology Association recommend that in asymptomatic, low-risk patients and those who are on postoperative prophylaxis, FCP less than 50 μg/g may obviate the need for a routine ileo-colonoscopy in first year after surgery. However, those with high-risk of POR and who are not on prophylaxis should undergo ileo-colonoscopy.[48]

RADIOLOGIC RECURRENCE

Cross-Sectional Imaging

Radiological evidence of recurrence may precede of follow endoscopic evidence of POR and may signify tissue damage (see **Fig. 1**). This is because of the fact that radiologic techniques can evaluate the intramural and mesenteric disease as compared to only mucosal disease in endoscopy. Cross-sectional imaging is highly sensitive (89%) but has low specificity (32%) in identifying those with endoscopic recurrence. This is mainly due to the ability to evaluate transmural disease activity with detection of isolated proximal small bowel involvement contributing in a small subset (3.3%) of patients. Radiologic disease activity in the absence of endoscopic activity predicted subsequent endoscopic and surgical recurrence.[49]

Several imaging factors in MRI correlated with endoscopic activity. The MRI in Crohn's Disease to Predict Postoperative Recurrence (MONITOR) index includes 7 such factors: bowel wall thickness/length/contrast enhancement, increase in T2 and diffusion-weighted signal, edema, and ulcers (all items weight 1 except ulcers weighing 2.5). In validation cohort of the index, sensitivity and specificity were 87% and 75%, respectively.[50]

Intestinal Ultrasound

Intestinal ultrasound (IUS) is emerging as a non-invasive tool to monitor inflammatory bowel disease (IBD). A recent prospective, multi-center Italian study in which colonoscopy and IUS were done within 1 year of surgery has shown that bowel wall thickness (BWT)$\geq$ 3 mm plus FCP greater than 50 μg/g could identify 75% patients with endoscopic recurrence with false-positive results in 5%. Presence of mesenteric lymph node could identify 56% of endoscopic recurrence. In contrast, BWT less than 3 mm plus FCP less than 50 μg/g could identify 74% patients without endoscopic recurrence with false-negative results in 4.5%.[51]

FCP, BWT, and mesenteric lymph node signify mucosal, intramural, and mesenteric disease highlighting that IUS along with FCP is useful in evaluating transmural nature of the disease akin to cross-sectional imaging.

CLINICAL RECURRENCE

Clinical recurrence is defined by Crohn's disease activity index (CDAI), Harvey Bradshaw Index (HBI), and patient-reported outcomes. CDAI greater than 150 is validated for defining postoperative recurrence which has a sensitivity and specificity of 70% and 81%, respectively.[52,53] However, there is gross discrepancy between symptoms and endoscopic recurrence as endoscopic recurrence could be clinically silent and symptoms could be due to surgical factors (bile salt diarrhea, dysmotility, bacterial overgrowth) rather than recurrence.[19,54] Clinical recurrence confirmed by endoscopic recurrence denotes tissue damage which may not be reversible.

SURGICAL RECURRENCE

Systematic review suggests that the rate of second intestinal resection is 28.7% (24.2% within first 5 years). The 10-year risk of second surgery has decreased over time after 1980 (45% to 33%).[2] A Swedish population-based study has showed that the rate of primary but not second surgery has deceased in the post-biologic era.[3] Another study has shown that ileo-colonoscopy in the first year after surgery reduced the risk of surgical recurrence significantly since early 2000.[55] This highlights that the main driver for lower surgical recurrence could be early detection before irreversible tissue destruction rather than only the use of biologics.

SUMMARY

Early ileo-colonoscopy within 6 to 12 months of ileocolonic resection is essential irrespective of the peri-operative risk stratification and prophylactic treatment to identify endoscopic predictors of clinical/surgical recurrence and adjust treatment to improve outcomes. The original Rutgeerts score is a simple score originally developed to predict future clinical course after first intestinal resection. It is important to grade endoscopic lesions in the neo-terminal ileum and anastomosis separately as mild ileal lesions are predictive of clinical recurrence whereas only more severe anastomotic lesions predict recurrence. With the advent of newer surgical techniques, it is important to recognize several anatomic landmarks to distinguish relevant areas predicting recurrence (neo-terminal ileum, ileal body, ileal inlet) as compared to those related to surgical technique (anastomosis/blind loops).

CLINICS CARE POINTS

- After ileocolonic resection, ileo-colonoscopy should be performed early within 6 to 12 months of resection to detect endoscopic recurrence.
- Endoscopic recurrence should be graded according to original, modified, or updated Rutgeerts score.
- Anastomotic lesions should be described separately and scores such as REMIND score and POCER index can be used to grade anastomotic lesions.
- Review the surgical history before performing ileo-colonoscopy to understand the anatomic landmarks in various surgical techniques.
- Describe the endoscopic lesions based on 6 anatomic landmarks namely anastomosis, ileal inlet, ileal body, neo-terminal ileum, ileal and colonic blind loop.
- Timing of repeat ileo-colonoscopy for those in endoscopic remission at 6 to 12 months should be based on standard surveillance guidelines (1–3 years).

DISCLOSURE

None of the authors have any commercial or financial conflicts of interest and any funding sources to disclose. The figures are the authors' original work and has not been used elsewhere.

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