

## REVIEW ARTICLE

Essential Updates 2016/2017: Colorectal (benign)

# Recent trends (2016-2017) in the treatment of inflammatory bowel disease

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Email: masaki@ks.kyorin-u.ac.jp**Abstract**

Prevalence of inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease has dramatically increased in Asian countries in the last three decades. In this period, many new medical therapies were introduced for the treatment of IBD, such as immunosuppressants, anti-tumor necrosis factor agents, leukocyte apheresis, anti-integrin antibody, and so on, which have contributed to induce remission and to reduce complications in IBD. As for surgical techniques for Crohn's disease, a stapled functional end-to-end anastomosis and conventional end-to-end anastomosis have similar perianastomotic recurrence rate and reoperation rate. Prospective randomized controlled studies which compare Kono-S anastomosis and stapled side-to-side anastomosis are ongoing. Variant two-stage ileal pouch anal anastomosis (IPAA) and transanal IPAA are new concepts for surgical treatment of ulcerative colitis. Various endoscopic procedures, such as balloon dilation for stenosis or stricture, endoscopic fistulotomy, injection of filling agents, and clipping for fistulas or perforations will be new options in the treatment of Crohn's disease. Adverse effects of preoperative treatments on postoperative complications should also be taken into account to improve surgical outcomes in IBD patients.

**KEYWORDS**

Crohn's disease, endoscopic procedure, Kono-S procedure, pouch failure, ulcerative colitis

## 1 | INTRODUCTION

The prevalence of inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease has dramatically increased in Asian countries in the last three decades.<sup>1</sup> In this period, many new medical therapies were introduced for the treatment of IBD, such as immunosuppressants, anti-tumor necrosis factor (TNF) agents, leukocyte apheresis, anti-integrin antibody, and so on.<sup>2</sup>

Therefore, it can be speculated that the role of surgical treatment for IBD might have changed as compared with that before 2000s.

In this bi-annual review article, recent improvements in IBD treatment will be reviewed. A literature search was conducted on PubMed and the Cochrane Library to identify papers mainly published in the last 2 years (2015-2017) that focused on surgical and endoscopic approaches for IBD. To facilitate understanding of the

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background of each procedure, papers published before 2015 were also reviewed when applicable.

## 2 | CROHN'S DISEASE

Crohn's disease has long been recognized as a formidable disease with high recurrence rates even after surgical treatment is attempted. It is well known that anastomotic recurrence occurs endoscopically as early as several months after bowel resection and anastomosis, followed by symptomatic recurrence; reoperation is then often required.<sup>3</sup> Anastomotic recurrence, bowel perforation or abscess formation are not avoidable in most cases 5 or 10 years after the initial operation. Rates of reoperation are approximately 25% at 5 years, and approximately 40% at 10 years.<sup>4</sup> Patients' quality of life is greatly worsened, which affects patients' education, working, or marriage status.

With the introduction of anti-TNF agents in the early first decade of the 2000s, several studies showed that postoperative use of anti-TNF agents could significantly reduce endoscopic recurrence rates,<sup>5-7</sup> and clinical recurrence rates in some studies.<sup>5</sup> However, a recent prospective randomized controlled study showed that clinical recurrence rates were not different between the infliximab group and the placebo group (12.9% vs 20% before or at week 76,  $P = .097$ ; 17.7% vs 25.3% before or at week 104,  $P = .098$ ).<sup>6</sup> Therefore, the implication of anti-TNF agents in reducing clinical recurrence and surgical recurrence has not yet been determined.

### 2.1 | Surgical treatment for Crohn's disease

A number of retrospective studies reported that a stapled functional end-to-end anastomosis was associated with a lower recurrence rate compared with other types of anastomosis.<sup>8</sup> Simillis et al<sup>9</sup> conducted a meta-analysis of eight studies reported up to 2005 (two prospective, randomized, controlled trials; one non-randomized, prospective; five non-randomized, retrospective studies), and they concluded that there was no significant difference in perianastomotic recurrence and reoperation needed between conventional end-to-end anastomosis and other anastomotic techniques. This finding was confirmed by a multicenter, randomized, controlled trial reported in 2009.<sup>10</sup>

However, the main concern to be considered is that the bowel stump is involved within the anastomosis whether conventional end-to-end anastomosis or other anastomotic techniques are used.

To reduce the risk of anastomotic recurrence of Crohn's disease, Kono developed a novel anastomotic procedure (Kono-S procedure) in 2003.<sup>11</sup> The resection is accomplished by transecting the bowel with a linear cutter so that the mesentery side is located in the center of the stump. Both stumps are sutured to create a supporting column to maintain the diameter and dimension of the anastomosis. Longitudinal enterotomies are made at the antimesenteric sides of the two segments of intestine. The side-to-side antimesenteric anastomosis is then carried out in a transverse method.<sup>9</sup> By using this method, both stumps are not involved within the anastomosis.

Furthermore, the supporting column is expected to prevent anastomotic distortion as a result of mesenteric longitudinal ulcers.

This technique has gradually been spreading in the leading hospitals of Japan, and was adopted by the University of Chicago, USA from 2010.<sup>12</sup>

In 2016, an excellent long-term result was reported by Kono et al.<sup>13</sup> A total of 187 patients in Japan (144 patients, group J) and the USA (43 patients, group US) underwent Kono-S anastomosis for Crohn's disease between September 2003 and September 2011. With a median follow up of 65 months, two surgical anastomotic recurrences occurred in group J. Kaplan-Meier analysis showed that the 5- and 10-year surgical recurrence-free survival rate was 98.6% in group J. No surgical anastomotic recurrences have been detected in group US with a median follow up of 32 months. The Kono-S anastomosis was technically feasible and was carried out in all patients. This excellent result suggests that the Kono-S anastomosis appears to be safe and effective in reducing the risk of surgical recurrence in Crohn's disease.

Prospective randomized controlled studies which compare Kono-S anastomosis and stapled side-to-side anastomosis are currently ongoing in the USA (NCT03256240) and in Italy (NCT02631967). Long-term results are awaited.

## 2.2 | Endoscopic treatment for Crohn's disease

### 2.2.1 | Endoscopic balloon dilation for stenosis or stricture

Endoscopic balloon dilation (EBD) is a minimally invasive procedure for Crohn's disease-related strictures. Some meta-analyses showed a short-term success rate of 90% for the passage of the endoscope through the stenosis or stricture after dilatation, and a rate of about 70% for symptomatic response (relief of abdominal pain, nausea, vomiting, or bloating).<sup>14</sup> However, bowel perforation or bleeding may occur after EBD. Complication rates were reported to be approximately 4%.<sup>15-17</sup> Although the definition of long-term efficacy of EBD has not yet been standardized, several authors reported satisfactory data.

Morar et al<sup>16</sup> observed that after 1, 2, or 5 years, the rate of redilation was approximately 32%, 26%, and 2%, respectively. In their systematic review, Navaneethan et al reported that over a median follow-up period of 15-70 months, 27% of patients required surgical intervention, and 44% required dilation only. They advocated that EBD has a role as a bridge to surgery in the long term. They also claimed that patients' satisfaction with EBD should be considered in clinical practice.<sup>15</sup> Klag et al<sup>14</sup> reported that 83% of patients treated with EBD were satisfied with this procedure, and they would again choose EBD as the first-line treatment, although 34% of these patients eventually underwent surgery after EBD.

### 2.2.2 | Endoscopic treatment for fistula and abscess

Crohn's disease-related fistula and abscess have been treated with medical or surgical therapy, and the role of endoscopic treatment for

this situation has not yet been determined. Quite recently, some clinicians attempted to expand the indications for endoscopic treatment of Crohn's disease-related fistula and abscess. Dr B. Shen, the Cleveland Clinic Foundation, Ohio, is the one of the pioneers in this field. He claimed that the main principles of endoscopic treatment for fistula are to open the fistula tract (i.e. fistulotomy) if possible, to close the primary orifice of the fistula (i.e. endoscopic clipping) and to maintain the secondary orifice, or to fill up the tract with various agents (i.e. fibrin glue or plug).<sup>18</sup>

### Endoscopic fistulotomy

Endoscopic fistulotomy can be indicated for fistulas with a short tract in the distal bowel or perianal area. Dr B. Shen attempted this procedure in several patients with fistulas at the ileocolonic anastomosis for Crohn's disease, or an extrasphincteric perianal fistula/abscess using needle-knife with proper topical anesthesia if needed.<sup>18</sup> However, the number of patients undergoing this procedure is still limited, and long-term results are awaited.

### Endoscopic injection of filling agents

Fibrin glue has been widely used to treat perianal fistula with or without Crohn's disease with various success rates from the early first decade of the 2000s.<sup>19–22</sup> However, the long-term closure rate of anorectal or perianal fistulas using fibrin glue has been disappointing. For Crohn's disease-related fistula, fibrin glue treatment alone may not be adequate, and may be used in combination with flap repair.<sup>18</sup>

Bone marrow-derived stromal cells or adipose tissue-derived mesenchymal stem cells have been studied for the treatment of perianal fistulas in patients with Crohn's disease.<sup>18</sup> In 1993, the first success case of an autologous hematopoietic stromal cell (HSC) transplantation for non-Hodgkin's lymphoma accompanied by Crohn's disease was reported.<sup>23</sup> This patient had undergone partial colectomy in 1985, and developed rectovaginal fistula in 1986. After HSC transplantation, no active Crohn's disease was present in the first 6 months. A similar case was reported in 1998.<sup>24</sup> In 2010, long-term follow-up results on HSC therapy for 24 patients with anti-TNF refractory Crohn's disease were reported.<sup>25</sup> Among 24 patients, 91% stayed in remission for 1 year, 57% for 3 years, and 19% for 5 years after HSC transplantation. However, allogenic HSC transplantation has high complication and mortality rates; therefore, it is not recommended for autoimmune disease.<sup>26</sup>

In contrast, adipose tissue-derived mesenchymal stem cells (ad-MSC) have emerged as the new candidate for therapeutic drugs for intractable complicated anal or rectovaginal fistulas. Compared with HSC, ad-MSC are abundant in human adipose tissues, and they can be harvested through liposuction with minimal adverse events.<sup>27,28</sup>

After the initial promising results,<sup>27,28</sup> the Phase III ADMIRE trial was conducted on 212 patients with complex perianal fistulas. Patients were randomly allocated to single intralesional injection of allogenic ad-MSC (107 cases) or placebo (105 cases). At week 24, the ad-MSC group obtained a significantly higher remission rate as compared with the control group (50% vs 34%) with fewer

treatment-related adverse events (17% vs 29%).<sup>29</sup> In 2017, Dietz et al, Mayo Clinic, reported promising results of a phase I trial on 12 patients using autologous ad-MSC attached to a bioabsorbable matrix (STOMP; Stem Cells on Matrix Plugs) that was placed surgically by the same surgeon. At week 24, 10 of 12 patients (83%) had complete clinical healing, which was confirmed by magnetic resonance imaging studies.<sup>30</sup> A larger study is now being planned.

### Endoscopic clipping

There are two types of clipping methods for gastrointestinal diseases. One is the through-the-scope clip (TTSC) method, and the other is the over-the-scope clip (OTSC) method. The former is mainly used for treatment of gastrointestinal bleeding, and anastomotic or suture line leak in non-IBD patients, whereas the latter is designed to close defects along the gastrointestinal tract.<sup>18</sup> A large, multicenter, retrospective study of 188 non-IBD patients (108 fistulas, 48 perforations, 32 leaks) using OTSC showed that the long-term success rate was 60%, and the rates of successful closure of perforations (90%) and leaks (73%) were significantly higher than that of fistulas (43%).<sup>31</sup> However, in patients with Crohn's disease fistulas, there have been few studies in the literature using the OTSC method.

A study from Germany reported that the OTSC method was effective in five out of six patients (83%) with Crohn's disease-associated fistulas;<sup>32</sup> however, a study from Denmark reported that the success rate was only 33% (1/3).<sup>33</sup>

The role of the OTSC method in the treatment of Crohn's disease-related fistula remains to be further clarified.<sup>18</sup>

## 2.3 | Preoperative treatment and postoperative complications

In western countries, ileocecal resection is the most frequent procedure in patients with Crohn's disease.<sup>34</sup> Several risk factors for postoperative complications after ileocecal resection have been reported in previous studies.<sup>35–40</sup> These were presence of abscess at the time of surgery, corticosteroid therapy, impaired nutritional status, and anti-TNF agents. However, most of the studies included in the meta-analyses were retrospective and from a single institution, and patients' backgrounds were heterogeneous.

Valizadeh et al<sup>41</sup> conducted a retrospective study using the National Surgical Quality Improvement Program (NSQIP)-targeted database. All records of Crohn's disease patients undergoing colectomy between 2012 and 2013 were retrieved. Of 2208 Crohn's disease patients, 1387 (63%) were on steroid or immunosuppressant (SI) therapy in a 30-day period before surgery. On multivariate analyses, SI was independently associated with sepsis, septic shock, and anastomotic leak (odds ratio = 1.58, 95% confidence interval 1.09–2.27). The authors claimed that a prediction of risk of anastomosis-related complications before surgery may help colorectal surgeons to decide to avoid an anastomosis or the creation of a defunctioning stoma.

A nationwide prospective study was conducted in nine French university medical centers by the REMIND group.<sup>34</sup> Two-hundred

and nine patients undergoing ileocecal resection between 1 September 2010 and 30 September 2014 were included. In this study, early postoperative complication was defined as a surgical or other medical event within 30 days after surgery. Fifty-four postoperative complications were observed in 43 patients (20.5%).

In 176 patients undergoing a one-stage operation, 40 (22.7%) experienced a total of 51 complications. In a multivariate analysis adjusted for center, gender, age, smoking status, previous intestinal resection, phenotype, presence of ano-perineal lesions and the Harvey-Bradshaw index at surgery, only use of corticosteroids in the 4 weeks before surgery was significantly associated with overall postoperative complication rate, occurrence of intra-abdominal septic complications, and occurrence of extra-abdominal septic complications. However, anti-TNF agent in the 4 weeks before surgery, combination therapy (immunosuppressants and anti-TNF agent), time interval between last anti-TNF dose and surgery, and trough serum level of anti-TNF agent were not significant.<sup>34</sup>

Vedolizumab is a new humanized monoclonal antibody (immunoglobulin G1) against  $\alpha_4\beta_7$  integrin, and functions by suppressing intestinal inflammation in IBD by blocking leukocyte trafficking to the digestive tract.<sup>42</sup> This drug is now increasingly used in inducing and maintaining remission in patients with ulcerative colitis and Crohn's disease in western countries.<sup>43,44</sup> Yamada et al<sup>42</sup> conducted a retrospective study at the University of Chicago. Four hundred and forty-three IBD patients (186 ulcerative colitis patients, 257 Crohn's disease patients) undergoing surgery between June 2014 and April 2016 were included, and postoperative complications within 30 days of the operation were reviewed. Multivariate analyses showed that age >65 years and low serum albumin level were independent and significant risk factors for postoperative complications. However, preoperative use of immunomodulators, anti-TNF agents, and vedolizumab was not significant.

For infectious complications (wound infection or dehiscence, anastomotic leak, abscess, sepsis, fistula, pulmonary infection or pneumonia, urinary tract infection etc.), multivariate analyses showed that steroid use and low hemoglobin were risk factors; however, preoperative use of immunomodulators, anti-TNF agents, and vedolizumab were not significant.<sup>42</sup>

Therefore, among several drugs widely used in Crohn's disease patients preoperatively, surgeons should pay special attention to corticosteroids or immunosuppressants use within 30 days before surgery when considering surgical procedures.

### 3 | ULCERATIVE COLITIS

Total proctocolectomy with ileal pouch anal anastomosis (IPAA) is the procedure of choice in the surgical treatment of ulcerative colitis. Herein, the new concept of surgical techniques, and the short-term and long-term surgical outcomes with special attention to pouch failure will be discussed.

### 3.1 | Surgical techniques

Samples et al<sup>45</sup> reported the clinical utility of variant two-stage IPAA beginning with total abdominal colectomy and end ileostomy followed by completion proctectomy and IPAA without a diverting loop ileostomy. Among 248 patients undergoing IPAA, 139 (56.1%) underwent classic two-stage and 109 (43.9%) underwent variant two-stage operation. There was no significant difference in the 3-year cumulative incidence of pouch leaks between the two groups. The variant two-stage group was more likely to have lower body mass index (BMI), an urgent/emergent procedure, biological use within 2 weeks of surgery, and high-dose steroid use. These results suggest that variant two-stage IPAA is a safe and effective surgical option even in a subset of patients with worse conditions.<sup>43</sup>

Transanal total mesorectal excision (ta-TME) is now a topic in rectal cancer surgery. The same approach has gradually been adopted in proctectomy for ulcerative colitis.<sup>46</sup> de Buck van Overstraeten compared postoperative morbidity between 97 patients with transanal IPAA and 119 patients with transabdominal IPAA. All patients underwent minimally invasive restorative proctocolectomy in one, two, or three stages. The odds for postoperative morbidity were 0.52-fold lower in the ta-IPAA group (95% CI [0.29; 0.92]  $P = .026$ ), suggesting a lower probability of complications in this group. The odds of having a leak were 1.09-fold higher in the ta-IPAA group (95% CI [0.36; 3.07]), although there was no significant difference between the two groups. Postoperative hospital stay in the ta-IPAA group was significantly shorter than that in the transabdominal IPAA group (7.34 days vs 9.08 days;  $P = .001$ ) as a result of earlier resumption of oral intake and the lower probability of ileus in the ta-IPAA group.<sup>47</sup>

### 3.2 | Preoperative treatment and postoperative complications

To assess the association of preoperative use of anti-TNF agents with adverse postoperative outcomes, Lau et al<sup>40</sup> examined Cedars-Sinai Medical Center experience with special reference to serum anti-TNF drug levels (detectable and undetectable). Among 94 ulcerative colitis patients, 60 (64%) underwent anti-TNF agent therapy, and serum anti-TNF drug level was detectable in 17 (28%) patients and undetectable in 43 (72%) patients. The authors combined both the 34 patients who did not undergo anti-TNF agent therapy and the 43 patients who underwent anti-TNF agent therapy; however, whose serum anti-TNF drug levels were undetectable in the undetectable group. There were no significant differences in adverse postoperative outcomes between the detectable (17 patients) and undetectable (77 patients) groups in the entire cohort (94 patients) or in patients stratified according to type of index surgery (subtotal colectomy or total proctocolectomy with end ileostomy, 42 patients; IPAA, 52 patients). Similar results were obtained with postoperative outcomes (infectious, surgical and medical complications) when only the 60 patients undergoing anti-TNF agent therapy were analyzed.

Limitations of this study were the small study population, and one institutional study.

Kulaylat et al<sup>48</sup> collected insurance claims data from the MarketScan commercial Claims and Encounters (CCA) database in the USA. Of a total of 2476 ulcerative colitis patients, 950 (38.4%) underwent subtotal colectomy or total abdominal colectomy, 354 (14.3%) underwent total proctocolectomy with end ileostomy, and 1172 (47.3%) received ileal pouch-anal anastomosis. In univariate analyses, increased postoperative complications were observed among patients in the ileal pouch cohort who received anti-TNF agents preoperatively versus those who did not (45.2% vs 37.6%;  $P = .02$ ), but not among those in the colectomy or proctocolectomy cohorts. On multivariate analyses, an increase in complications was also observed in the ileal pouch cohort. This study showed that anti-TNF agent use within 90 days of surgery among patients who underwent ileal pouch-anal anastomosis was associated with higher 90-day postoperative complication rates, suggesting that carrying out a total proctocolectomy with concurrent IPAA should be avoided or at least delayed for more than 90 days after anti-TNF agent use.<sup>48</sup>

Lightner et al<sup>49</sup> compared short-term surgical outcomes between 84 patients with ulcerative colitis who received vedolizumab within 12 weeks of their abdominal operation and 62 patients who received anti-TNF agents. Vedolizumab-treated patients had more superficial surgical site infections ( $P = .047$ ) and more mucocutaneous separation at the ileostomy ( $P = .047$ ), but there was no difference in overall surgical infectious complication rate, deep space SSI, 30-day hospital readmission or return to the operating room. On univariate analysis of SSI among patients with ulcerative colitis, exposure to vedolizumab was not a significant predictor of SSI, but steroids were predictive of SSI on univariate and multivariate analysis. After ileal pouch anal anastomosis, there was a higher rate of intra-abdominal abscess (31.3% vs 5.9%) and mucocutaneous separation (18.8% vs 0%) in the vedolizumab group compared with the anti-TNF group, without significant difference statistically.<sup>49</sup>

### 3.3 | Pouch-related problems

Uchino et al<sup>50</sup> conducted a multicenter nationwide cohort study to evaluate the rate of pouch failure and its risk factors in Japanese ulcerative colitis patients who underwent restorative proctocolectomy with ileal-pouch reconstruction.

Among a total of 2376 patients, 27 non-functional pouches (1.1%) were observed. Anastomotic leakage was selected as a risk factor for pouch failure (odds ratio, 9.1). Cumulative pouch failure rate was 4.2% at 10 years, which was similar to the previous reports from western countries.<sup>51–53</sup> The authors advocated that the optimal staged surgical operation should be selected according to a patient's condition to avoid anastomotic failure during proctocolectomy.<sup>50</sup>

In a recent review by Chang et al,<sup>54</sup> obesity, defined as a BMI of 30 or higher, and pelvic radiation, before or after pouch surgery have been associated with pouch complications, such as anastomotic leak, anastomotic/pouch strictures, and inflammatory pouch

complications. It is better to encourage weight loss in obese patients, if applicable. Patients should be informed of the potential risks of radiation exposure to the pouch, and limiting radiation exposure and targeting narrower fields are advisable.

Furthermore, older and elderly patients and women with a history of obstetric complications have increased rates of incontinence after IPAA. Surgeons should pay special attention to preserve sphincter function in these subgroups of ulcerative colitis patients, and a stapled anastomosis should be preferred over a hand-sewn anastomosis.<sup>54</sup>

Segal et al<sup>55</sup> conducted a systematic review with meta-analysis on the management of chronic refractory pouchitis, showing that antibiotics (74%; 95% CI: 56%–93%) and biologics (53%; 95% CI: 30%–76%) significantly induced remission in patients with chronic pouchitis; however, steroids, bismuth, elemental diet, tacrolimus and fecal microbiota failed to achieve remission with significance.

## 4 | CONCLUSIONS

As has been reviewed in this article, the recent improvements of IBD treatment not only contain new medical therapies based on basic science, but also new surgical and endoscopic techniques. Colorectal surgeons should always keep in touch with these novel ideas and concepts to improve the quality of life of IBD patients.

### DISCLOSURE

Conflicts of Interest: Authors declare no conflicts of interest for this article.

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