

## ANSWERING REVIEWERS



November 8, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Revised 5620.doc).

**Title:** Surgery for luminal Crohn's disease

**Author:** Takayuki Yamamoto, Toshiaki Watanabe

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 5620

The authors thank you for your communication of October 20, 2013 in connection with the above manuscript. We were pleased to read the evaluation report and have revised the manuscript precisely in line with the comments provided by our reviewer colleagues.

The style of the text has been corrected as suggested.

The revisions in the manuscript are marked in 'blue' and are itemized below.

### **Reviewer 00504182:**

#### **Comments:**

It is a nice and well written review paper on surgery in Crohn's disease. A part a few changes regarding number and percentage presented, such as that in page 21 about incidence of postoperative Crohn's disease .....than UC patients (?). Moreover, I also suggest to mention the possibility that the new biological treatment has been changed the natural course not only of the disease itself, but also concerning surgery therapies.

#### **Authors' response:**

We are very grateful for your evaluation report and supportive view.

As suggested, the previous sentences in page 21 were difficult to understand. They have been revised as follows (pages 22-23):

Seventeen patients with preoperative CD were identified, whereas the preoperative diagnosis was UC in 261 patients. Seven of the 17 patients (41%) in the preoperative CD group developed postoperative CD (recurrence in the afferent limb 3, pouch fistulizing disease 4) vs 27 of the 261 patients (11%) in the UC group (afferent limb inflammation 23, perianal disease 4) ( $P = 0.002$ ). Of the seven CD patients with recurrent inflammation, three patients were maintained on immunosuppressive therapy and another three patients were controlled with antibiotics alone. Only one patient (6%) of the preoperative CD patient cohort with severe pouch inflammation and perianal disease required pouch excision and permanent ileostomy after failing aggressive medical therapy. The incidence of pouch failure was not statistically significant between patient groups.

As suggested, we have discussed about the impact of biological treatment on surgery for Crohn's disease in new sections (pages 26-33): '**PREOPERATIVE CONDITIONS AND RISK OF POSTOPERATIVE COMPLICATINS**' and '**POSTOPERATIVE MANAGEMENT FOR THE PREVENTION OF RECURRENCE**'.

**Reviewer 00068308:**

**No Comments**

**Reviewer 02545699:**

**Comments:**

This is a well written, sensible, practical summary of the place of surgery in the management of luminal Crohn's Disease. It might have been useful for the reader to have been guidance on (1) pre-operative assessment and preparation (use of immunosuppressives; elimination of sepsis; pre-operative nutrition) (2) intra-operative decision making (re emergency presentations - when is an anastomosis safe in presence of peritonitis; what should be done when confronted with a patient who has peritonitis due to a perforated segment of Crohn's disease but who also has multiple proximal strictures; when should a gastrostomy tube be placed intra-operatively for post-operative enteral nutrition) (3) What need to be considered post-operatively (use of immunosuppressives; follow up colonoscopy; timing of reconstructive surgery)

**Authors' response:**

Thank you very much for your positive comments. We are very grateful.

All suggested issues were presented in new sections (pages 26-33): '**PREOPERATIVE CONDITIONS AND RISK OF POSTOPERATIVE COMPLICATINS**' and '**POSTOPERATIVE MANAGEMENT FOR THE PREVENTION OF RECURRENCE**'.

## **PREOPERATIVE CONDITIONS AND RISK OF POSTOPERATIVE COMPLICATINS**

### ***Nutritional status and septic conditions***

Currently, the use of biological agents constitutes one way to diminish local, and alleviate mucosal inflammation, thereby allowing surgery to be performed at complicated disease sites. However, evidence to date would suggest that there has been little change in the natural history of the disease and hence surgical therapies. Surgery provides good long-term disease control in many patients, and that delay in operating may result in more advanced disease and hence more postoperative complications<sup>[67]</sup>. Yamamoto *et al*<sup>[67]</sup> reviewed 343 patients who underwent 1,008 intestinal anastomoses during 566 operations for primary or recurrent CD between 1980 and 1997. Intra-abdominal septic complications, defined as anastomotic leak, intra-abdominal abscess, or enterocutaneous fistula, developed after 76 operations (13%). Intra-abdominal septic complications were significantly associated with preoperative low albumin level (< 30 g/L), preoperative steroids use, abscess at the time of laparotomy, and fistula at the time of laparotomy. The intra-abdominal septic complication rate was 50% (8/16 operations) in patients with all of these 4 risk factors, 29% (10/35 operations) in patients with 3 risk factors, 14% (14/98 operations) in patients with 2 risk factors, 16% (33/209 operations) in patients with 1 risk

factor, and 5% (11/208 operations) in patients with none of these risk factors ( $P < 0.0001$ ). The following factors did not affect the incidence of septic complications; age, duration of symptoms, number of previous bowel resections, site of disease, type of operation (resection, strictureplasty, or bypass), covering stoma, and number, site, or method (sutured or stapled) of anastomoses. Preoperative low albumin level, steroid use, and the presence of abscess or fistula at the time of laparotomy significantly increased the risk of septic complications after surgery in CD. A surgical decision about avoiding an anastomosis must take into account many issues, especially age, degree of malnutrition, severity of coexisting sepsis and the dose of steroids or immunosuppressants. However, we must conclude from our data that an anastomosis is much more likely to break down if three or four of the four risk factors are present in a particular patient. It is not clear that preoperative nutritional intervention can reduce the risk of postoperative complications. Preoperative management of septic conditions may be associated with a lower incidence of complications after surgery. However, there has been no striking evidence that management of malnutrition and sepsis before surgery improves the surgical outcomes in CD. Delay in operation may be associated with an increased risk of serious complications. Further studies are necessary on these practical issues.

#### *The impact of biologic therapy on postoperative complications*

The immunosuppressive effects of preoperative anti-tumor necrosis factor (TNF)- $\alpha$  therapy may increase the risk for postoperative complications among CD patients undergoing abdominal surgery. A number of meta-analyses<sup>[68-70]</sup> were conducted to compare the rates of postoperative complications among CD patients treated with anti-TNF- $\alpha$  therapy *vs* alternative therapies. A total of eight studies including 1,641 patients were included in the meta-analysis by Kopylov *et al*<sup>[68]</sup>. Preoperative infliximab therapy in CD patients undergoing abdominal surgery was associated with a trend toward an increased rate of total complications (OR = 1.72, 95% – CI: 0.93-3.19). Anti-TNF- $\alpha$  treatments were associated with a modestly increased risk of infectious complications (OR = 1.50, 95% – CI: 1.08-2.08), mostly remote from the surgical site (OR = 2.07, 95% – CI: 1.30-3.30) and with a trend toward a higher rate of noninfectious complications (OR = 2.00, 95% – CI: 0.89-4.46). Preoperative infliximab treatment was associated with an increased risk of postoperative infectious complications, mostly nonlocal. A trend toward an increased risk of noninfectious and overall complications was also observed. In the meta-analysis by Billioud *et al*<sup>[69]</sup>, the prevalence of infectious postoperative complications was increased in CD patients who underwent preoperative anti-TNF- $\alpha$  therapy (OR = 1.45, 95% – CI: 1.03-2.05). In the meta-analysis by Rosenfeld *et al*<sup>[70]</sup>, data were extracted from 6 studies including 1,159 patients among whom 413 complications were identified. The most common complications were wound infections, anastomotic leak and sepsis. There was no significant difference in the major complication rate (OR = 1.59, 95% – CI: 0.89-2.86), minor complication rate (OR = 1.80, 95% – CI: 0.87-3.71), reoperation rate (OR = 1.33, 95% – CI: 0.55-3.20) or 30 day mortality rate (OR = 3.74, 95% – CI: 0.56-25.16) between the infliximab and control groups. Thus, the impact of anti-TNF- $\alpha$  therapy on postoperative complications remains unclear.

## **POSTOPERATIVE MANAGEMENT FOR THE PREVENTION OF RECURRENCE**

### *Risk factors for postoperative recurrence*

In the surgical management of CD, postoperative recurrence is common, and many patients require repeat operation for recurrence. The reoperation rates for recurrence have been reported to be 10-30% at 5 years, 20-40% at 10 years and 40-60% at 20 years after surgery<sup>[71]</sup>. The reoperation rate tends to steadily increase with time, reaching approximately 50% at 20 years after surgery. The most significant factor affecting postoperative CD recurrence was found to be smoking<sup>[71,72]</sup>. Smokers had an increased risk of recurrence compared to non-smokers. Similarly, perforating CD appeared to be associated with a higher recurrence rate compared with non-perforating CD<sup>[71,72]</sup>.

### ***Monitoring for postoperative recurrence***

Rutgeerts *et al*<sup>[73]</sup> reported that recurrent lesions were observed endoscopically in the neo-terminal ileum (the proximal site of the ileocolonic anastomosis) within 1 year of resection in 73% of patients, although only 20% of the patients had symptoms. Three years after surgery, the endoscopic recurrence rate increased to 85% and symptomatic recurrence occurred in 34%. Patients with severe endoscopic lesions within 1 year after resection developed early clinical recurrence. In contrast, patients with no or mild endoscopic lesions had a low frequency of subsequent clinical recurrence. The severity of the endoscopic inflammation in the neo-terminal ileum during the first year after resection was found to be a reliable predictive risk factor for future clinical recurrence. Ileocolonoscopy is the gold standard in the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course. Ileocolonoscopy is recommended within the first year after surgery where treatment decisions may be affected.

### ***Prophylactic medications***

Prophylactic treatment is recommended after small intestinal resection<sup>[74,75]</sup>. High dose mesalazine is an option for patients with an isolated ileal resection<sup>[74,75]</sup>. Thiopurines are more effective than mesalazine or imidazole antibiotics alone for preventing both clinical and endoscopic recurrence<sup>[74,75]</sup>. In patients with a risk factor for early postoperative recurrence the drug of choice is azathioprine/mercaptopurine<sup>[74,75]</sup>. Imidazole antibiotics have been shown to be effective after ileocolonic resection but are less well tolerated. Probiotics have failed to show efficacy in postoperative CD recurrence, but should merit further investigations<sup>[72,75]</sup>. There has been no RCT evaluating the efficacy of enteral nutrition in the prevention of postoperative CD recurrence<sup>[72,75]</sup>. Several RCTs<sup>[76-78]</sup> investigated the efficacy of biologic agents for the prevention of recurrence after resection for CD. Regueiro *et al*<sup>[76]</sup> randomly assigned 24 patients who had undergone ileocolonic resection to receive intravenous infliximab (5 mg/kg), administered within 4 weeks of surgery and continued for 1 year, or placebo. The primary end point was the proportion of patients with endoscopic recurrence at 1 year. Secondary end points were clinical recurrence and remission and histologic recurrence. The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (1/11 patients; 9.1%) compared with the placebo group (11/13 patients; 84.6%). There was a nonsignificant higher proportion of patients in clinical remission in the infliximab group (8/10 patients; 80.0%) compared with the placebo group (7/13 patients; 53.8%). The histologic recurrence rate at 1 year was significantly lower in the infliximab group (3/11 patients; 27.3%) compared with the placebo group (11/13 patients; 84.6%). Administration of infliximab after intestinal

resection was effective at preventing endoscopic and histologic recurrence of CD. In the study by Yoshida *et al*<sup>[77]</sup>, 31 patients who had ileocolonic resection within the past 4 weeks were randomly assigned to scheduled infliximab at 5 mg/kg intravenously every 8 weeks for 36 months (n=15) or without infliximab (control, n=16). At 12 and 36 mo, 100% and 93.3% of patients in the infliximab group were in remission, respectively *vs* 68.8% and 56.3% in the control arm ( $P < 0.03$ ). Further, the infliximab group achieved higher endoscopic remission at 12 mo (78.6% *vs* 18.8%,  $P = 0.004$ ). Savarino *et al*<sup>[78]</sup> randomly assigned 51 patients who had undergone ileocolonic resection to receive after 2 weeks from surgery adalimumab at the dose of 160/80/40 mg every two weeks, azathioprine at 2 mg/kg/day, or mesalamine at 3 g/day, and they were followed up for 2 years. The primary end point was the proportion of patients with endoscopic and clinical recurrence. The rate of endoscopic recurrence was significantly lower in adalimumab (6.3%) compared with the azathioprine (64.7%; OR = 0.036, 95% –CI: 0.004-0.347) and mesalamine groups (83.3%; OR = 0.013, 95% –CI: 0.001-0.143)). There was a significantly lower proportion of patients in clinical recurrence in the adalimumab group (12.5%) compared with the AZA (64.7%; OR = 0.078, 95% –CI: 0.013-0.464) and mesalamine groups (50%; OR = 0.143, 95% –CI: 0.025-0.819). The administration of adalimumab after intestinal resection was effective in preventing endoscopic and clinical recurrence of CD. Further larger studies are necessary to confirm the therapeutic advantage and to show the economic implications of biologic therapy in this field. Antibiotics, immunomodulatory medications and anti-TNF- $\alpha$  agents have been shown to be efficacious in preventing postoperative recurrence of CD, although the potential risks and benefits of therapy need to be balanced in individual patients.

**Reviewer 00538743:**

**Comments:**

A very well written and structured paper and it will certainly be published. However, regarding to recurrence rate after colectomy (page 18), the discussion should be more balanced. The risk of recurrence above the permanent ileostomy was estimated at 30% at 10 years in a recent study. In the same study, 44% of the patients who experienced clinical recurrence underwent re-operation despite medical treatment. So, an end ileostomy is probably not the end of the story for CD patients and your discussion should reflect this. Page 21: The following sentence is quite difficult to understand “The incidence of post-operative CD was significantly higher in CD patients (41%) than UC patients (11%)”. Please, explain or modify.

**Authors’ response:**

We are very grateful for your evaluation report and supportive view.

Regarding to recurrence rate after colectomy, we have added the following comments and a new reference no. 53(page 19):

A recent literature review confirms an approximately 30% risk of recurrence of CD after an end ileostomy<sup>[53]</sup>. A penetrating phenotype and preexisting ileal disease are risk factors for disease recurrence. A thorough evaluation of the stoma/peristomal area and evaluation of the small bowel by ileoscopy and small bowel imaging are required to assess the extent of disease and extraluminal complications such as stomal retraction and fistulas that require

further surgical intervention. While postoperative medical treatment with immunosuppression or biological therapy is often employed, these therapies are unproven to prevent postoperative recurrence in the setting of a stoma.

As suggested, the previous sentence in page 21 was difficult to understand. It has been revised as follows (pages 22-23):

Seventeen patients with preoperative CD were identified, whereas the preoperative diagnosis was UC in 261 patients. Seven of the 17 patients (41%) in the preoperative CD group developed postoperative CD (recurrence in the afferent limb 3, pouch fistulizing disease 4) *vs* 27 of the 261 patients (11%) in the UC group (afferent limb inflammation 23, perianal disease 4) ( $P = 0.002$ ). Of the seven CD patients with recurrent inflammation, three patients were maintained on immunosuppressive therapy and another three patients were controlled with antibiotics alone. Only one patient (6%) of the preoperative CD patient cohort with severe pouch inflammation and perianal disease required pouch excision and permanent ileostomy after failing aggressive medical therapy. The incidence of pouch failure was not statistically significant between patient groups.

We hope that this revised version is now acceptable for publication in *World Journal of Gastroenterology*.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading 'Takayuki Yamamoto' in a cursive script.

**Takayuki Yamamoto, MD, PhD, FACC**

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