Management of Crohn’s disease after intestinal resection: Look hard, act fast

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The sample size, calculated as 170, was achieved. There were dropouts in both groups during the study. Those who became symptomatic and had a colonoscopy and withdrew were included for the analysis of 18 month colonoscopies. Those who withdrew without a colonoscopy were also included with a Rutgeerts score of ≥2 (recurrence, >5 apthous ulcers or larger lesions confined to the mucosa) in the analysis of 18 month colonoscopies. Where Crohn’s disease activity index (CDAI) had not been calculated at withdrawal, a score of ≥200 was assigned. Thus, a modified intention-to-treat analysis (mITT) was carried out.

While numerous other aspects were studied and commented upon, definite conclusions could not be drawn in some of these due to inadequate numbers or an inadequate length of the study.

The salient results were as follows:

- **Primary end-points:** The active care strategy results in statistically significant reduction in mucosal recurrence (49% v. 67%, p=0.03).
- **Secondary end-points:** The only other statistically significant difference was less clinical recurrence (CDAI=200) in the active care group (27% v. 49%, p=0.08)

Only two patients in the standard care arm underwent a further procedure, both for adhesions. There was no statistically significant difference in elevation of CRP. There was no difference in recurrence between upfront and stepped up biological strategies, though the study was not powered to answer this question. Metronidazole was not tolerated by 20% of patients; thiopurines caused alopecia, headaches and wound infections; and adalimumab led to systemic lupus erythematosus in 2 patients, and vasculitis and injection site reaction in 1 patient each.

The other conclusions derived from the study were: (i) treatment intensification at 6 months brings some patients into remission 1 year later (a minority); (ii) early endoscopic remission does not guarantee maintenance of remission; (iii) some patients have recurrence despite surveillance and intensive treatment; and (iv) mucosal healing is a difficult target to achieve.

**COMMENT**

This study has several weaknesses that are of concern. A high proportion of patients seemed to be at high risk—83% in the active group and 85% in the standard care group. This might mean some in both groups would have received less than adequate therapy. One wonders if such results are generalizable to the population at large. It may be that the 17 centres, being referral centres, see a high proportion of high-risk patients, who might need stepped up as having one or more of the following: smoking, perforating disease or previous resection. These patients received a thiopurine (azathioprine or 6-MP) or adalimumab if intolerant to thiopurine for 18 months. All other patients were deemed to be ‘low risk’ and received no further treatment after metronidazole.

Patients were then randomized in a ratio of 2:1 into two groups. One group underwent routine colonoscopy at 6 months (active care strategy); they received stepped up therapy if active disease was detected. The other group received standard optimum risk-adjusted therapy without routine colonoscopy at 6 months. The primary end-point was endoscopic mucosal normality at 18 months. Secondary end-points were clinical recurrence, need for further surgery, C-reactive protein level (CRP) and drug efficacy.

Rutgeerts score was used to assess endoscopic remission at the end of 6 and 18 months by colonoscopies. Adequate blinding and masking were done.

Low-risk patients in the active care arm were stepped up to thiopurine at 6 months if there was evidence of disease recurrence. High-risk patients with recurrence and already on thiopurines were stepped up to adalimumab. High-risk patients already on thiopurines and adalimumab received increased doses of adalimumab.

Since endoscopic recurrence precedes clinical recurrence, most workers would treat such patients postoperatively with immunosuppressive therapy. What is not known is how aggressive this immunosuppression should be, and which subgroup of patients at high risk of recurrence should be administered therapy.

De Cruz et al. set out to answer this question by conducting a randomized controlled trial. They randomized 174 patients with Crohn’s disease undergoing resection with no residual macroscopic disease and with an endoscopically accessible anastomosis. Patients were stratified into high- and low-risk groups after resection. All patients received metronidazole for 3 months. ‘High risk’ was defined
therapy anyway. The argument that randomization would address this issue may not hold if the study population is a biased one.

A recurrence rate of 49% in the active care group is high by any standards. Again, one wonders whether or not the population studied is representative of the general population.

Withdrawals in each group were high (56 total), 22 with disease recurrence and 34 with comorbid conditions. Other reasons for withdrawal were loss to follow-up, patient preference, protocol violation and pregnancy. Although the sample size calculation had factored a high dropout rate, this in itself is a cause for worry, and again, may reflect a patient population with severe disease.

Rutgeerts score is not a formally validated score. The strength of the study is that it is a randomized controlled trial, which has never been done before. The design and analysis is robust, with mITT and per protocol analysis reported adequately. The study is based on the fact that mucosal healing has been shown to result in more clinical remission, less hospital admissions and less bowel resections. Thus, mucosal healing was used as the end-point. Since evidence suggests that anti-tumour necrosis factor (TNF) therapy reduces endoscopic and clinical recurrence in postoperative patients, the study investigated if stepping up therapy when mucosal recurrence occurs will lead to long-term healing. However, universal, immediate postoperative treatment with anti-TNF agents is expensive, has its own complications and will over-treat some patients. This study provides some rationale for using such therapy in high-risk patients.

The study is a pragmatic, real-life therapeutic strategy trial; and this is one of its major strengths. The sample size was calculated with an anticipated dropout rate of 31%.

However, more questions remain to be answered. Can we extrapolate these results to patients where mucosal recurrence cannot be seen? Are there other reliable ways to detect recurrence when the anastomosis is not within the reach of a colonoscope? Faecal markers, capsule endoscopy and cross-sectional imaging may be of value.

With all its drawbacks, this study provides level 1 evidence for aggressive immnosuppressive therapy in high-risk postoperative patients.

REFERENCES

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Rectal cancer: Time to change?

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SUMMARY
There has been an increase in laparoscopic surgery for colorectal cancers in the past decade owing to favourable short-term as well as oncological outcomes. The COLOR II trial aimed to compare laparoscopic and open surgery for rectal cancers in terms of locoregional recurrence, disease-free survival (DFS) and overall survival (OS). It was a non-inferiority, open-label, multicentre, randomized controlled trial conducted at 30 centres in 8 countries. Patients with solitary adenocarcinoma of the rectum within 15 cm from the anal verge without distant metastasis were included. The localization of the tumour was categorized as upper rectum (distal border of tumour, 10–15 cm from the anal verge), middle rectum (5–10 cm from the anal verge), and lower rectum (<5 cm from the anal verge). Patients with T4 or T3 tumours within 2 mm of the endopelvic fascia, as determined on imaging, were excluded.

Randomization was stratified according to the hospital, tumour location and use of preoperative radiotherapy. Patients were assigned in a ratio of 2:1 to undergo either laparoscopy or open surgery according to a list of randomization numbers with treatment assignments. A total of 1103 patients were randomized, among them 739 were assigned to laparoscopic surgery and 364 to open surgery. For various reasons 40 patients in the laparoscopic group and 19 patients in the open group were excluded. In the laparoscopic group, 699 patients were included in the analysis; however, 7 patients had open surgery. Of 349 patients in the open surgery group, 5 had laparoscopy. Both groups did not differ in baseline characteristics. Multidisciplinary cancer boards at the participating hospitals determined the use of neoadjuvant therapy. Stringent quality assessment of the surgical technique—by using unedited videos, and pathology reports—was done by the study management committee.

The presence of tumour cells within 2 mm from the lateral surface of the mesorectum was considered as a positive circumferential resection margin. In this trial the primary end-point was locoregional recurrence 3 years after the index surgery and the secondary end-points were DFS and OS. The follow-up protocol was annual clinical examination 5 years after surgery and CT or MRI scan of the pelvis, abdomen and chest 3 years after surgery. Appropriate statistical analyses were done.

The conversion rate from laparoscopic surgery to open surgery was 16%. In the laparoscopic surgery group, the operating time was 52 minutes longer, the short-term outcomes such as bowel function returned one day earlier in the laparoscopic group and the hospital