ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Early Surgery for Patients With Ileal Crohn's Disease

Geert D'Haens, MD, PhD
Professor of Gastroenterology
Chair of the Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Boelelaan, Amsterdam, The Netherlands

G&H Could you explain the concept of early surgery in ileal Crohn's disease?

GD Surgery has traditionally been used for the treatment of medically intractable disease or complications. In Crohn's disease, complications typically involve a perforation with an abscess or a stenosis that cannot be endoscopically managed and is symptomatic, where the patient has cramps after eating, and medically intractable disease refers to symptoms continuing despite use of the medical treatments currently available. Almost half of patients with Crohn's disease have some type of surgery in which the diseased part of the bowel is resected at some time in their disease course. Essentially, traditional surgery can be considered late surgery, as it is performed when all other options have been tried but none work.

Early surgery refers to the performance of resection in the first years after diagnosis without the presence of complications. There is no stenosis or perforation, nor is there an abscess. The disease is limited and typically located in the last part of the small bowel or terminal ileum. When the length of the diseased bowel is not too long, the idea is to resect it so that the patient is free from disease. This is called surgical remission. Essentially, the patient can start over with no Crohn's disease visible and is then followed intensively. As soon as disease recurs, it can be treated with medication. Early disease is much more responsive to medication than advanced or established disease.

G&H What has research shown regarding the outcomes associated with performing surgery early on in patients who have ileal Crohn's disease?

GD My colleagues and I conducted the LIR!C trial, which examined patients with ileal disease limited to 40 cm of small-bowel disease who had 1 line of treatment (azathioprine in most cases) that failed. We randomized these patients to surgical resection or a further line of medical treatment (infliximab) and found that quality-of-life improvement was equally good with surgery as with infliximab. There was earlier improvement in quality of life with infliximab, whereas the improvement came a little later with surgery; however, surgery also led to better quality of life a year later. Therefore, surgery eventually led to superior outcomes looking a little further in time.

> It became clear that the patients who underwent early surgery had a more favorable disease course.

We also performed cost-benefit analysis (quality-of-life improvement vs cost), which was essentially more favorable for surgery than for infliximab. Of course, that depends on the cost of the surgery as well as the cost of infliximab, which vary in different centers and countries. Additionally, we looked at the long-term benefits of the treatments with a median follow-up of more than 4 years. Only 1 of the patients who had been randomized to surgery needed a second procedure, which was a very low number. Looking at patients randomized to infliximab, a

much higher number needed a second treatment. Thus, long-term follow-up of the trial was even more instructive than its short-term results.

G&H Have any other studies examined the use of early surgery in ileal Crohn's disease patients?

GD Last year in *Gastroenterology*, the Mount Sinai group published findings from their retrospective study of a Danish database of patients who had undergone surgery during the course of their Crohn's disease. It became clear that the patients who underwent early surgery had a more favorable disease course. Essentially, the findings of the LIR!C trial were reproduced and validated, albeit retrospectively.

G&H Could you discuss research that has looked at different surgical techniques in this patient population?

GD The surgical techniques are being investigated intensively in a number of studies. One of the latest studies is from our center and looked at whether it made sense to take out the mesentery or the peritoneal tissue around the terminal ileum in addition to the bowel. We found that mesenteric resection was not superior. Removing the bowel was enough; it was not necessary to remove the mesentery as well.

Studies have also looked at different types of anastomosis. Surgeons have tried to modify the way they connect the small bowel and the colon, but so far they have not been able to come up with an ideal strategy. All studies so far have demonstrated comparable recurrence rates however the bowel is connected. Research is still ongoing. What we believe is most efficient after early surgery is close monitoring of the spot where the disease comes back, the neoterminal ileum, and then starting treatment as soon as it does.

G&H Overall, what are the main advantages and disadvantages of performing surgery early for the treatment of ileal Crohn's disease?

GD The main advantages are that patients recover rapidly and that these surgeries are performed laparoscopically, which means that they require a very small incision. Because only a small part of the small bowel is being removed, metabolic consequences such as deficiencies in vitamin B12 are uncommon.

There are very few disadvantages, but the biggest one would be if multiple surgeries were needed because Crohn's disease recurred, which could result in short bowel. However, that was not observed in the LIR!C population; only 1 patient needed a second surgery, which was very favorable.

G&H Who are the ideal patients with ileal Crohn's disease to consider for early surgical intervention?

GD Patients who should be offered surgery early on are those with very short ileal disease, I would even say less than 20 cm, and who already have stenosis at diagnosis. It is often thought that regardless of what is done with such patients, medical treatment will not work because they already have a complication at diagnosis.

G&H What else should be taken into account when deciding whether or not to pursue early surgery?

GD Of course, patients should be involved in a shared decision-making process. Medical treatment can always be offered to patients if they do not want to undergo surgery. Some patients may consider surgery to be the treatment of last resort, but in my practice, we get many patients referred specifically for surgery who have read about it and know the data, and they often want early surgery, of course, in experienced hands. It is important that surgery occurs uneventfully without complications and by experienced surgeons. When talking with patients about surgery, physicians have to be honest and tell them that there is a slight risk of complications, mostly anastomotic leak. That complication occurs in 2% to 3% of surgeries and usually involves a temporary stoma. That information needs to be communicated with patients and should not be hidden. It is one of the reasons some patients opt for medical treatment rather than surgery even though the former has potential side effects that have to be taken into consideration.

G&H How has early surgery in this patient population been embraced by the medical community?

GD Many gastroenterologists still hold the misconception that surgery is only reserved for complicated disease. That strategy is suboptimal. When it is used, patients only undergo surgery when they are already malnourished or have a lot of symptoms such as dilated bowel or complications for which much of the bowel has to be resected. It is more attractive to perform surgery at a stage where the disease is limited and so the resection is limited as well. My colleagues and I have already changed our practice in Europe. I think physicians should communicate openly

about this option and, of course, in good collaboration. Patients need to be approached by a multidisciplinary team. It is not only the gastroenterologist who treats inflammatory bowel disease; it is a joint venture, and surgeons and gastroenterologists should ideally talk with patients together.

Interestingly, in the United States, there has been much more reluctance to move early surgery forward than in Europe.

Interestingly, in the United States, there has been much more reluctance to move early surgery forward than in Europe. I do not understand why it has been so difficult to adopt this approach there. All of the papers in this area come from Europe, and even the one written by the Mount Sinai group in New York was based on data from Denmark.

G&H What further research is needed?

GD Further research is needed on the timing of assessing patients for postoperative recurrence. Even though recovery is rapid after surgery, many patients will experience recurrence of their disease after months or years, and we are looking for the ideal way to monitor them and pick up recurrence early before symptoms develop. An important area of research in this field is the use of intestinal ultrasound, likely in combination with the biomarker fecal calprotectin, which can be measured in feces. Those two tools used in combination allow physicians to pick up early recurrence of disease potentially supplemented by colonoscopy. Treatment could then be started to try to reverse recurrence of disease. There are now many treatments that are capable of halting further progression of disease. This is an area of research currently being investigated. When should physicians search for recurrence? What is the ideal time point? How long can physicians wait to start treatment and still be able to reverse the disease completely?

Disclosures

Professor D'Haens has received research grants from AbbVie, Alimentiv, Bristol Myers Squibb, Johnson & Johnson, Pfizer, and Takeda; consulting fees from AbbVie, Agomab, Alimentiv, AM-Pharma, AMT, Arena Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Gilead, GlaxoSmithKline, Gossamer Bio, Immunic, Index Pharmaceuticals, Johnson & Johnson, Kaleido, Origo, Pfizer, Polpharma, ProciseDx, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist, and Roche; speaking fees from AbbVie, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Galapagos, Gilead, Pfizer, and Takeda; and has served on the data and safety monitoring board of AstraZeneca, Galapagos, and Seres Health.

Suggested Reading

Agrawal M, Ebert AC, Poulsen G, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared with anti-tumor necrosis factor therapy: a population-based cohort study. *Gastroenterology*. 2023;165(4):976-985.e3.

de Groof EJ, Stevens TW, Eshuis EJ, et al; LIR!C study group. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C trial. *Gut*. 2019;68(10):1774-1780.

Maruyama BY, Ma C, Panaccione R, Kotze PG. Early laparoscopic ileal resection for localized ileocecal Crohn's disease: hard sell or a revolutionary new norm? *Inflamm Intest Dis*. 2021;7(1):13-20.

Ponsioen CY, de Groof EJ, Eshuis EJ, et al; LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol*. 2017;2(11):785-792.

Stevens TW, Haasnoot ML, D'Haens GR, et al; LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial. *Lancet Gastroenterol Hepatol*. 2020;5(10):900-907.

van der Does de Willebois EML, Bellato V, Duijvestein M, et al; SPICY collaborator group. Effect of mesenteric sparing or extended resection in primary ileocolic resection for Crohn's disease on postoperative endoscopic recurrence (SPICY): an international, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024;9(9):793-801.