In favour of early surgery in Crohn's disease: A hypothesis to be tested

Giovanni Latella,⁎ Renzo Caprilli, Simon Travis

Dept. of Internal Medicine, Gastroenterology Unit, University of L’Aquila, Piazza S. Tommasi, 1–Coppito, 67100 L’Aquila, Italy
Dept. of Clinical Sciences, Gastroenterology Unit, University of Rome "La Sapienza," Rome, Italy
Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK

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Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) most frequently affecting the terminal ileum and right colon, with a high rate of strictureing or penetrating complications. Twenty years ago, the surgeon was often the main actor in the management of CD, but today’s physicians (and consequently their patients) are tempted to see surgery as ‘the end of the road’ rather than part of a management strategy. The question is whether this displacement of surgery is appropriate, or necessarily in the best interests of patients.

Although the mortality attributable to CD is relatively low, the chronic and relapsing course of the disease often results in substantial morbidity, poor quality of life, frequent use of health services and high direct and indirect costs of care. Surgery is an almost inevitable event in the natural history of ileal or ileocolic disease. The challenge facing physicians treating CD is, of course, not just to alleviate symptoms and prolong periods of remission, but also to reduce the need for surgery.

Nevertheless, gastroenterologists have to recognise that no current medical approach has been shown to reduce the need for abdominal surgery for CD within 1 year after treatment with anti-tumour necrosis factor alpha (anti-TNFα) antibody therapy, but it is long term follow up that is needed. However, surgery is not curative, because lesions and symptoms almost inexorably recur after resection. Mesalazine prophylaxis may reduce the postoperative recurrence rate, but the reduction of risk is small and possibly limited to small intestinal resection alone. On the other hand, remission induced by surgery lasts longer than that induced by medical therapy in a mathematical model.

In the last decade a more conservative approach to CD has prevailed, reflecting a wider armamentarium of medical treatments, including immunosuppressives and biological therapies, with others emerging. Surgery tends to be delayed for as long as possible by patients, physicians and even surgeons themselves. As a consequence, patients often come very late to surgery, with advanced or complicated disease, carrying an increased risk of surgical (especially septic) complications, in spite of improvements in peri-operative and post-operative care.

The most common indications for surgery in CD are strictureing and perforating complications and/or failure of medical treatment. Longitudinal studies suggest that patients spend a quarter (24%) of their disease course in medical remission, 41% in post-operative remission and a further quarter (27%) with mild disease. It is only very recently that longer-term follow up of a cohort of steroid-naive patients treated ‘top down’ with first line biological therapy has shown that mucosal healing is associated with...
fewer operations, relapse, or complications.\textsuperscript{18,19} There are, however, no reliable markers to identify patients who will benefit from early biological therapy or, indeed, surgery. The presence of nucleotide oligomerization domain-2 (NOD2) allelic variants and of antibodies to microbial antigens are primarily associated with small bowel CD and a fibrostenotic phenotypic as well as (somewhat inevitably) small bowel resection,\textsuperscript{20} but these markers are not yet used to influence management in clinical practice. Instead, the large majority of patients will have biological therapy introduced at a later stage (generally several years after diagnosis, for severe, steroid-dependent or immunosuppressive-refractory disease).\textsuperscript{21} It is not at all clear that biological therapy will achieve the same benefit in these patients, notwithstanding the demonstrable and welcome short-term control of refractory disease. It has, nevertheless, become unusual for patients to have surgery without being exposed to biological therapy, which will often delay timely surgery, conceivably increase the risk of complications and interrupt biological therapy with the effect of enhancing immunogenicity and decreasing the response to future therapy. No one can advocate surgery if medical therapy achieves a good quality of life without undue risk of complications from immunosuppression, but it is for physicians as much as surgeons to question whether the pendulum has swung too far in a medical direction.

The clinical behaviour of CD is not fixed, but is a dynamic evolution with striking changes over the course of the disease, although the location remains relatively stable.\textsuperscript{22–24} Half the patients already have strictureing or penetrating disease at the time of diagnosis.\textsuperscript{24} Of those with uncomplicated disease at the time of diagnosis, about half will then develop either strictureing or penetrating complications during follow up. An overlap exists between strictureting and penetrating disease, since internal fistulae may complicate long-standing intestinal stenosis and many patients undergoing surgery for intestinal obstruction will be found to have entero-enteric fistulae.\textsuperscript{25–27} Current treatment options (antibiotics, steroids, immunosuppressive drugs, biological therapies) may relieve inflammatory symptoms, but do not improve fibrostenotic obstruction.\textsuperscript{5,6,28–31} The outcomes of medical treatment of strictureing or penetrating CD are poor, because 64% ultimately require surgery within 1 year.\textsuperscript{32} This should be considered (and discussed with the patient!) when planning medical therapy. It is likely that progression to strictureting or penetrating disease phenotype is an endstage sequel of CD associated with either irreversible fibrosis or severe inflammation that will not abate despite optimal medical therapy introduced at a too late stage.

Anti-TNF\textsubscript{α} antibody therapy reduces the need for CD-related hospitalization and surgery during 54-week trials.\textsuperscript{10,11,33,34} but the duration of these effects is unknown. Although biological therapies have shown disease-modifying characteristics in other diseases, more data are required before it can be known whether they can influence the long term natural history of CD.\textsuperscript{35–37} There is no doubt that such agents work best when introduced early in the course of the disease, when they could reasonably be expected to change the course of CD. The fact is that they are not: the median duration of disease when practice is audited approaches 10 years. It is these patients, who are not only commonplace in practice, but also represent the majority that we are concerned about: new medical therapy adds yet more delay and may ultimately be associated with a higher burden of disease.

Both medical and surgical treatment of ileocaecal CD have improved markedly in the last two decades. Nevertheless, despite managing the same individual patient, multidisciplinary discussion is rare and multidisciplinary research, addressing the timing of surgery or medical treatment versus surgery, is exceptional. It is quite conceivable that in limited ileocaecal CD, early ileocolic resection is a good alternative to long-term medical therapy,\textsuperscript{38} in terms of recurrence-free interval, less need for immunosuppressive drugs, corticosteroids, or further intestinal resection.\textsuperscript{39} The fact is that we do not know, although the irony that a better outcome from early treatment through surgery also applies to biological (or indeed any medical) therapy is not lost. The ECCO Consensus states that localized ileocaecal CD with obstructive symptoms may best be treated by primary surgery.\textsuperscript{5,6} In support of this view, a report on 139 CD patients who underwent ileocolonial resection between 1980 and 2000 showed that the long-term outcome of this cohort of patients was excellent, with 48% remaining symptom-free and only 35% requiring further resection within 10 years.\textsuperscript{40} The authors conclude that patients with isolated ileal or ileo-caecal CD do well after surgical resection. These data are similar to another series of 181 patients undergoing ileocaecal resection for CD between 1970 and 1993, of whom only 31% required a further surgical resection within 10 years.\textsuperscript{41} The authors noted that surgical resection of ileocaecal CD may well minimize overall disease-related patient morbidity by avoiding long periods of active disease inadequately treated by medical therapy. We have also reported that surgery performed at diagnosis in 115 patients with CD, was associated with a lower risk of repeat surgery and a longer time to surgery after diagnosis, compared to 375 patients managed medically.\textsuperscript{39} Furthermore, surgery at diagnosis of CD spared steroids and immunosuppressants over the course of the disease, which confirms earlier reports.\textsuperscript{42} In this latter study it was shown that early surgery prolonged clinical remission and reduced the need for immunosuppressives compared to late surgery.

These observations are consistent with the pathology of CD. Intestinal fibrosis is a chronic and progressive process characteristic of CD.\textsuperscript{30,43–45} It is important to recognise that while inflammation necessarily triggers the onset of the fibrotic process, it subsequently plays a minor role in the progression of the stricture.\textsuperscript{46} The poor response of fibrosis to anti-inflammatory drugs in many different organs supports the concept that inflammation is not a pivotal perpetuating process in the progression of fibrosis. Since no effective preventive measures or medical approaches are available for intestinal fibrosis, operative intervention (dilatation, strictureplasty, or resection) is currently the only antifibrotic strategy for the management of CD.\textsuperscript{16,17,30,31,38} So surgery should not be dismissed as the end of the road after all medical options have failed. Instead, it is a valid part of an overall management strategy and should often be considered at an early stage, before patients are immunised against anti-TNF\textsubscript{α} therapy that has itself been started too late. The data support the premise that current medical therapies for CD are little able to modify the natural history of the disease and the fibrostenotic process in particular, except (perhaps) when biological therapy is introduced at
the earliest stage. Early surgery represents a valid alternative to medical therapy, particularly in patients with isolated stenotic ileocaecal CD, which is readily managed by video laparoscopic resection. A prospective controlled trial comparing surgery versus medical therapy with outcome measures that include quality of life, work performance and objective assessment of the burden of disease with pharmaco-economic costs over an appropriate period (5–10 years) in this group of patients is overdue.

References


