Is the length of postoperative recurrence on the neo ileum terminal ileum predictable in Crohn's disease?

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Abstract

Crohn's disease (CD) often has a stricturing phenotype on the terminal ileum requiring surgery due to obstruction. Recurrence is frequent, creating a risk of multiple surgeries. We studied patients with ileal or ileo-colic CD who had undergone at least two surgical bowel resections between 1968 and 2008 for obstructive symptoms.

Aims: The aim of this retrospective study was to determine if the length of the removed diseased bowel varied from one surgical resection to the next. The measurements obtained from radiology (small bowel follow-up), surgery and histology were compared.

Results: Twenty four patients were included. Seventeen had 2 resections, 5 patients had 3 resections and two had 4 resections. The resected length of the diseased ileum was significantly shorter for the second intervention than for the first as assessed by radiology (median 16 cm vs 37 cm; p = 0.0005), surgery (20 cm vs 40 cm; p = 0.005) and histology (15 cm vs 25 cm; p = 0.02) while there was no difference between the second and third resections (16 cm, 13 cm, 19.5 cm respectively) for the three types of measurements (p = NS). The surgeon's assessment of the diseased segment was longer than the histologist's (p = 0.003). No factor was found to be significantly associated with the length of the diseased bowel on recurrence.

Conclusion: This study shows that the length of the excised neo-terminal ileum during the first episode of recurrence was shorter than during the first episode of disease and remained stable for the third episode. This is an important prognostic finding that could influence the therapeutic choices for this disease and reduce hesitation to indicate surgery.

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1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that frequently affects the terminal ileum and right colon (70%) and is associated with a stricturing pattern (10–15% of
patients). The course of the location of CD is known to be stable over time. Thus, with or without surgery the disease only changed location in 15.9% of patients over 10 years.

Forty to 70% of patients with ileal CD undergo resection of the diseased bowel due to complications or failure of medical treatment. The most frequent surgery is ileocaecal resection. Clinical relapse of CD is expected in approximately 20–30% of patients at 5 years requiring a second intervention.

The definition of recurrence varies from endoscopically in 15.9% of patients over 10 years. Clinical symptoms are stable over time. Thus, with or without surgery the disease inflammation does not progress longitudinally over time.

The cumulative risk of multiple surgeries for recurrence varies between 38% and 50% and between 20 and 35% for terminal ileal disease. Multiple resections of the diseased bowel may result in functional diarrhoea, fat malabsorption, and ultimately short bowel syndrome, requiring preventive treatment.

Factors predictive of relapse and the need for additional surgery are well known: terminal ileum location, disease pattern (penetrating behaviour), age at diagnosis under 40; smoking and family history.

A previous study has suggested that the length of the recurrence was correlated to the preoperative length of the diseased ileum. A radiological study has also suggested that inflammation does not progress longitudinally over time.

However, the length of the diseased segment on recurrence has never been studied in patients who have undergone several resections, and this data could help when making therapeutic choices after clinical relapse following a previous resection.

2. Aims

The major aim of this retrospective study was to determine if the length of the removed diseased bowel was the same for the first and second resections and the second and third resections in patients who underwent three operations.

The second aim was to compare the lengths of the diseased ileum measured radiologically, surgically and histologically for the second operation. Measurements were compared for the second operation because the data was most complete. Indeed, many patients had no small bowel follow-up before the first resection which was usually performed in an emergency setting. The histological measurement was the reference length of the diseased bowel.

The third aim was to identify factors that could determine the length of the diseased bowel.

3. Study population

Patients who had at least two bowel resections for ileal or ileo-colic CD between 1968 and 2008 which removed all the diseased bowel were included in the study. The indication for surgery was obstructive symptoms. Ileo-colic anastomosis was performed immediately or within three months after resection. Data collected included: age at diagnosis and at each operation, gender, tobacco consumption, site of the disease including anal involvement, and numbers of flare before the first surgery.

A smoker was defined as someone who had smoked more than 7 cigarettes per week for more than a year. During the post operative period, patients who had stopped smoking for more than a year at the end of follow-up were categorized as non-smokers.

The length of the resection was taken from surgical reports as measured during the surgery. The histological length was measured after biochemical fixation and collected from the reports. Patients had at least one small bowel follow-up after each operation. The time for radiological evaluation differed for each patient depending on their symptoms. The length of the diseased small bowel segment was measured by two observers with a flexible ruler in the center of the lumen beginning at the ileocaecal valve or the ileo-colic anastomosis. Disease involvement was defined as thickened folds, irregular lumen, ulcers, string signs, nodularity or cobblestoning.

The following factors were studied: age at diagnosis, time between the first operation and the first symptoms, delay between the first operation and the diagnosis, delay between the 2 operations, ano-perineal disease, disease progression (number of relapses per year), and tobacco consumption.

4. Statistical analysis

Data were analysed with R version 2.4.1 software. P < 0.05 was considered to be statistically significant. The median length of the resected small bowel was compared between the first and second and the second and third operations. The comparison was made separately for surgical, radiological and histological assessed lengths of resected diseased small bowel tissue using a non parametric Wilcoxon test on matched series.

To compare surgical, radiological and histological assessments of diseased segments, only the second resection with the most complete data was taken into account.

Errors between surgically and histologically assessed lengths, and between radiologically and histologically assessed lengths were expressed in centimetres. A non parametric Wilcoxon test was used to determine if the median value of errors significantly differs from 0.

For the second operation, the influence of several factors on the histologically assessed lengths of diseased segment (no more than 10 cm vs more than 10 cm) was tested by non parametric Wilcoxon test for quantitative variables and by Fisher test for qualitative variables.

5. Results

Twenty four patients were included (9 males, 15 females). Fifteen patients had ileal disease, 9 ileo-colic disease. None had gastro-duodenal lesions. At the last evaluation, 13 were
smokers. Seventeen had undergone 2 resections, six 3 resections and two 4 resections.

The mean age at diagnosis was 22.5 years (11–36); the mean age at the first operation was 26.5 years (15–41); 34 (24–50) at the second operation and 35 (29–50) at the third.

Twelve patients had only had one episode of CD before the first operation, ten between 2 and 5 episodes. Data were not available for 2 patients.

Perianal disease was present in seven (29.2%) patients.

The median delay between diagnosis and first resection was 2.5 years (0–10); between the first and the second resection was 7 years (2–15) \( (n=24) \); between the second and third resection was 7 years \( (3–9) \) \( (n=5) \).

At the first operation, the median length of resected small bowel measured by the surgeon was 40 cm (8–80) \( (n=20) \); 25 cm (14–60) \( (n=20) \) by the histopathologist and 37 cm (10–62) \( (n=13) \) by the radiologist.

The resected segment at the second operation was 20 cm (3–60) \( (n=23) \) measured by the surgeon and 15 cm (3.5–50) \( (n=24) \) by the histopathologist. On the last small bowel follow-up before the second resection, the median length of the diseased bowel was 15.5 cm (3–30) \( (n=22) \).

The resected segment at the third operation was 11.5 cm measured by the surgeon (10–30) \( (n=6) \), 19.5 cm (10–30) \( (n=4) \) by the histopathologist, and 16 cm (2–28) \( (n=7) \) by the radiologist.

The resected segment at the fourth operation for the 2 patients was 20 cm measured by the surgeon, 19 cm by the histopathologist and 27 cm by the radiologist.

The portion of diseased ileum was significantly longer at the first operation than the second according to the radiologist \( (p=0.0005) \), surgeon \( (p=0.005) \) and histologist \( (p=0.02) \) while there was no difference in the three measurements between the second and third resections \( (p=NS) \).

There was no difference in the radiological and histological assessments of the diseased ileum. On the other hand, the lengths found by the surgeons were longer than the histologist \( (p=0.003) \).

No factors listed in the study population section were found to determine the length of the diseased bowel.

6. Discussion

The present study shows that the length of the diseased segment was shorter at the second surgery than the first and remained stable at the third surgery for the three episodes of recurrence after surgery. The histologist measured the diseased bowel after biochemical fixation which might have included a disease free segment to perform the anastomosis. The histologist measured the diseased bowel after biochemical fixation which might reduce the length of the resected small bowel. Because histological and radiological lengths were similar, a small bowel follow-up after clinical recurrence would provide the length to be resected after medical failure. D’Haens et al. studied the radiological length of the recurrence after first resection. No difference was found between the length of the diseased segments before surgery and after recurrence (26 vs 24 cm).17

The outcome of penetrating or strictureting phenotypes of CD may be surgery. Medical treatment is partially effective in controlling flares and avoiding complications but there is a risk of side effects. Treatment may only delay surgery. Besides medical treatment, surgery is a therapeutic option even when it is not obligatory. However, recurrence after surgery is inevitable within a delay that varies. Multiple ileum resections can lead to malabsorption of biliary salts and a risk of fat malabsorption. A major length of resected small bowel after one or several surgeries can lead to a short bowel syndrome. However we have no data about the quality of life, risk of adhesions, chronic pain and malabsorption for those patients. Indications for a second intervention must also take into account the 3 major characteristics of the disease: the location of recurrence after surgery, the delay between resection and clinical relapse and the length of the diseased segment on the neo-terminal ileum after recurrence.

In this study, all patients had ileal or ileo-colonic disease and recurrence always occurred on the anastomosis and/or the neo-terminal ileum. There is very little data concerning the length of the diseased segment and none in patients with 2 resections or more on the terminal or neo-terminal ileum. After a first operation, recurrence usually occurs on the anastomosis and the neo-terminal ileum endoscopically and radiologically.\(^\text{11,13}\) In the study by Olaison et al., diseased areas were limited to the neo-terminal ileum in patients without associated colitis. In patients with associated colitis, the inflammation was more pronounced above than below the anastomosis.\(^\text{11}\) Another study showed that recurrence after resection was located on the ileo-colonic anastomosis with a proximal limb extension. However when the disease was limited to the small bowel, recurrence was limited to the anastomosis (58.5%).\(^\text{19}\) The length of the recurrence was not evaluated.

For the analysis of the delay between resection and clinical relapse, the only factor shown to be predictive of clinical relapse was endoscopic signs within the first year after resection.\(^\text{12}\)

No relationship was found in this study between the length of recurrence and factors such as age at diagnosis, delay between the first surgery and the first symptoms, delay between the first surgery and diagnosis, delay between the 2 surgeries, ano-perineal disease, disease activity or tobacco consumption. There are many data about the risk factors of recurrence in the literature but none about length. The well established risk factors of recurrence include: multiple site vs single site involvement, family history and tobacco consumption.\(^\text{3,16,20,21}\) Small bowel localization was associated with a significantly increased risk of surgery as were strictureting and penetrating diseases.\(^\text{22}\) Only one study found a link between the length of resection and the risk of recurrence but this has not been confirmed.\(^\text{13,23}\)

Because recurrence is inevitable, the aim of ideal therapeutic management would be prevention. The European Consensus recommended a prophylactic treatment after small intestinal resection. Thiopurines are more effective than mesalazine for prevention.\(^\text{24–26}\) Infliximab has only been tested in a few patients and has shown a benefit at one year. Nevertheless, these results must be confirmed.\(^\text{27}\) When recurrence is symptomatic particularly for obstructive symptoms, the efficacy of treatments is also limited.
Steroids are the most extensively used treatment but can result in dependency and side effects. The results on Infliximab are conflicting and there is some concern about the risk of inducing symptomatic stenosis.\textsuperscript{28,29} Surgery must also be indicated with caution for the reasons we have discussed previously, although it still has an important place in the treatment options. For patients with obstructive symptoms after an operation for ileo-colic CD, the length of the obstructed neo-terminal ileum is at worst similar to that of the initial operation; therefore, elective surgery followed by post operative preventive medical therapy to arrest recurrence of disease is a valid option as indicated also by the recently updated ECCO guidelines. We did not find any bias in our population that might affect this result. In particular, the only treatment received by some patients was 5-ASA, which only slightly affects the risk of recurrence and should not influence its length.

No conflicts of interest exist. We have disclosed to the study participants that no conflicts of interest exist.

References