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Cumulative Length of Bowel Resection in a Population-based Cohort of Patients With Crohn's Disease

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Abstract

Background & Aims—Little is known about the cumulative extent of bowel resection among patients with Crohn's disease.

Methods—Using the resources of the Rochester Epidemiology Project, we identified a cohort of 310 incident cases of Crohn's disease from Olmsted County, Minnesota, who were diagnosed between 1970 and 2004. Operative and pathology reports were reviewed for bowel resection length. Median bowel resection lengths (with interquartile range, IQR) were calculated per resection, cumulatively, and as a rate per year of follow-up.

Results—One hundred forty-seven patients underwent 1 or more bowel resection. The median follow-up time per patient was 13.6 years (range, 0.2–39 years). Among the 141 patients with resection data available, 211 resections were performed (100 patients with 1 resection, 24 with 2 resections, 9 with 3 resections, 6 with 4 resections, 1 with 5 resections, and 1 patient with 7

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resections). The median length of bowel resected was 40 cm (IQR, 22–65 cm) at any resection. The median cumulative length of bowel resected was 64 cm (38–93 cm) during the follow-up period. The median (IQR) rate of bowel resected was 4.2 cm total bowel annually (2.8–7.7 cm). The median length resected was highest for the first resection (52 cm; IQR, 32–71 cm). A mixed regression analysis showed that the length of the first resection was significantly greater than that of the second ($P=.002$), without significant differences between the 2nd and 3rd or subsequent resections.

Conclusions—In a population-based cohort of patients with Crohn’s disease, the median cumulative length of total bowel resected was 64 cm during the follow-up period; the median rate of bowel loss due to resection was 4.2 cm annually.

Keywords

IBD; progression; outcome; bowel damage; surgery

INTRODUCTION

Crohn’s disease is a chronic, progressive and destructive disease¹. It is characterized by transmural inflammation, and progression to intestinal complications (stricture, fistula and/or abscess) occurs in about half of patients 20 years after diagnosis². Despite an increasing use of immunomodulators and anti-tumor necrosis factor (TNF) therapy, the need for surgery remains high in Crohn’s disease^{1,3}. In a population-based cohort of U.S. adult patients diagnosed with Crohn’s disease between 1970 and 2004, the cumulative probability of major abdominal surgery approached 60% after 20 years of disease⁴. However, surgery is not curative, and post-operative recurrence is common in Crohn’s disease⁵. In population-based studies, approximately half of patients experienced clinical recurrence at 10 years⁵. Also, many patients required second or third surgeries⁴. It has been determined previously in the Olmsted County Crohn’s cohort that factors associated with onset of intestinal complication include ileal/ileocolonic/proximal gastrointestinal involvement relative to colonic disease², while factors associated with time to first major abdominal surgery include male gender, ileal/ileocolonic/proximal GI involvement, cigarette smoking, early need for corticosteroids, and penetrating or stricturing phenotype relative to non-penetrating, non-stricturing phenotype⁴.

In the mid-1980s, J.T. Sharp promoted a more extensive use of radiological analysis in therapeutic trials to better evaluate cumulative joint damage and the potential for disease modification of drugs in rheumatoid arthritis⁶. Similar to rheumatoid arthritis, the concept of bowel damage in Crohn’s disease is receiving growing interest from gastroenterologists. Along these lines, the first bowel damage score in Crohn’s disease, the Lémann Index, has been developed^{7,8}. When developing this tool, a panel of international experts in the field of inflammatory bowel disease agreed that intestinal resection should be considered the maximum level of bowel damage, as it is by definition irreversible⁷.

In 1994, Cosnes and colleagues found that bile salt diarrhea occurred in about half of patients with Crohn’s disease following bowel resection⁹. Repeated intestinal resections may lead to impaired gastrointestinal functioning associated with nutritional and vitamin

deficiencies, including short bowel syndrome and vitamin B12 deficiency¹⁰. Furthermore, loss of the ileocecal valve may increase the risk of small bowel bacterial overgrowth¹¹, and ileal resection may result in loss of the “ileal brake”¹².

We therefore sought to estimate the cumulative length of bowel resection in Crohn’s disease in a well-defined population-based inception cohort.

METHODS

Patient Selection

A previously identified population-based inception cohort of subjects with Crohn’s disease⁴ was updated through March 2009 for this study.

Study Setting

Olmsted County is situated in southeastern Minnesota and had approximately 124,000 people at the 2000 U.S. Census. In 2000, 90.3% of the population was white, 7.0% black, and 2.9% Hispanic. Among county residents, the level of education was higher (34.7% had completed college as of 2000 vs. 24.4% nationwide), and the prevalence of individuals below the poverty level was lower (6.4% in 2000 vs. 12.4% nationwide)¹³.

Rochester Epidemiology Project

The Rochester Epidemiology Project (REP) is a unique medical records linkage system developed in the 1960s and funded in part by the National Institutes of Health. It exploits the fact that virtually all of the health care for the residents of Olmsted County is provided by two organizations: Mayo Medical Center (Mayo Clinic and its hospitals, Rochester Methodist and Saint Marys); and Olmsted Medical Center (a multispecialty clinic and its hospital, Olmsted Community Hospital). Diagnoses generated from all outpatient visits, emergency room visits, hospitalizations, nursing home visits, surgical procedures, diagnostic studies, autopsy examinations, and death certificates for all county residents seen since 1908 are recorded in a central diagnostic index^{13–16}. In any three-year period, over 90% of county residents are examined at one of the two health care systems^{13–16}. Thus, it is possible to identify all diagnosed cases of a given disease, and all diagnostic examinations, including radiological studies, performed in these subjects.

Case Ascertainment

With approval from the Institutional Review Boards of Mayo Foundation and Olmsted Medical Center, the records of 310 patients who had not denied permission for research access to their medical records and who were first diagnosed with Crohn’s disease between January 1, 1970 and December 31, 2004 were reviewed^{4,17–19}. Demographic information including date of birth, date of symptom onset, date of diagnosis, disease type and extent were previously obtained⁴. Using the date of symptom onset to the last date of follow-up (through March 2009), the duration of follow-up was recorded for each patient. All pathology reports were abstracted for bowel resection length. It has been standard practice in the Division of Anatomic Pathology to measure the length of bowel prior to formalin fixation.

Statistical Analysis

Demographic and clinical factors such as age, gender, smoking status, family history, and extraintestinal manifestations were recorded at the date of diagnosis, while disease extent, disease behavior, perianal disease, and medication use during the first 90 days after diagnosis were also recorded. Median bowel resection lengths (with interquartile range, IQR) were calculated per resection, cumulatively, and as a rate per year of follow-up. Differences in the length of resection per year of follow-up were assessed across the four decades using an analysis of variance. A mixed linear model was used to assess whether the length of the first resection was significantly greater than that of the 2nd, 3rd, or subsequent surgeries. A within-patient AR(1) covariance structure was assumed in the model for subsequent surgeries. Similarly, for assessment of differences in resected length across the decades, a mixed linear model was used.

The alpha-level was set a 0.05 for statistical significance.

RESULTS

Patient Characteristics at Diagnosis

Using the resources of the Rochester Epidemiology Project, we have previously identified a cohort of 310 incident cases of Crohn's disease among Olmsted County, Minnesota residents diagnosed between 1970 and 2004. One hundred fifty-six patients underwent at least one abdominal surgery, including 147 patients who underwent at least one bowel resection⁴.

Pathology reports for bowel resection length were available for all but 6 patients. Hence, a total of 141 patients were included in this study. Seventy-eight of the 141 patients (55.3%) were male (Table 1). According to the Montreal classification²⁰ only 12 patients (8.5%) were younger than 16 years old at diagnosis (A1), 91 (64.5%) were between 17 and 40 years old at diagnosis (A2), and 38 (27.0%) were older than 40 years at diagnosis (A3). Fifty-five patients had ileitis (39.0%), 22 had colitis (15.6%), and 60 patients had ileocolitis (42.6%) at the time of diagnosis, with the remaining 4 (2.8%) being gastroduodenal. Eighty-seven patients (63.5%) had non-stricturing and non-penetrating disease (B1), 11 patients (8.0%) had stricturing disease (B2), and 39 (28.5%) had penetrating disease (B3). Perianal disease (p) was noted in 25 patients (17.7%) prior to or within 90 days of Crohn's disease diagnosis. Sixty-five patients (47.8%) were non-smokers at the time of Crohn's diagnosis, while 57 patients (41.9%) were current smokers. A familial history of IBD was reported by 24 patients (17.6%). Extra-intestinal manifestations at the time of diagnosis were noted in 15 patients (11.0%). Median follow-up per patient was 13.6 years (range, 0.2–39).

Bowel Resection Lengths at Any Resection

Among the 141 patients with resection data available, a total of 211 resections were performed (100 patients with 1 resection, 24 with 2, 9 with 3, 6 with 4, 1 with 5, and 1 patient with 7 resections). The median lengths of small bowel, colon and total bowel resected at any resection and cumulatively are shown in Table 2. The median length of total bowel resected was 40 cm (IQR, 22–65) at any resection: 10 cm (7–31) for colon resected, and 23 cm (12–40) for small bowel resected. The cumulative length of total bowel resected

during follow-up was 64 cm (IQR, 38–93): 15 cm (8–50) for colon resected, and 36 cm (17–60) for small bowel resected. The median rate of total bowel resected per year of follow-up was 4.2 cm (IQR, 2.8–7.7): 1.5 cm (0.5–3.6) for colon resected, and 2.4 cm (1.2–4.8) for small bowel resected.

Removing those patients with colonic only disease at baseline, there were 119 patients who underwent 180 resections (85 patients with 1 resection, 18 with 2, 9 with 3, 5 with 4, 1 with 5, and 1 patient with 7 resections). The median lengths of small bowel, colon and total bowel resected at any resection and cumulatively are shown in Table 3. The median length of total bowel resected was 41 cm (IQR, 25–61) at any resection: 9 cm (7–20) for colon resected, and 26 cm (17–45) for small bowel resected. The cumulative length of total bowel resected during follow-up was 57 cm (IQR, 35–84): 11 cm (7–25) for colon resected, and 45 cm (19–60) for small bowel resected. Excluding the patients with isolated Crohn's colitis at baseline, the median rate of total bowel resected per year of follow-up was 4.1 cm (IQR, 2.5–7.8): 1.1 cm (0.5–2.6) for colon resected, and 2.8 cm (1.6–5.6) for small bowel resected.

Bowel Resection Lengths at First, Second and Third Resections

The median lengths of small bowel, colon and total bowel resected at first, second and third resections are shown in Table 2. The median length of total bowel resected was 52 cm (IQR, 32–71) at first resection: 10 cm (7–36) for colon resected, and 30 cm (13–45) for small bowel resected. The median length of total bowel resected was 23 cm (15–35) at second resection: 8 cm (4–19) for colon resected, and 19 cm (11–30) for small bowel resected. The median length of total bowel resected was 24 cm (13–33) at third resection: 15 cm (6–28) for colon resected, and 15 cm (12–20) for small bowel resected. A mixed regression analysis showed the length of the first resection was significantly greater than that of the second ($p=0.002$), without significant differences between the second and third or subsequent resections. Largely similar median bowel lengths were seen when repeating this analysis after excluding patients with isolated Crohn's colitis at baseline (Table 3). When the mixed regression analysis was repeated after excluding the baseline colonic only patients, the difference in bowel lengths between the first and second resection was no longer statistically significant ($p=0.07$).

Bowel Resection Lengths According to Study Period

The mean length of total bowel resected per year of follow-up was 4.0 cm (± 6.9) at any resection during 1970–1979: 1.8 cm (± 3.8) for colon resected, and 2.1 cm (± 4.7) for small bowel resected. The mean length of total bowel resected per year of follow-up was 9.6 cm (± 16.9) at any resection during 1980–1989: 4.7 cm (± 8.5) for colon resected, and 4.9 cm (± 10.4) for small bowel resected. The mean length of total bowel resected per year of follow-up was 5.2 cm (± 11.1) at any resection during 1990–1999: 1.4 cm (± 3.9) for colon resected, and 2.3 cm (± 7.4) for small bowel resected. The mean length of total bowel resected per year of follow-up was 5.0 cm (± 9.8) at any resection during 2000–2004: 1.2 cm (± 2.6) for colon resected, and 3.8 cm (± 7.9) for small bowel resected.

The length of small bowel resected per year of follow-up within the decade did not differ significantly across the four decades of this study ($p=0.10$). However, the length of the colon resected per year of follow-up differed significantly across the decades ($p<0.001$).

Effect of Medications on Bowel Resection

Among the 141 patients who underwent one bowel resection, we assessed the influence of medications on the risk of a second bowel resection using Cox proportional hazards regression, treating use of medications as a time-dependent variable. There were no significant associations between the risk of a second resection and the use of 5-aminosalicylates (hazard ratio [HR], 1.4; 95% confidence intervals [CI], 0.6–2.9), immunosuppressives (HR, 1.2; 95% CI, 0.5–2.8), or biologics (HR, 1.8; 95% CI, 0.4–7.3). However, the use of corticosteroids was significantly associated with time to second resection (HR, 3.3; 1.4–7.4). Similar results were seen when patients with colonic involvement were excluded.

DISCUSSION

In the era of disease modification²¹, preventing surgeries has emerged as a major therapeutic goal in Crohn's disease patients. Data from randomized controlled trials indicated that both infliximab and adalimumab were associated with a decrease in number of surgeries at one year^{22–23}. Indeed, in some jurisdictions such as Denmark, the risk of major abdominal surgery in the first 5 years after diagnosis of Crohn's disease has declined over time, coincident with an increase in the use of thiopurines and anti-TNF agents²⁴. The impact of anti-TNF agents on the need for surgery in Crohn's disease beyond one year remains a matter of debate^{3,4}. While several studies have investigated the need for surgery in Crohn's disease at the population level, the cumulative length of bowel resection had yet to be determined.

We assessed the length of bowel resection in a population-based inception cohort of patients with Crohn's disease. We found that the majority of patients (68%) underwent only one intestinal resection. About one third of patients had at least 2 intestinal resections. The median length of total bowel resected was 40 cm (IQR, 22–65 cm) at any resection, and was two times longer for small bowel compared to the colon (23 cm versus 10 cm, respectively). Interestingly, the cumulative length of bowel resected during follow-up (median, 13.6 years) was 15 cm (IQR, 8–50 cm) for colon resected and 36 cm (17–60) for small bowel resected. The upper quartile for small bowel resected (>60 cm) is consistent with the fact that short-bowel syndrome is rare in Crohn's disease. Only 24 of 721 patients (3%) experienced a short bowel syndrome in a retrospective Japanese study (1970–2010)²³. At least 200 cm of small bowel had to be preserved to prevent short bowel syndrome²⁵. A preliminary report from the Olmsted County Crohn's disease cohort showed that the need for home parenteral nutrition (HPN) was relatively low—the cumulative risk of need for HPN was 0.5% at 1 year, 0.9% at 10 years, and 1.5% at 20 years after diagnosis²⁶.

We found that the length of the first resection was significantly greater than that of the second, without significant differences between 2nd and 3rd or subsequent. This is likely explained by the fact that the indication for second and third surgeries is stricture in most of

cases (unpublished data). Of note, there were no differences in the length of small bowel resected per year of follow-up across study decades.

The impact of repeat interventions on gastrointestinal physiology, including multiple nutrition and vitamin deficiencies (e.g., vitamin B12 deficiency), bile salt diarrhea, small bowel bacterial overgrowth, and full-blown short bowel syndrome, should be taken into account when managing Crohn's disease requiring surgery. Over twenty years ago, Cosnes and coworkers developed a postoperative handicap index designed to predict diarrhea and malnutrition following bowel resection in patients with Crohn's disease⁹. Among 112 patients operated on for Crohn's disease, the handicap index correlated significantly with fecal weight and fecal fat, surrogates for impaired GI functioning⁹.

The ileocecal valve serves several critical functions, including limiting the reflux of colonic contents into the ileum and inhibiting jejunal motility in response to fat perfusion (the "ileal brake")¹², thus contributing to maintenance of a normal transit. Cosnes and colleagues paid particular attention to ileocecal resection when developing this postoperative handicap index⁹. Importantly, ileocecal resection was the main indication for surgery and was performed in about two-thirds of patients with Crohn's disease in two population-based cohorts^{4,27}.

Overall, we should keep in mind that intestinal resection may have disabling consequences at the patient level, possibly requiring antidiarrheals together with nutrition support and vitamin supplementation, even in the absence of short bowel syndrome.

The Lémann index assesses globally the cumulative structural bowel damage that can occur in Crohn's disease^{7,8}. Surgical resection of the bowel, being irreversible, is considered the maximum level of bowel damage in this index. Furthermore, regulating defecation is a key component of the first disability index in IBD²⁸. It is the reason why perianal disease is one of the four disease locations (upper gastrointestinal tract, small bowel, colon and/or rectum, and anal locations) in the Lémann index^{7,8}. Interestingly, we previously showed that the first abdominal surgery was a total proctocolectomy in 10.5% patients in Olmsted County in patients diagnosed between 1970 and 2004⁴. This rate is higher than in Cardiff, where only 5% of patients had this surgical procedure²⁷, but is similar to that observed in the same population-based cohort in patients diagnosed between 1935 and 1975²⁹, indicating that this surgical procedure is still required in a significant number of patients.

Preventing surgeries became a realistic goal in the biologics era. In this context, a better knowledge of the cumulative length of bowel resection in Crohn's disease will allow a better understanding of its natural history and may be used to better assess the long-term efficacy of potential disease-modifying anti-inflammatory bowel disease drugs (DMAIDs)³⁰, such as thiopurines and anti-TNF therapy^{24,28}.

One of the strengths of our study resides in the fact that this is a population-based study linked to the Rochester Epidemiology Project, which allows accessibility to all medical records of patients diagnosed with Crohn's disease. This provides complete medical follow-up for county residents. Furthermore, the median follow-up per patient was 13.6 years. Limitations of this study include the fact this is a retrospective medical-records based study.

However, despite the retrospective nature of the study, we could review all operative reports and corresponding pathology reports were reviewed for bowel resection length and only few data were missing (n=6).

In conclusion, in this population-based cohort of Crohn's disease, the median length of bowel resected was highest for the first resection (52 cm). The median cumulative length of bowel resected among the 141 patients who underwent at least one resection was 64 cm. The median rate of bowel loss due to resection in this subset was 4.2 cm annually, highlighting the fact that Crohn's disease can be a progressive, destructive illness in a substantial fraction of patients with the condition. Because repeat interventions are often needed in Crohn's disease, these patients may benefit from bowel-sparing techniques and minimally invasive approaches.

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Table 1

Baseline characteristics of 141 patients from Olmsted County, Minnesota, 1970–2004, who had undergone at least one bowel resection during their clinical course.

Factors at Crohn's diagnosis	N (%)
Gender	
Male	78 (55.3)
Female	63 (44.7)
Age	
Less than 16 years (A1)	12 (8.5)
Age between 17 and 40 years (A2)	91 (64.5)
Age more than 40 years (A3)	38 (27.0)
Disease Location	
Small Bowel (L1)	55 (39.0)
Colitis (L2)	22 (15.6)
Ileocolonic (L3)	60 (42.6)
Gastroduodenal (L4)	4 (2.8)
Disease behavior	
Non-Strictureing/Non-Penetrating (B1)	87 (63.5)
Strictureing (B2)	11 (8.0)
Penetrating (B3)	39 (28.5)
Perianal Disease prior to or within 90 days of diagnosis	
Yes	25 (17.7)
Smoking history	
Current smokers	57 (41.9)
Non-smokers	65 (47.8)
Family History of IBD	
Yes	24 (17.6)
Extra-intestinal manifestation	
Yes	15 (11.0)

Table 2

Median bowel resection lengths in the 141 Crohn's disease patients who underwent at least one bowel resection.

	Median SB, cm (IQR)	Median colon, cm (IQR)	Median total bowel, cm (IQR)
Any resection	23 (12–40)	10 (7–31)	40 (22–65)
First resection	30 (13–45)	10 (7–36)	52 (32–71)
Second resection	19 (11–30)	8 (4–19)	23 (15–35)
Third resection	15 (12–20)	15 (6–28)	24 (13–33)
Cumulative	36 (17–60)	15 (8–50)	64 (38–93)

SB, small bowel; IQR, interquartile range.

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Table 3

Median bowel resection lengths in the 119 Crohn's disease patients who underwent at least one bowel resections, excluding those with colonic only involvement at baseline.

	Median SB, cm (IQR)	Median colon, cm (IQR)	Median total bowel, cm (IQR)
Any resection	26 (17–45)	9 (7–20)	41 (25–61)
First resection	32 (17–45)	9 (7–20)	47 (28–65)
Second resection	18 (9–31)	8 (5–17)	21 (14–36)
Third resection	15 (12–20)	15 (6–23)	22 (13–32)
Cumulative	45 (19–60)	11 (7–25)	57 (35–84)

SB, small bowel; IQR, interquartile range.

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Table 4

Median bowel resection lengths in the 119 Crohn's disease patients who underwent at least one bowel resection, stratified by baseline disease behavior and by number of surgeries.

	Median SB, cm (IQR)	Median colon, cm (IQR)	Median total bowel, cm (IQR)
Baseline Disease Behavior			
Stricturing	30 (24–49)	8 (5–8)	46 (24–57)
Penetrating	33 (21–45)	10 (8–15)	42 (31–54)
Non-stricturing, non-penetrating	25 (16–41)	9 (7–22)	40 (25–61)
Number of surgeries			
Single	30 (15–45)	9 (7–21)	48 (26–67)
Multiple	25 (20–34)	9 (7–14)	35 (25–44)

SB, small bowel; IQR, interquartile range.