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Natural history of Crohn's disease following total colectomy and end-ileostomy

Joanna Lopez, MD¹, Gauree G Konijeti, MD MPH^{1,2}, Deanna D Nguyen, MD^{1,2,3}, Jenny Sauk, MD^{1,2,3}, Vijay Yajnik, MD PhD^{1,2,3}, and Ashwin N Ananthakrishnan, MD MPH^{1,2,3}

¹ Department of Medicine, Massachusetts General Hospital, Boston, MA

² Division of Gastroenterology, Massachusetts General Hospital, Boston, MA

³ Harvard Medical School, Boston, MA

Abstract

Background—Crohn's disease (CD) requires surgical management in up to two-thirds of patients. Few studies have addressed the issue of ileal recurrence after colectomy and permanent ileostomy. The aims of our study were to assess the rate and predictors of postoperative recurrence of CD in patients with permanent ileostomy.

Methods—In a retrospective study from a tertiary referral center, we analyzed the natural history of CD patients who underwent total colectomy and permanent ileostomy. Our primary outcomes were (1) overall disease recurrence including luminal recurrence, perianal disease or peristomal lesions requiring therapy, and (2) luminal recurrence alone defined as endoscopic and clinical recurrence within the terminal ileum. We examined if patient characteristics predicted recurrence using multivariate Cox proportional hazard models.

Results—Our study included 73 CD patients followed for a mean of 28 months (range 0-168 months) after total colectomy and permanent ileostomy. Twenty patients had overall disease recurrence within 10 years after surgery, at rates of 15% and 50% 1 and 5 years. Rate of luminal recurrence was 8% and 35% at 1 and 5 years. Diagnosis at age less than 18 years (HR 2.94, 95% CI 1.14 – 7.62) and anti-TNF therapy prior to surgery (HR 4.75, 95% CI 1.25 – 18.13) were the only independent predictive factors for overall disease recurrence.

Conclusions—Up to one-third of CD patients have overall recurrence of disease after treatment with total colectomy and permanent ileostomy. There is need to develop algorithms for surveillance and management of this select subgroup of patients.

Correspondence: Ashwin N Ananthakrishnan, MD, MPH Division of Gastroenterology Massachusetts General Hospital, 165 Cambridge Street, 9th Floor Boston, MA 02114 aananthakrishnan@partners.org Tel 617-724-9953 Fax 617-726-3080.

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Author Contributions:

J Lopez study design, data collection, drafting of the manuscript, critical revision of the manuscript for important intellectual content

G Konijeti data collection, critical revision of the manuscript for important intellectual content.

D Nguyen data collection, critical revision of the manuscript for important intellectual content.

J Sauk data collection, critical revision of the manuscript for important intellectual content.

V Yajnik data collection, critical revision of the manuscript for important intellectual content.

A Ananthakrishnan study design, data collection, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Keywords

Crohn's disease; ileostomy; recurrence; post-operative

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that often has its onset during young adulthood and is characterized by a protracted course of relapses and remission^{1, 2}. Advances in medical therapy over the past two decades has significantly revolutionized the management of CD and improved our ability to achieve remission, and reduce the number of surgeries and hospitalization²⁻⁴. Yet, nearly half the patients with CD continue to require at least one surgical resection during the course of their disease⁵. Unlike ulcerative colitis (UC), surgery is not curative in CD and is characterized by recurrence of disease.

Most of the literature on post-operative recurrence in CD focuses on patients undergoing terminal ileal resection and ileocolonic anastomosis⁶⁻⁸. Up to 90% of such patients may have endoscopic recurrence within 2 years, and 50% may have clinical symptoms over the same time period⁶⁻¹⁰. The natural history of CD in such patients has led to guidelines and expert opinions recommending either prophylactic medical therapy after resection, or early endoscopic surveillance followed by re-initiation of immunosuppressive therapy in a large proportion of patients¹¹⁻¹³. However, for a subgroup of patients with refractory CD with more extensive colonic or perianal involvement, limited ileocecal resection is not a therapeutic option and such patients often require total colectomy with an end-ileostomy. There is limited data to help understand the natural history of ileal recurrence in such patients¹⁴⁻¹⁸. Yet such information will help inform key decisions including whether there is the need for prophylactic medical therapy post-operatively or if there is need for endoscopic surveillance in a high-risk subset.

We performed this study with the following aims: (1) to examine the natural history of ileal recurrence in patients with CD undergoing total colectomy with endileostomy; (2) to identify subgroups of patients who may be at high risk of recurrence in this clinical setting; and (3) to perform a review of literature of prior studies examining post-operative recurrence following end-ileostomy for refractory CD.

METHODS

Study population

This was a single center retrospective study of patients receiving care at a major tertiary referral hospital (Massachusetts General Hospital) serving over 3 million people in the Greater Boston metropolitan area and neighboring states. We identified all potentially eligible patients through a query of the Research Patient Data Repository (RPDR). Described in previous publications including from our group¹⁹⁻²³, the RPDR is a continually updated registry of all patients seeking inpatient or outpatient care at our hospital by automatically populating data from electronic medical record billing codes, prescription information, laboratory and radiologic tests, operating reports, and scheduling data.

Diagnoses are coded using the International Classification of Diseases, 9th edition, clinical modification codes (ICD-9-CM) while procedures are coded with an ICD-9-CM and/or a current procedural terminology (CPT) code. First, we performed a search of all patients with an ICD-9-CM code for Crohn's disease (555.x). From this subset, we extracted all patients with a diagnosis or procedure code for ileostomy (46.2x, V44.2, V55.2) or total colectomy (45.8x). Manual chart review of all eligible patients was performed by one of the study investigators (J.L.) to identify eligible patients. Patients with a diagnosis of ulcerative colitis, or who underwent only temporary fecal diversion procedures were excluded. A diagnosis of CD was established using accepted clinical, endoscopic, and radiologic criteria^{1, 24}.

Outcomes

We had two study outcomes. Our primary outcome was overall disease recurrence defined as recurrence of luminal, perianal, or peristomal lesions requiring initiation of specific medical therapy. Our secondary outcome was luminal recurrence alone which was defined as endoscopic or clinical recurrence within the terminal ileum. Recurrence of symptoms alone (abdominal pain, increased ileostomy output) that was not accompanied by either endoscopic or radiologic evidence of disease activity and did not require initial of specific CD-directed therapy was not considered as meeting our study endpoint. Study outcomes were confirmed by at least two of the study investigators (J.L., G.G.K, or A.N.A).

Variables

Information on age at diagnosis and gender was extracted from review of the medical records. CD location was defined using the Montreal classification as being ileal only, colon only, or ileocolonic disease with modifiers for perianal involvement²⁵. Disease behavior was classified as inflammatory, stricturing, or penetrating disease. Medical therapy prior to the definitive end-ileostomy was recorded, and patients who continued medical therapy after the definite surgery were specifically noted as having done so. Data was also extracted about endoscopic and radiologic investigations performed, and the mode of confirmation of disease recurrence.

Review of the literature

We queried PubMed between 1966 and 2013 to identify studies examining postoperative recurrence following end-ileostomy for CD using the search terms “Crohn's disease” or “Crohn disease” and “ileostomy” or “post-operative recurrence”. Titles and abstracts were searched through to identify relevant studies and results summarized.

Statistical Analysis

All statistical analysis was performed using Stata SE 12.0. Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions and compared using the chi-square test with Fisher's exact modification where required. All patients contributed person-time from the date of definitive colectomy with end-ileostomy to overall disease recurrence or luminal recurrence in patients who reached the primary outcomes, or to end of follow-up. Cox proportional hazards models with time to disease or luminal recurrence were constructed to identify independent

predictors of recurrent disease. Variables meeting the p-value threshold < 0.15 on univariate analysis were included in our final multivariate model. A two-sided p-value < 0.05 indicated independent statistical significance. Kaplan-Meier curves were constructed to define the incidence of recurrent disease, and compared using the log-rank test. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

A total of 73 CD patients were included in our study. The mean age at diagnosis was 26.9 years (**Table 1**). Over half the cohort were women ($n=44$, 60%) and nearly all were of Caucasian ethnicity. Less than one-fifth of the patients were current smokers at the time of the colectomy with end-ileostomy. As expected, the majority of patients had colonic involvement with their CD with half of the cohort having isolated colonic disease. Over half the patients also had perianal involvement (53%). Three-quarters of the patients had been on at least one anti-TNF agent at the time of their initial surgery with infliximab being the most common agent utilized. Half the patients had at least one prior IBD-related surgery prior to definitive end-ileostomy, and one-third had already undergone more than one surgery in the past. The indication for definitive total proctocolectomy in all patients was medically refractory disease. All patients with prior history of ileal involvement had no macroscopic residual disease at the time of the proctocolectomy. The median follow-up was 19 months (interquartile range 7-35 months).

A total of 21 patients were classified as having overall disease recurrence and twelve as luminal recurrence alone. Among the 9 patients classified as having overall disease recurrence but without objective evidence of luminal recurrence, four were suspected to have luminal recurrence and were started on treatment with steroids or immunomodulator therapy and noted to subsequently have improvement in their symptoms. Three patients had recurrence of their perianal disease requiring therapy initiation, all of whom presented with perianal abscesses. Three patients (including one patient with perianal disease) had recurrent disease defined as development of peristomal pyoderma gangrenosum. **Figure 1** describes the time to overall disease recurrence and luminal recurrence alone following total colectomy with permanent end-ileostomy. At 1 year, 85% of patients were free of recurrent disease with this proportion dropping to 76% at 2 years. At 5 years after end-ileostomy, only 50% of patients were free of overall disease recurrence though the number of patients with follow-up beyond that duration was small. Twelve patients had luminal recurrence alone at rates of 8%, 16% and 35% respectively at 1, 2, and 5 years respectively (**Figure 1**). **Figure 2** presents the time to repeat surgery in this cohort. The risk of re-operation at 5 years was 32%. Only one patient had involvement of proximal duodenum. All other patients with recurrent disease had involvement of the terminal ileum. All cases of luminal recurrence were diagnosed on ileoscopy (erythema, aphthous or deep ulcerations) and histologic confirmation with a small subset of patients having confirmatory radiographic findings. None underwent a capsule endoscopy to establish diagnosis.

On univariate analysis, gender, disease phenotype, location prior to surgery (colon only vs. other), and perianal involvement were not predictive of overall disease recurrence or luminal recurrence (**Table 2, Supplementary Table 1**). Neither prior hospitalization nor IBD-

related surgery was predictive of recurrent disease. In contrast, diagnosis before the age of 18 years, requirement for anti-TNF therapy prior to surgery, and duration of disease prior to definitive stoma were associated with our study outcome with a univariate p-value < 0.15. In the adjusted Coz proportional hazards model, CD diagnosis before the age of 18 years (hazard ratio (HR) 2.94, 95% confidence interval (CI) 1.14 – 7.62) and requirement for anti-TNF therapy prior to surgery (HR 4.75, 95% CI 1.25 – 18.13) were independent predictors of disease recurrence. A total of 16 patients were on medications following the surgery, of whom 11 were only on prednisone which was tapered off over 2 months, 2 were on azathioprine, and 3 on infliximab. Continuing medical therapy following surgery did not influence likelihood of recurrence (HR 2.22, 95% CI 0.66 – 7.47). Analysis of predictors of luminal recurrence alone or recurrent surgery yielded similar associations. Forcing disease behavior or extent in the final model did not significantly change our estimates. Our review of the literature identified 5 prior studies that allowed for estimation of rates of post-operative recurrence following endileostomy (**Table 3**). Most prior studies focused on patients with Crohn's colitis alone, and were limited in their analysis of predictors of disease recurrence and identification of patients at high risk.

DISCUSSION

Recurrence of CD following surgically induced remission is common^{6, 8, 11, 26}. Data informing natural history of recurrent disease is primarily from patients undergoing curative ileocecal resection with ileocolonic anastomosis⁶⁻⁸. Much less is known about the recurrence of disease in the terminal ileum following total colectomy with endileostomy in patients with medically refractory disease¹⁴⁻¹⁸. In the largest series examining this question to date in the anti-TNF era, we report that nearly a quarter of patients developed recurrent disease or required re-initiation of therapy by 2 years though half the patients were able to remain disease-free 5 years after the definitive surgery.

Few prior studies have examined the natural history of Crohn's disease following total colectomy and end-ileostomy (**Table 3**). Amiot *et al.* identified 55 such patients over a 15 year period, two-thirds of which were prior to availability of anti-TNF therapy¹⁴. Clinical recurrence at 5 years in their study was 27% which is lower than the rate identified in our study. Penetrating disease behavior and perianal disease were risk factors for recurrence in the French study¹⁴ but were not associated with overall disease recurrence or luminal recurrence in our center's experience. Fichera *et al.* compared rates of recurrence following segmental resection, total colectomy, or total proctocolectomy in patients with isolated Crohn's colitis¹⁶. They found a 9% rate of recurrence in the group that underwent total proctocolectomy with a longer time to recurrence when compared to those with segmental resection or total colectomy. A smaller Spanish series of only 16 patients identified a recurrence rate of 31% at a median follow-up of 77 months¹⁷. In a smaller series by Onali *et al.* 5/14 patients with an ileostomy (35%) experienced postoperative recurrence²⁷. The largest reported series was by Bernell *et al.* who examined outcomes of patients with Crohn's colitis undergoing various types of resective procedures in Stockholm¹⁵. The rate of symptomatic recurrence was 37% at 10 years following a proctocolectomy and end-ileostomy compared to 58% in those with a subtotal colectomy and ileorectal anastomosis. The higher overall recurrence rates reported in our study could be due to several reasons.

First, we defined our primary outcome of post-operative recurrence to include either luminal recurrence which was the definition adopted by most of the prior studies, or recurrence of perianal or peristomal disease requiring medical therapy. Indeed, restricting our outcome to luminal recurrence alone, our recurrence rate of 25% at 5 years is consistent with existing data.

Endoscopic ileal recurrence can occur in up to 90% of patients who undergo a curative ileocecal resection with the rates of clinical recurrence as high as 50% in observational cohorts as well as the placebo arms of the randomized controlled trials examining strategies for post-operative prevention^{6-8, 11, 13, 28-30}. Well recognized risk factors for post-operative ileal recurrence include continued smoking, surgery for penetrating disease, and prior requirement for bowel resection^{9, 10, 12, 13, 29-31}. Less well defined risk factors relate to the surgical technique (type or patency of the anastomosis), length of bowel resected, or histologic findings including inflammation at the margins, plexitis, or granulomas³². However, few studies have examined whether these are also risk factors for ileal recurrence after end ileostomy as the clinical characteristics of patients undergoing the latter surgery is different from the former. In our study, none of the above risk factors were significantly associated with our primary outcome. However, early age at diagnosis was an independent risk factor for disease recurrence, consistent with literature describing an association between early diagnosis and more aggressive course of CD³³⁻³⁵. It is also intuitive that patients who require the most aggressive medical therapy (anti-TNF use) pre-operatively are also at a higher risk for recurrent disease.

There are a few implications to our findings. First, CD recurrence in the ileum occurs in 30-50% of patients who undergo total colectomy with end-ileostomy. A review of the literature confirms that this rate of recurrence is lower than following an ileocolonic resection and primary anastomosis, but nevertheless significant. Expert opinions suggest stratification of patients undergoing ileocolonic surgery for CD into low, intermediate, or high-risk groups based on presence of risk factors, with consideration for early endoscopic surveillance at 6-12 months in the low and intermediate risk group and prophylactic anti-TNF therapy in those at high risk for recurrence^{11, 13, 29, 30}. The lower rate of ileal recurrence following end-ileostomy suggests that a more conservative strategy may be adopted in this patient population. However, whether patients undergoing end-ileostomy would benefit from endoscopic or radiologic surveillance is unclear and requires larger prospective cohorts to definitively inform this practice. One may presume that such surveillance strategies would focus on patients with multiple risk factors for aggressive disease given the overall lower rate of recurrence. Furthermore, for any surveillance program, it is essential to first establish that identification of endoscopic recurrence and initiation of therapy prior to development of clinical symptoms improves natural history and patient outcomes to a greater degree when compared to initiation of therapy at clinical recurrence alone. While such a principle has been established for ileocolonic recurrent disease, further study of the population with end ileostomy is essential to demonstrate if this approach holds promise. There is virtually no data to recommend prophylactic therapy in this population; however with larger multicenter series, we may be able to define and validate characteristics for accurate risk stratification and develop management algorithms specifically relevant to this population.

There are several limitations to our study. First, it is a single center study based at a referral center, consequently with skew towards greater severity of disease. However, we do not believe this to be a significant limitation as patients undergoing definite total colectomy for refractory CD are often managed at such referral centers. Second, as this was a retrospective study, protocols to identify and manage suspected recurrent disease varied between different providers and over time. The relatively small number of patients limited our power to identify weaker associations. Third, we did not have information on some potentially important factors that may influence disease recurrence such as changing smoking status following surgery. However we modeled smoking at the time of the surgery³⁶. Finally, assessment for recurrent disease using endoscopic or radiologic tools was at the discretion of the treating physician. Thus, there may be an ascertainment bias in that milder endoscopic recurrent disease may have been missed in the absence of standard surveillance protocols.

In conclusion, we demonstrate that 15% and 24% of patients with CD undergoing total colectomy and end-ileostomy experience disease recurrence by 1 and 2 years respectively. This suggests that such patients continue to need to be monitored clinically with consideration for endoscopic or radiologic surveillance pending larger multicenter prospective studies. There may be need to expand currently proposed algorithms for management of post-operative recurrence to this select subgroup of patients and inform clinical practice to optimize patient outcomes.

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Figure 1. Overall disease recurrence and luminal recurrence following total colectomy and end-ileostomy in Crohn's disease

N – number at risk

Figure 2. Repeat surgery following total colectomy and end-ileostomy in Crohn's disease

Table 1

Characteristics of the study population (n =73)

Characteristic	Number (%)
Mean age (SD) (in years)	46.7 (15.3)
Gender	
Female	44 (60)
Male	29 (40)
Mean age at diagnosis (in years)	26.9 (14.4)
White race	70 (96)
Extraintestinal manifestations	16 (22)
Smoking status at the time of surgery	
Never	56 (77)
Former	5 (7)
Current	12 (16)
Disease location	
Ileal	1 (1)
Colonic	38 (52)
Ileocolonic	25 (34)
Pan GI	9 (12)
Disease behavior	
Inflammatory	52 (71)
Stricturing	11 (15)
Fistulizing	10 (14)
Perianal disease	39 (53)
Medications prior to surgery	
Immunomodulator *	58 (80)
Steroids	69 (95)
Budesonide	13 (18)
Biologic therapies	
Any anti-TNF	55 (75)
Infliximab	53 (73)
Adalimumab	24 (33)
Certolizumab pegol	18 (25)
Natalizumab	10 (14)
IBD related hospitalization	55 (75)
IBD related surgery	42 (58)
Multiple surgeries (≥ 2)	26 (36)

* Immunomodulators include azathioprine, 6-mercaptopurine or methotrexate

Table 2

Univariate analysis of predictors of recurrence following total colectomy and end-ileostomy in Crohn's disease

Characteristic	Hazard Ratio	95% confidence interval	p-value
Age at diagnosis			
18 years	1.0		
> 18 years	2.01	0.83 –4.86	0.12
Gender			
Female	1.0		
Male	1.18	0.48 –2.89	0.72
Disease duration	0.97	0.92 –1.02	0.19
Extraintestinal manifestations			
No	1.0		
Yes	1.13	0.44 –2.89	0.79
Smoking status at the time of surgery			
Never	1.0		
Former	1.23	0.44 –3.44	0.70
Current	0.87	0.11 –6.72	0.90
Isolated colonic disease			
No	1.0		
Yes	1.09	0.44 –2.72	0.84
Disease behavior			
Inflammatory	1.0		
Stricturing	0.44	0.10 –1.91	0.27
Penetrating	1.06	0.31 –3.69	0.92
Perianal disease			
No	1.0		
Yes	0.85	0.34 –2.14	0.73
History of anti-TNF use			
No	1.0		
Yes	3.65	1.10 –12.14	0.03
History of IMM use			
No	1.0		
Yes	2.59	0.60 –11.18	0.20
IBD related hospitalization			
No	1.0		
Yes	1.56	0.52 –4.71	0.43
IBD related surgery			
No	1.0		
Yes	0.98	0.38 –2.53	0.98

Table 3

Prior studies defining post-operative recurrence following total colectomy and end-ileostomy

Author	Year of publication	Number of patients	Rate of recurrence
Bernell ¹⁵	2001	89	37% at 10 years
Fichera ¹⁶	2005	76	9% at 5 years
Onali ²⁷	2009	14	36%
Amiot ¹⁴	2011	55	4% at 1 year; 27% at 5 years
Leal-Valdivieso ¹⁷	2012	16	31% (median follow-up of 77 months)
Present study	-	73	15% at 1 year; 50% at 5 years