Recurrence rates following ileo-colic resection in pediatric patients with Crohn's disease

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Research Article

Keywords: ileo-cecal resection, post-operative recurrence, crohn's disease, pediatric

Posted Date: November 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2213747/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Pediatric Surgery International on January 16th, 2023. See the published version at https://doi.org/10.1007/s00383-022-05346-1.

Abstract

Background: Ileo-colic resection (ICR) is an important therapeutic option for Crohn's disease (CD) patients. There is limited updated data of clinical and endoscopic post-operative recurrence (POR) in pediatric patients with CD for the long run. We aimed to determine recurrence rates following ICR over an extended period of time and asses its risk factors.

Methods: This is a single-center retrospective review of 35 patients with CD between the ages of 6 to 17.9 years who required ICR between 2003 and 2021at Schneider Children Medical Center of Israel. Medical charts were reviewed at different time-points post-ICR.

Results:

Clinical recurrence following ICR was demonstrated in only 11.4% and 28.6% (n=4, n=10) in the first two and five years- much lower rates than what was reported so far. We found no specific risk factor that correlated with clinical recurrence, although patients that were treated with early prophylaxis of anti TNF medications following ICR tend to have less recurrence.

Conclusions:

We found lower POR following ICR, especially in the first years after surgery- which can be attributed to close surveillance and early medical treatment. Such surveillance seem to improve recurrence rates in the first years following ICR.

Introduction

A significant number of adult and pediatric patients with Crohn's disease (CD) present with terminal ileitis, and require immunosuppressive medications to control disease activity. Despite increasing numbers of medications, including different biologics, many patients fail to respond or lose response over time. Ileo-cecal resection (ICR) should be considered in CD patients with either fibrostenotic disease, medical refractory inflammatory disease or when local complications develop (fistulas and/or abscess formation). The surgical approach is often used when disease extent in the terminal ileum is not long, and offers an opportunity to remove diseased/inflamed segment, which allows to guide therapy to prevent recurrence after surgery, rather than treat an inflamed intestine.

Laparoscopic assisted ileo-colonic resection is, in most of the cases, the standard surgical approach in recent years worldwide. It offers better visualization and faster recovery, as opposed to an open surgery that used to take place more than a decade ago.

Post operative recurrence (POR) refers to "*de novo*" development of Crohn's disease (CD) after a curative surgical intent (in which the macroscopic inflamed bowel is removed) []. Clinical recurrence (i.e, reappearance of symptoms that indicate an active disease) and endoscopic recurrence (endoscopic lesions that are compatible with CD) can co-exist; however endoscopic recurrence tends to occur much

earlier, sometimes even within weeks to months following surgery []. Most of the risk factors regarding POR are based on adult studies, and include smoking, colonic inflammation or upper gastro-intestinal involvement. Data regarding POR in pediatric CD is broadly based on retrospective observational studies conducted more than 15 years ago, with high clinical recurrence rates in the first 1–2 years post ICR, reaching 55% [-]. When assessing endoscopy as an outcome, recurrence rates following ICR were even higher, suggesting that endoscopic inflammation might precede clinically active disease. Most recurrences, according to adult literature, occur in the 1st year after surgery (REF). Nevertheless, there is limited data on POR in pediatric patients. We aimed to investigate POR in the first 1,2,5 and 10 years following ICR in large pediatric hospital in Israel, and to assess risk factors that are associated with such recurrence.

Methods

A retrospective study was conducted that included data collection on all pediatric CD patients, aged 6-17.9 years, who underwent ICR between 2003 and 2021 in a tertiary pediatric center. We reviewed the medical charts for demographic and clinical data including age, gender, medical and surgical history. preoperative interventions (including administration of antibiotics, anti-TNF medications, immunomodulators, corticosteroids), preoperative nutritional support, surgical details and post operative course. We also assessed for long-term data, including follow-up visits, labs, endoscopies, post-operative medical therapy and assessment of clinical and endoscopic recurrence. For the current analysis we included patients that had at least 12 months of follow-up after ICR.

Statistical analysis was performed using SAS/STAT software version 9.4 by Statistical Analysis System corporation, North Carolina, United States of America. Data were compared using Fisher's exact test and $\chi 2$ to evaluate differences between qualitative variables and a t-test to compare quantitative variables. A P value of < 0.05 was considered significant. The study was approved by the local institutional review board committee.

Results

Overall, 38 patients with CD underwent laparoscopic assisted ileo-cecal resection at Schneider Children's Medical Center of Israel between 2003–2021. Three patients were lost to follow up following surgery and were not included in our cohort (total of 35 patients). The cohort included 19 males (54.2%) and 16 females (45.7%) with a mean age of 15.11 years at time of surgery (range 10.0-17.8). The Mean interval between age at diagnosis and age at surgical intervention was 40.6 months (range 1-110 months, median- 40).

Fourteen patients (40%) required special pre-operative management that took place during admission (pre-operative optimization, such as special enteral or parenteral nutrition, IV antibiotics or intra-abdominal percutaneous abscess drainage. in eight patients, severe fibro-stenotic disease and subsequent imminent obstruction were noted during colonoscopy, that necessitated special enteral

and/or parenteral nutrition prior to ICR. In six patients, an intra-abdominal abscess was noted in CT scans, but only half of them (n = 3) necessitated percutaneous or laparoscopic intra-abdominal drainage.

Details regarding pre-operative medical treatment is presented in **Table 1**.

Table 1: Demographic and pre-operative data:

Characteristics	
Gender (M:F)	19:16
Age at diagnosis of CD (median, range)	12.3 (6.0, 17.5)
Age at time of ICR (median, range)	15.1 (10-17.8)
Time from initial diagnosis to surgery in months (range)	40.68 (1-110)
Pre-operative steroids (n,%)	12 (34%)
Pre-operative immune-modulators (n,%)	11(31.4%)
Pre-operative anti TNFa (n,%)	21 (60%)
Pre-operative enteral or parenteral nutrition (n,%)	18 (51.4%)
Pre-operative IV antibiotics (n,%)	20 (57.14%)
Pre- operative intra-abdominal abscess drainage	3 (8.57%)

All patients underwent laparoscopic assisted ICR with primary anastomosis. 29 patients (82.8%) underwent stapled side to side anastomosis and the remaining 6 patients (17.1%) underwent hand sewn end to end anastomosis.

Mean length of stay following surgery was 8.53 days. There were no post-operative complications, except in a single patient that developed wound infection and required wound exploration. The median follow-up of patients following ICR was 4.7 years. One patient died 15 years following initial surgery due to small bowel adenocarcinoma. Two more patients underwent a second surgical resection, 7 and 10 years following first surgery, respectively, due to active medical-refractory CD.

All patients had close surveillance following ICR by pediatric gastroenterologists and pediatric surgeons. In all patients, a recommendation to start early prophylaxis (immunomodulators in the first years of our study or anti-TNF medications in recent years) was given, and in the past years a follow up colonoscopy was also part of the surveillance, usually in the first year to follow ICR. Median time of follow up was 4.5 years (min – 1 year, max- 16 years).

Clinical recurrence was defined as recurrence of abdominal pain, diarrhea or fever lasting more than 2–3 weeks when an infectious process was ruled out. Out of 35 patients, 18 (51.4%) had recurrent symptoms during the study period, of whom 4 patients demonstrated clinical recurrence in the first two years (11.4%), and 10 patients (28.6%) in the first five years to follow.

Endoscopic recurrence was defined during colonoscopy based on Rutgers score, including anastomotic aphthous lesions, ulcers or diffusely inflamed mucosa, with or without stenosis. In recent years a scheduled colonoscopy was planned in each patient, according to newer protocols. However, in earlier years colonoscopy was performed only after signs of clinical recurrence and/or laboratory results that demonstrated an active inflammatory process. In two patients an endoscopic recurrence was noted, although without clinical recurrence. Details regarding clinical and endoscopic recurrence are outlined in Table 2:

Table 2
Surgical data and post-operative long term follow up:

Characteristic	Clinical recurrence	Endoscopic recurrence
Recurrence in the 1st year following surgery	1	1
Recurrence 1–2 years following surgery	3	5
Recurrence 2–5 years following surgery	6	6
Recurrence 5–10 years following surgery	2	2
Recurrence 10 + years following surgery	6	6
Total no. of patients with recurrence	18	16

Table 3 outlines risk factors that may be associated with POR. In our cohort, patients that were treated immediately with anti-TNF medications tend to have lower recurrence rate, although not statistically significant. Other factors that were previously reported as risk factors (such as, young age at diagnosis or longer duration to surgery) were not statistically significant, in our cohort, as risk factors of post operative recurrence.

Table 3
– risk factors associated with post operative recurrence:

	No Recurrence (n = 17)	Recurrence (n = 18)	p value
Age at diagnosis (median, range)	13 (7, 15.3)	10 (6, 17.5)	0.64
Time (months) to surgery (median, range)	27 (1,110)	43 (3,104)	0.34
Anti-TNFa therapy following initial surgery	12	6	0.09
Follow up time in Years (average, range)	4.1 (1–12)	9.3 (2–16)	0.14

Discussion

Ileo-colonic resection is the most frequent operation performed in CD patients []. However, the term “curative resection” does not truly imply a definite cure, and many efforts have been made in the last decades in order maintain quiescent disease and postpone recurrence. Such efforts include early routine endoscopic monitoring (6–12 months following surgery) and/or early postoperative pharmacological prophylaxis []. In the pediatric population, there is little up-to-date data on recurrence rates.

The NASPGHAN Clinical Report on Postoperative Recurrence that was published in 2017 states that clinical recurrence is frequent, occurring in up to 55% in the first 1 to 2 years post surgery. Moreover, approximately 50–73% of patients had clinical recurrence by 5 and 10 years after surgery. However, the review was based on observations that were published more than a decade ago. Spencer et al. [] recently published updated data regarding pediatric endoscopic rate recurrence in the biological era and revealed that the rate of endoscopic recurrence was 46% at 2 years, demonstrating the need for postoperative surveillance and effective prophylaxis. The study also reinforces the findings that both younger age at diagnosis and longer disease duration in pediatric CD are associated with disease recurrence postoperatively []. Nevertheless, the article focuses mainly on endoscopic and histological recurrence, and less on clinical recurrence and long term follow up.

In the current study, we investigated long term follow up (median-4.5 years) post ICR in the pediatric population. We found that in the first two years following surgery, only 11.4% (n = 4) patients had clinical recurrence, much lower than what was reported so far. These findings shed new light and demonstrate potentially improved outcomes, especially in the first years to follow ICR. It can be attributed to both initiation of anti-TNF medications (shortly after ICR) and routine post op colonoscopy.

In our cohort, 18 patients (51%) received early anti-TNFa medications following ICR, which is higher significantly than what was reported in other cohorts (0–10%) [6,]. This likely represents a universal trend of initiation of early prophylaxis with anti-TNFa medications within several weeks of ICR [8]. We have noticed lower rates of recurrence in this group (33%/n = 6 compared to 64.7%/n = 11 in the group that had not receive such prophylaxis) but without statistical significance. It is possible that with larger numbers the true effects of early anti-TNFa prophylaxis following ICR would be evident.

Albeit other reports precluded that younger age at diagnosis and longer duration to surgery as risk factors regarding POR, and although patients that had POR in our cohort tend to be younger at diagnosis and have longer duration to ICR, we did not identify these features as risk factors associated with POR.

Although lower POR were observed in the first two years, when looking on long term follow up, half (n = 18/35) of the patients had clinical recurrence. Such rates need to be revised in the years to come when more data will be available on patients that were operated in the last 1–3 years.

Our paper has several limitations. First, this is a retrospective study. Second, patients that underwent ICR more than a decade ago were compared to patients that underwent more recent procedures, when close

surveillance practices were applied. However, it demonstrates a clear trend and a better benchmark to set upon when dealing with POR in the pediatric population.

In conclusion, the combination of performing ICR and continue with close surveillance that includes early anti – TNF prophylaxis and a scheduled colonoscopy yielded, in the last years, much lower POR. Such results are critical in terms of growth and development in children suffering from crohn's disease.

Declarations

Statement of ethics: This study was approved by the local ethics committee at Rabin Medical Center.

Disclosure statement: The authors declare that they have no conflict of interest.

Funding source: none.

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