



POSITIVE RESECTION MARGINS IN CROHN'S DISEASE SIGNIFICANTLY INCREASE THE LIKELIHOOD OF DISEASE RECURRING AFTER SURGERY.

Surgery

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ABSTRACT

Disease recurrence postoperatively in Crohn's disease remains a significant concern despite rapid progress in surgical and medical treatments. To better identify at-risk patients and develop targeted therapeutic approaches, more criteria are required. The influence of resection margins on disease recurrence is still uncertain, and general guidelines are lacking. A single-center retrospective study was conducted, including all patients who underwent ileocecal resection due to Crohn's disease. The resection margins were evaluated by two independent pathologists using histopathological criteria from previous consensus reports. The study included 114 patients, with a median follow-up of 35 months. The analysis revealed that while postoperative morbidity was unaffected, positive resection margins are significantly increased the rates of severe endoscopic recurrence at 6 months (15.6% vs. 2.0%, $p = 0.02$) and overall (19.6% vs. 4.2%, $p = 0.001$), leading to a higher rate of surgical recurrence (4.5% vs. 0%, $p = 0.04$). The presence of positive margins was identified as an independent risk factor for severe recurrence of endoscopic disease in a multivariate analysis. Therefore, positive margins are an independent risk factor for both postoperative endoscopic and surgical disease recurrence. Prospective studies are required to determine whether patients with positive resection margins would benefit from extended resection or postoperative medical prophylaxis.

KEYWORDS

Recurrence , Surgery , Resection , Crohns disease

INTRODUCTION

Crohn's disease (CD) poses a significant socio-economic challenge for healthcare systems and patients worldwide. The disease's clinical presentation can be highly variable, requiring a comprehensive approach that encompasses both medical and surgical treatments. Despite advancements in medical therapies, including biological agents, the proportion of patients with complicated CD requiring surgery has remained consistent over the decades.

For cases of isolated terminal ileitis, current guidelines suggest that surgical resection is a viable alternative to medical treatment as the primary therapy. This recommendation is mainly supported by data from the LIR!C trial and has been confirmed by subsequent studies. Therefore, surgery is not only a therapeutic option for complicated CD but also a feasible alternative for localized terminal ileitis.

In certain cases, surgical resection offers advantages over medical treatment. However, postoperative disease recurrence at the anastomosis site is still a major concern. Studies have revealed high rates of disease recurrence, leading to many patients needing extra immunosuppressive medication or further surgery over time. Various strategies have been explored to reduce local disease recurrence rates. While the orientation or technical aspects of creating the anastomosis have not shown clear advantages, novel approaches like the Kono-S anastomosis and extended mesenteric resection show promise in potentially decreasing recurrence rates. However, these strategies still need validation in ongoing prospective randomized trials.

In addition to surgical strategies, pharmacological prophylaxis is another important aspect of managing disease recurrence. The postoperative medical treatment guidelines vary internationally, and there is a lack of clear definitions for risk factors. It could be important to consider histopathological factors like residual inflammation at resection margins to better identify patients at higher risk for disease recurrence after surgery and allow for targeted medical prevention.

"The recent evidence regarding the impact of resection margins on postoperative disease recurrence in localized Crohn's disease is mixed, with different studies showing varying outcomes. As a result, no definitive recommendation on the role of resection margins can currently be made. To address this, a retrospective analysis was conducted to assess the potential impact of positive resection margins on postoperative disease recurrence in a large cohort of patients with localized Crohn's disease.

MATERIALS AND METHODS

Study design

A retrospective single-center analysis was conducted on all patients who underwent ileocecal resection (ICR) for Crohn's disease at the departments of general surgery and pediatric surgery at Narayana Medical College between 2022 and 2024. The study included patients with terminal inflammatory (Montreal classification L1 and L3), penetrating and/or stricturing ileitis (Montreal classification B1–B3).

Data acquisition and study population

Information on patients' baseline characteristics, such as age, gender, symptoms, medical and surgical history, and sociodemographic details, was collected from a local database. Before surgery, the degree of inflammation was determined using endoscopy and MRI scans. Each case was then discussed by a multidisciplinary IBD team, which included a gastroenterologist, surgeon, pathologist, and radiologist, to decide on the necessity of surgery. To evaluate the impact of resection margins on disease recurrence, patients were divided into two groups based on whether their resection margins showed signs of inflammation.

Histopathological assessment

Surgical resection was carried out in areas that appeared non-inflamed to the naked eye. The resection margin was evaluated by two independent pathologists using internationally accepted standards based on previous studies. Criteria for identifying positive resection

margins included signs of active inflammation.

Outcome

The main focus of the study was to measure the long-term rate of severe endoscopic disease recurrence, which was identified using the Rutgeerts-score i3 and i4. This method was selected based on established research and international guidelines. Secondary outcomes included assessing short-term endoscopic recurrence at six months, as well as clinical and surgical recurrence, such as the need for postoperative immunosuppressive medication. An experienced gastroenterologist specialized in inflammatory bowel disease (IBD) evaluated and assigned Rutgeerts-scores for all patients. Surgical recurrence was defined as the necessity for re-operation due to disease recurrence at the anastomosis site. Additional secondary endpoints involved examining short-term postoperative follow-up, including the rates of surgical and non-surgical complications. For patients with positive resection margins, subgroup analyses were conducted to explore the impact of the location of positive resection margins (oral, aboral, or both) and the effect of postoperative medical therapy on disease recurrence.

Statistics

The data was analyzed and presented as medians with ranges or as total numbers with percentages. To compare patient characteristics and primary and secondary endpoints, we used t-tests, Fisher's exact tests, or ANOVA tests based on the data scale and distribution. To find independent risk factors for severe endoscopic recurrence, we used a Cox multivariate model and presented the results as hazard ratios (HR) and 95% confidence intervals (95% CI). A p-value of less than 0.05 was considered statistically significant for all analyses. We used GraphPad Prism (version 8, Graph Pad Software, Inc., San Diego, USA) for descriptive analyses and SPSS statistics (version 28, IBM, Armonk, USA) for multivariate analyses.

Ethical Approval

The study received ethical approval from the Ethics Committee of the Narayana Medical College and Hospital Nellore. The requirement for informed consent was waived by the Ethics Committee. All analyses were conducted according to the appropriate guidelines and regulations.

RESULTS

Patient Characteristics

Between 2022 and 2024, a total of 114 patients underwent ileocolic resection (ICR) at the Department of General Surgery at the Narayana medical college and hospital. Following the exclusion of 34 patients due to loss of follow-up or the presence of long-term stomas, an independent pathological evaluation of surgical specimens identified 46 patients with positive (inflamed) resection margins and 34 patients with negative (non-inflamed) margins. Sociodemographic characteristics, including sex, age, BMI, and smoking habits, were similar between both groups (Table 1). Additionally, no differences were noted in the technical aspects of the anastomosis or the use of preoperative immunosuppressive medication between the two cohorts.

Short-Term Postoperative Outcome

In terms of short-term perioperative morbidity, the rates of anastomotic leakages were similar between the two groups (6.5% vs. 11.7%, p = 0.39). Additionally, the overall complication rates, as measured by the comprehensive complication index (CCI), showed no significant impact of positive resection margins on short-term postoperative outcomes (6.8 vs. 7.2, p=0.86) (Table 1).

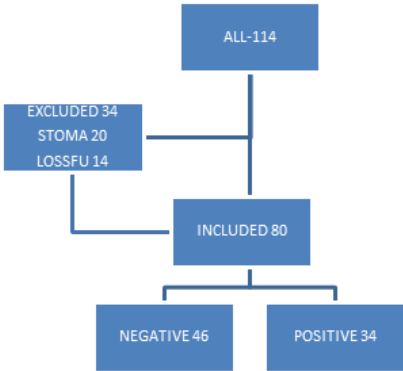


Table 1 Patient characteristics

	Neg. (n = 46)	Pos. (n = 34)	p-value
Sex			
Male	27	18	0.57
Female	19	16	
Age, years, median	37.9	35.3	0.28
BMI, median	23.5	23.2	0.62
ASA classification, median	2.01	2.02	0.79
Smoking, n (%)	14(30.4)	8(23.5)	0.24
Previous abdominal surgery, n (%)	10 (21.7)	7 (20.5)	0.82
Preoperative immunosuppressive medication, n (%)			
None	17 (36.9)	14 (41.2)	0.58
Steroids	20 (43.5)	10 (29.4)	
TNF	11 (23.9)	8 (23.5)	
Biologicals	2 (4.3)	6 (17.6)	
Surgical approach, n (%)			
Laparoscopic	26 (56.5)	20 (58.8)	0.89
Open	20 (43.4)	14 (41.2)	
Anastomosis, n (%)			
Side-to-side	16 (34.7)	13 (38.2)	0.60
Side-to-end	17 (36.9)	10 (29.4)	
Kono-S	7 (15.2)	6 (17.6)	
End-to-end	1 (2.2)	0	
Stoma	5 (10.8)	5 (14.7)	
Anastomotic leakage, n (%)	3 (6.5)	4 (11.7)	0.39
CCI	6.8	7.2	0.86

Disease Recurrence

For the analysis of primary and secondary outcomes, 80 patients were included, with 46 having negative resection margins and 34 having microscopic disease. Concerning the primary outcome of severe endoscopic disease recurrence during follow-up, patients with positive resection margins showed significantly higher rates of severe endoscopic recurrence (Rutgeerts-score i3-i4) compared to those with negative margins (19.6% vs. 4.2%, p = 0.001). The median follow-up duration was similar between the groups (33.0 months vs. 34.1 months, p = 0.99) (Table 2). Positive resection margins were also identified as an independent risk factor for severe endoscopic disease recurrence in a multivariate analysis (p = 0.015, OR 5.94, 95% CI 1.41–25.13) (Table 4).

	Neg. (n = 25)	Pos. (n = 16)	p-value
Endoscopic recurrence (i1-i4), n (%)	16 (64.0)	10 (62.5)	0.98
Severe endoscopic recurrence (i3-i4), n (%)	1 (2.0)	3 (15.6)	0.02
Postoperative prophylaxis, n (%)	7 (28.3)	6 (37.5)	0.59

Regarding secondary outcomes, there were no differences in the median Rutgeerts-scores between patients with negative and positive resection margins (1.23 vs. 1.18, p = 0.73). However, severe endoscopic disease recurrence (Rutgeerts-score i3-i4) was significantly higher at 6 months in patients with positive resection margins compared to those with negative margins (15.6% vs. 2.0%, p = 0.02). Overall endoscopic recurrence rates (i1-i4) were similar between both groups at 6 months (62.5% vs. 64.0%, p = 0.98), and the rates of postoperative medical prophylaxis were also comparable (37.5% vs. 28.3%, p = 0.59) (Table 3). Over the entire follow-up period, there were no differences in clinical recurrence rates (19.4% vs. 18.5%), but surgical recurrence rates were significantly higher in patients with positive resection margins (4.5% vs. 0%, p = 0.04).

The need for postoperative immunosuppressive medication did not differ between the groups.

Table 2. Overall follow up. Significant values are given in bold.

	p-Value	Odds ratio (OR)	95% CI
Smoking	0.06	3.68	0.96–14.1
Previous abdominal surgery	0.17	0.20	0.02–1.96
Immunosuppressive medication	0.69	1.36	0.30–6.24
Positive resection margins	0.015	5.94	1.41–25.13

Table 3. Six months follow up. Significant values are given in bold.

	Neg. (n = 46)	Pos. (n = 34)	p-value
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Follow up, months	33.0	34.1	0.99
Rutgeerts-score, median	1.23	1.18	0.79
Severe endoscopic recurrence (i3-i4), n (%)	2/36 (4.2)	5/26 (19.6)	0.001
Clinical recurrence, n (%)	9 (18.5)	7 (19.4)	0.88
Surgical recurrence, n (%)	0 (0)	2(4.5)	0.04
Immunosuppressive medication/biologicals, n (%)	57 (61.9)	48 (71.6)	0.24

DISCUSSION

In Crohn's disease, recurrence at the anastomosis site after ileocecal resection is a significant challenge for patients. Even with advancements in surgical techniques, real-world data show high rates of recurrent inflammation at the anastomosis site during follow-up. Addressing inflamed resection margins is crucial for improving postoperative outcomes and reducing disease recurrence rates. Our findings indicate that while overall endoscopic recurrence rates are not dependent on resection margins, severe endoscopic and surgical recurrence rates are linked to positive resection margins. Therefore, we have identified positive resection margins after ileocecal resection in Crohn's disease as a risk factor for severe disease recurrence.

Despite resecting tissue from areas that showed no signs of inflammation, 42.4% of patients had positive resection margins, which is consistent with previous studies highlighting this issue. When analyzing the impact of resection margins in patients with localized terminal ileitis, we found that positive margins were not linked to perioperative complications. However, positive margins significantly increased the rates of severe recurring disease seen during endoscopy (Rutgeerts-score i3-i4) at both the 6-month mark (15.6% vs. 2.0%, $p = 0.02$) and throughout the overall follow-up (19.6% vs. 4.2%, $p = 0.001$), despite similar rates of postoperative preventive treatment.

Further analysis confirmed that positive margins were an independent risk factor for severe endoscopic recurrence ($p = 0.015$). Notably, while no patient with inflammation-free margins needed further surgery due to disease recurrence at the anastomosis site during the follow-up, positive margins were significantly associated with higher surgical recurrence rates (4.5% vs. 0%, $p = 0.04$). These findings emphasize the clinical significance of addressing positive inflamed resection margins. Identifying patients who will benefit the most from postoperative preventive treatment while avoiding unnecessary treatment poses a significant challenge. European guidelines recommend initiating preventive treatment for patients with at least one risk factor (such as smoking, penetrating disease, or previous surgery). In contrast, the American Gastroenterology Association (AGA) recommends early postoperative medical prevention for all patients, regardless of risk factors. It has been suggested, however, that endoscopy-guided pharmacological treatment might be a better approach for patients at low risk of disease recurrence, to minimize potential adverse events. Despite the lack of a clear definition of "low risk" and limited evidence, this underscores the need to identify additional risk factors to optimize treatment and reduce unnecessary treatment and healthcare costs. Current guidelines do not provide specific recommendations regarding positive resection margins due to inconsistent evidence and the absence of standardized histopathological criteria. Some studies and reviews have found no correlation between microscopic disease at resection margins and disease recurrence. For example, a prospective randomized controlled trial showed no increase in clinical or surgical recurrence rates associated with active inflammation at resection margins. Conversely, Riault et al. reported higher rates of clinical and surgical recurrence in patients with microscopic disease, though they did not assess endoscopic outcomes. Similarly, Poredska et al. found that inflammation at resection margins was linked to an increased risk of early postoperative disease recurrence within 6 months. Other studies, such as those by Wasmann et al. and Hammoudi et al., identified positive resection margins in specific locations (distal colonic or ileal) as significant risk factors for postoperative recurrence. Recent meta-analyses have supported the negative impact of positive resection margins on clinical and surgical recurrence, although these analyses included heterogeneous patient cohorts.

The variability in study outcomes is due to differences in inclusion criteria, surgical techniques, and histopathological definitions. There are no universally accepted criteria for defining positive resection margins, leading to challenges in distinguishing disease-associated inflammation from surgery-induced inflammation. Our study

addressed these challenges by defining relevant histopathological criteria based on an international consensus of pathologists specializing in IBD. The findings highlight the importance of defined microscopic disease at resection margins as a predictor of severe disease recurrence.

Bowel-sparing surgery is a fundamental aspect of treating Crohn's disease (CD) to avoid the risks associated with repeated surgeries, which could ultimately result in short-bowel syndrome. While examining resection margins for inflammation during surgery is not currently a standard practice, recent evidence emphasizes the impact of positive resection margins on the recurrence of the disease. Our extensive study stresses the importance of identifying microscopic disease at resection margins as a significant risk factor for recurrence. It is crucial to establish clear criteria for defining CD-associated inflammation at these margins, and all patients with positive margins should be considered for postoperative medical prophylaxis.

Decisions about medical treatment should take into account not only patient characteristics and disease history but also histopathological findings. Our findings indicate that evaluating resection margins based on our defined criteria can help pinpoint patients who are most likely to benefit from postoperative prophylaxis. Therefore, histopathological reports should meticulously assess these criteria and be integrated into clinical decision-making, especially since there are currently no established strategies for managing positive resection margins.

It's important to note that this study has limitations, such as its retrospective nature and single-center design. Additionally, the loss of patients during follow-up can be attributed to the German healthcare system, where many postoperative visits and treatments are managed by private practices. Despite these limitations, this study is one of the largest examining this issue and involves a homogeneous cohort of patients with localized terminal ileitis, reflecting everyday clinical practice. Furthermore, it provides a clear definition of resection margins positive for CD-associated inflammation.

CONCLUSIONS

After surgery, disease recurrence remains a significant challenge, and we still don't fully understand why it happens. Currently, we don't have comprehensive strategies to identify and manage patients at risk. Our study discovered a strong link between positive resection margins and higher rates of severe endoscopic and surgical recurrence. These findings highlight the importance of carefully evaluating resection margins and suggest that patients with positive margins should receive postoperative prophylaxis. Future guidelines should include a standardized definition of positive resection margins as a recognized risk factor for disease recurrence.

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