Original article

A positive proximal resection margin is associated with anastomotic complications following primary ileocaecal resection for Crohn's disease.

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Abstract

Purposes: Bowel resection in patients with Crohn's disease (CD) has a high reported rate of postoperative complications and surgical recurrence. A macroscopically normal resection margin is recommended in CD surgery as wider margins do not translate in reduced recurrence rates. The aim of this study was to evaluate the association between resection margin status and anastomotic complications following ileocaecal resection for primary CD.

Methods: All patients treated with ileocaecal resection for primary CD from 2010 to 2018 were included in this retrospective observational study. Emergency operations and recurrent CD were excluded. Patients in whom an anastomosis was not fashioned at the time of the surgery were also excluded. Histopathology data collected included specimen length and macroscopic description, presence of macroscopic and microscopic involvement of the proximal and distal resection margins. The primary outcome was the rate of positive resection margin in patients who developed anastomotic complications and the secondary outcomes were overall complications rate, length of hospital stay, reoperations and rehospitalisation within 30 days.

Results: 104 patients were included. The proximal resection margin was microscopically involved in 19 patients (18.2%). 10 patients (9.6%) developed intra-abdominal anastomotic related complications, with 5 patients out of 10 (50%) in the group of postoperative anastomotic complications having a positive microscopic proximal margin at histology, compared to 14 patients (14.9%) in the group that did not develop anastomotic complications ($p<0.0001$).

Conclusions: Microscopic involvement of the proximal resection margin is more frequent in patients who develop postoperative anastomotic complications following elective ileocaecal resection for primary CD.

Keywords: Crohn's disease, inflammatory bowel disease, ileocecal resection, resection margins, anastomotic leak.

Introduction

Despite many improvements in the multidisciplinary treatment of Crohn's disease (CD), there is still a substantial risk of surgical resection for lack of response to medical management or complications during a patient's lifetime [1]. Although disease patterns within the gastrointestinal system vary, the terminal ileum and cecum are the most frequently impacted areas (55%). Other areas include small bowel disease only (11-48%), colon disease only (19-51%), and combined small and large intestine (26-48%) [2].

Intestinal resection for CD has a high reported rate of postoperative complications [3,4] increased by risk factors such as malnutrition, active inflammation or infection at the time of surgery and immune suppression [3-5], with reported rates of intra-abdominal sepsis and anastomotic leak as high as 14% and 17% respectively [6].

In addition, a high rate of recurrence following ileocaecal resection for CD has been reported, which can lead to reoperation in 20-30% of patients at 5 years after surgery [7], with approximately 40 to 50% of patients who underwent surgery likely to need further operations within 10 to 15 years [8]. Recurrence generally happens at the anastomosis and the neo-terminal ileum [9] and different anastomotic techniques have been assessed with the belief that a wide calibre anastomosis, such a side-to-side configuration, can result in reduced recurrence rates [10]. It is important to note that a more radical surgical approach, extending the margins of resection proximally and distally to the diseased segment, does not reduce the risk of recurrence, but contributes to the occurrence of short bowel syndrome and must be avoided [11] and for this reason a macroscopically normal margin is accepted in CD surgery [12]. However, the association of the microscopic resection margin status with perioperative complications is still to be evaluated. The aim of this observational study was to correlate the

association between positive resection margin status and anastomotic complications following ileocaecal resection for primary CD.

Methods

Study design:

This retrospective observational study included all patients receiving ileocaecal resection for primary CD from 1st of January 2010 to 31th of December 2018. All patients undergoing emergency operations or surgery for CD recurrence were excluded. Patients in whom an anastomosis was not fashioned at the time of the surgery or in whom the anastomosis was protected by a diverting ileostomy were also excluded. The study was designed according to the STROBE checklist [13].

The indication for surgical resection was agreed at dedicated Inflammatory Bowel Disease multidisciplinary team meetings involving gastroenterologists, colorectal surgeons, radiologists and pathologists. Preoperative evaluation included ileocolonoscopy, MRI enterography and intestinal ultrasound.

Data collection:

Preoperative parameters included age, sex, body mass index (BMI), comorbidities, American Society of Anaesthesiologists (ASA) status, smoking status, weight loss, indication for surgery and preoperative medical treatment.

Operative data included operating time, occurrence of intraoperative complications, estimated operative blood loss, conversion to open surgery with reason for conversion. Follow up data included postoperative length of hospital stay (LOS), time to tolerate oral fluids and oral diet, time to resolution of ileus and complications reported according to the Dindo-Clavien classification [14]. The definition of intraabdominal anastomotic complications included intraabdominal abscesses, pus collections and anastomotic leaks [6]. Histopathology data collected from the pathology report included specimen length and macroscopic description, presence of macroscopic and microscopic involvement of the proximal and distal resection margins, presence in the resected specimen of granulomas, crypt abscesses, myenteric plexitis and pyloric metaplasia. Resections margins were inflammation or granuloma were identified at histopathological assessment were classified as positive.

Primary and secondary outcomes:

The primary outcome was the rate of positive resection margins in patients who developed anastomotic complications compared to patients with a negative resection margin following elective ileocaecal resection for CD. The secondary outcomes were overall complications rate, LOS, reoperations and readmissions within 30 days.

Statistical analysis:

Categorical variables are reported as frequency counts and associated percentage and were compared with the use of the chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as mean (±standard deviation) or median (range) and were compared

with the use of Student's t test. The Mann-Whitney U test was used for continuous, not normally distributed outcomes. Statistical analysis was performed by using GraphPad Prism version 8.0.2 for Windows, (GraphPad Software, La Jolla California USA). All reported p values were two-tailed, and p values of less than 0.05 were considered to indicate statistical significance.

Ethics:

The study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. Informed consent has been obtained from the patients.

Results:

Patient characteristics:

165 patients underwent ileocaecal resection during the study period. 51 patients underwent emergency surgery and were excluded, while 10 patients were excluded because an ileostomy was fashioned at the time of the index operation. 104 patients were finally included in the analysis and baseline patients' characteristics and cumulative postoperative outcomes are detailed in table 1.

Postoperative outcomes

No mortalities occurred. 26 patients (25%) developed postoperative complications within 30 day of surgery. These consisted in wound infection in 6 patients (5.7%), prolonged postoperative ileus requiring total parenteral nutrition in 4 patients (3.8%), chest infection in 2 patients (1.9%). urinary tract infection in 2 patients (1.9%), bleeding requiring transfusion in 1 patient (0.9%) and re-feeding syndrome in 1 patient (0.9%). No statistically significant difference was present in the preoperative use of anti-TNF and steroids between patients who developed postoperative complications and patients who did not. Ten anastomosis related complications (9.6%) were reported, table 2.

Resection margin status and histopathological assessment:

The proximal resection margin was microscopically involved in 19 patients (18.2%). The median length of the resected terminal ileum was 19.5 centimetres (range 3.5 – 50). Granulomas were identified in the resected specimen in 23 patients (22.1%), while crypt abscesses were found in 21 patients (20.2%). Myenteric plexitis occurred in 19 patients (18.2%) and pyloric metaplasia in 3 (2.9%).

Resection margin status in patients with anastomotic complications:

10 patients (9.6%) developed intra-abdominal anastomosis related complications, consisting in 4 anastomotic leaks (3.8%) and 6 intra-abdominal collections (5.7%) requiring radiological guided drainage. 3 patients with anastomotic leak required relaparotomy and stoma formation, while one case was successfully treated conservatively.

5 patients out of 10 (50%) in the group of postoperative anastomotic complications had a positive proximal margin at histology, compared to 14 patients (14.9%) in the group that did

not develop anastomosis related complications ($p<0.0001$) as summarised in table 3. Having a positive microscopic resection margin was associated with postoperative anastomotic complications in 5 cases out of 19, with a 26.3% reported rate. No differences were found in the rate of crypt abscesses, myenteric plexitis, granulomas and pyloric metaplasia between the two groups.

Discussion:

Repeated surgery for anastomotic related complications represent one of the main reasons for short bowel syndrome in CD [15] rather than multiple resections over time for surgical recurrence [16]. More importantly, multiple resections of the diseased bowel may result in functional diarrhoea, fat malabsorption, and only ultimately in short bowel syndrome requiring parenteral nutrition treatment, while affecting patients' quality of life with selective vitamins deficiencies and malnutrition. The Lémann index evaluates globally the cumulative structural bowel damage that can occur in CD [17]. Surgical resection of the bowel, being irreversible, is considered the maximum level of bowel damage in this index. For these reasons preoperative optimisation of patients and experienced decision making on when to operate and whether to fashion an anastomosis or to create a diverting stoma [18] is paramount to minimise the risk of anastomotic related complications.

We found a 50% rate of positive proximal resection margin in the group of patients who suffered postoperative anastomosis related complications, which was significantly higher than the rate of positive margin in patients without anastomotic complications (14.9%). There are conflicting data regarding the prognostic value of CD histologic features in bowel resection specimens [19]. Karesen et al. [20] initially reported that the presence of microscopic CD at surgical resection margins was associated with increased postoperative

CD recurrence, recommending a wide resection with frozen section evaluation of the resection margins. This finding was also confirmed by Heimann et al [21] while, other studies [22, 23] suggested no association between positive margin status and surgical recurrence. Finally, Fazio et al [11] demonstrated no advantage in terms of lower surgical recurrence rate for wider resection margins in a randomised study. As surgery cannot cure CD, but only treat complications of the disease, a segmental resection of the diseased bowel within macroscopically normal margins is widely accepted [24] and the results of our study do not support a more extended resection. It would be erroneous to assume that margin status per se influences the anastomotic failure, as demonstrated by the 14 patients who did not develop complications despite a positive microscopic margin. As we acknowledge that CD recurrence is multifactorial and unlikely to be influenced only by a single surgical variable, such as anastomosis configuration or mesenteric resection for example, we must do the same for CD anastomosis related complications, as nutritional status, preoperative medical therapy and disease phenotype may all play a role. A recent meta-analysis [25] found a mean reported rate of histopathological margins involvement of 41% in CD resections, with significant heterogeneity across the included 18 studies due to the lack of a standardised definition. For all these reasons, a standardised reporting of CD histopathological specimen is required as advocated by Setoodeh et al [19] and our study highlights a possible correlation between positive microscopic proximal resection margin status with anastomotic complications, adding to the existing literature mainly focused on the association between extent of resection and CD surgical recurrence.

Current discussion on CD recurrence is concentrating on the role of the mesentery, with Coffey et al showing a significantly decreased surgical recurrence rate when incorporating a substantial portion of mesentery in the resected specimen [26]. While the mesentery is likely to play a pathogenic role in CD, it is also crucial for intestinal perfusion, and extensive

removal may compromise bowel tissue with concerns also regarding haemorrhagic dangers associated with division of the mesentery in patients with CD and potential need for increased length of resected bowel if larger mesenteric segments are excised [27]. For now it still remains unclear how much mesentery should be resected in CD surgery and it does represent a limitation that our study did not assess histopathological features of the mesenteric involvement. Another limitation of our study is that no direct Patient Reported Outcome Measures have been assessed as well as the single centre retrospective nature of the study with limited power and patients being recruited within a study period of several years.

Our study highlights the importance of dedicated histopathology support to the IBD multidisciplinary team [28]. It is, in fact, a quality requirement that patients having surgery for IBD have it undertaken by a colorectal surgeon who is a core member of the IBD multidisciplinary team [29] auditing stoma rate, complications, re-interventions and mortality [30]. Larger studies are needed to evaluate the association between margin status and anastomotic complications in CD.

Conclusions:

Microscopic involvement of the proximal resection margin is more frequent in patients who develop postoperative anastomotic complications following elective ileocaecal resection for primary Crohn's disease.

References:

1. Shaffer V O, Wexner S D (2013) Surgical management of Crohn's disease. Langenbecks Arch Surg 398:13–27.

2. Dasari B V, McKay D, Gardiner K (2011) Laparoscopic versus open surgery for small bowel Crohn's disease. Cochrane Database Syst Rev; 19:CD006956.
3. Fumery M, Seksik P, Chirica M, et al. (2015) Postoperative Complications After Ileo-Caecal Resection for Crohn's Disease: A Prospective Multicentre Study Gastroenterology, Apr, Vol.148(4) Suppl 1, pp.S132-S133
4. Alves A, Panis Y, Bouhnik Y, Pocard M, Vicaut E, Valleur P (2007). Risk Factors for Intra-Abdominal Septic Complications After a First Ileocecal Resection for Crohn's Disease: A Multivariate Analysis in 161 Consecutive Patients. Dis Colon Rectum 50: 331–336.
5. Lau C, Dubinsky M, Melmed G, et al. (2013) Higher Preoperative Serum Biologic Levels Are Associated With Postoperative Complications in Crohn's Disease Patients. Gastroenterology, Vol.144(5) Suppl 1, pp.S190-S190
6. Yamamoto T, Allan RN, Keighley MR (2000) Risk factors for intra abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum 43:1141–1145
7. Yamamoto T. Keighley MR (1999) The association of cigarette smoking with a high risk of recurrence after ileocolonic resection for ileocecal Crohn's disease. Surg Today 29(6): 579 – 580
8. Gordon PH, Nivatvongs S (2007) New York, NY: Informa Healthcare. Crohn's disease:820–907.
9. Olaison G. Smedh K. Sjodahl R (1992). Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. Gut 33 (3):331 – 335
10. He X, Chen Z, Huang J, et al. (2014) Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease: a meta-analysis. Dig Dis Sci 59(7):1544-51.
11. Fazio VW, Marchetti F, Church M, et al. (1996) Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Annals of Surgery 224(4):563-73.
12. Buisson A, Chevaux JB, Allen PB, Bommelaer G, Peyrin-Biroulet L (2012) Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther. 35(6):625-33.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. (2008) STROBE Initiative. The Strengthening the Reporting of Observational Studies

in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 61(4):344-9

14. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205-213
15. Uchino M, Ikeuchi H, Bando T, et al. (2012) Risk factors for short bowel syndrome in patients with Crohn's disease. Surg Today. 42(5):447-52.
16. Nightingale JM, Lennard-Jones JE. (1995) Adult patients with a short bowel due to Crohn's disease often start with a short normal bowel. Eur J Gastroenterol Hepatol. 7(10):989-91.
17. Pariente B, Mary JY, Danese S, et al. (2015) Development of the Lémann Index to assess digestive tract damage in patients with Crohn's disease. Gastroenterology. 148:52–63.
18. Morar PS, Hollingshead J, Bemelman W, et al. (2017) Establishing Key Performance Indicators [KPIs] and Their Importance for the Surgical Management of Inflammatory Bowel Disease-Results From a Pan-European, Delphi Consensus Study. J Crohns Colitis 11(11):1362-1368.
19. Setoodeh S, Liu L, Boukhar SA, Singal AG, Westerhoff M, Waljee AK, Ahmed T, Gopal P. (2019) The Clinical Significance of Crohn Disease Activity at Resection Margins. Arch Pathol Lab Med. 143(4):505-509.
20. Karesen R, Serch-Hanssen A, Thoresen BO, Hertzberg J. (1981) Crohn's disease: long-term results of surgical treatment. Scand J Gastroenterol. 16(1):57–64.
21. Heimann TM, Greenstein AJ, Lewis B, Kaufman D, Heimann DM, Aufses AH Jr. (1993) Prediction of early symptomatic recurrence after intestinal resection in Crohn's disease. Ann Surg 218(3):294–298; discussion 298–299.
22. Adloff M, Arnaud JP, Ollier JC. (1987) Does the histologic appearance at the margin of resection affect the postoperative recurrence rate in Crohn's disease? Am Surg. 53(10):543–546.
23. Kotanagi H, Kramer K, Fazio VW, Petras RE. (1991) Do microscopic abnormalities at resection margins correlate with increased anastomotic recurrence in Crohn's disease?: retrospective analysis of 100 cases. Dis Colon Rectum. 34(10): 909–916.
24. Bemelman WA, Warusavitarne J, Sampietro GM, et al. on behalf of the European Crohn's and Colitis Organisation [ECCO] and the European Society of Colo-

Proctology [ESCP]. (2018) ECCO-ESCP Consensus on Surgery for Crohn's Disease. Journal of Crohn's and Colitis, 12(1):1–16.

25. Ryan JM, Rogers AC, O'Toole A, Burke JP. Meta-analysis of Histological Margin Positivity in the Prediction of Recurrence After Crohn's Resection. Dis Colon Rectum. 2019 Jul;62(7):882-892.
26. Coffey JC, Kiernan MG, Sahebally SM, et al. (2018) Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. J Crohns Colitis. 12(10):1139-1150.
27. Buskens CJ, de Groof EJ, Bemelman WA, Wildenberg ME (2017). The role of the mesentery in Crohn's disease. Lancet Gastroenterol Hepatol. 2(4):245-246.
28. IBD Standards Group (2013) Standards for the Healthcare of People Who Have Inflammatory Bowel Disease [IBD]. 2013 update. St Albans, UK: Oyster Healthcare Communications; 2013.
29. NICE Quality Standard [QS81]—Inflammatory Bowel Disease. http://www.nice.org.uk/guidance/qs81/chapter/quality-statement-2-multidisciplinary-team-support.
30. Calvet X, Panes J, Alfaro N, et al (2014) Delphi consensus statement: Quality Indicators for Inflammatory Bowel Disease Comprehensive Care Units. J Crohns Colitis 8:240–51.

Table 1. Baseline patients characteristics and cumulative postoperative outcomes.

Table 1

Patients' baseline characteristics and postoperative outcomes

Included patients	***n* = 104**
Age (years)	38.5 ± 14.4
Sex (M/F)	55:59
BMI	25.1 ± 5.9
ASA	
- I	20
- II	69
- III	15
Previous abdominal surgery	28 (26.9%)
Penetrating CD with intra-abdominal fistulae/abscesses	31 (29.8%)
Surgical approach:	
- Open	4 (3.8%)
- Laparoscopic	100 (96.2%)
Conversion to open	4 (4%)
Operating time (minutes)	127.2 ± 52.1
Blood loss (ml)	44.7 ± 62.3
LOS (days—range)	6 (2–49)
30-day overall complications	26 (25%)
30-day readmissions	15 (14.4%)
30-day re-interventions	3 (2.9%)

CD Crohn's disease, *LOS:* length of hospital stay, *M* male, *F* female, *BMI* body mass index, *ASA* American Society of Anaesthesiologists status, *ml* millilitres

Table 2. Patients who developed anastomosis related complications

Table 2
Patients who developed anastomosis-related complications

	Sex	Age	BMI	Previous surgery	Disease phenotype	Operating time (minutes)	Microscopic positive margin	Type of complication	LOS (days)
1	F	50	35	No	Fibrostenotic	300	Yes	IAC	12
2	M	52	25	Yes	Penetrating	380	No	AL	13
3	F	19	22.6	No	Fibrostenotic	190	No	IAC	9
4	M	29	20.1	No	Fibrostenotic	120	Yes	IAC	8
5	F	55	35	Yes	Fibrostenotic	180	No	AL	6
6	M	32	29.7	Yes	Penetrating	315	No	IAC	9
7	F	47	17	No	Penetrating	270	Yes	IAC	7
8	M	51	27.3	No	Fibrostenotic	310	Yes	IAC	7
9	M	51	36	No	Fibrostenotic	180	No	AL	12
10	F	18	21	No	Penetrating	140	Yes	AL	22

BMI body mass index, *F* female, *M* male, *AL* anastomotic leak, *IAC* intra-abdominal collection, *LOS* length of hospital stay

Table 3. Patients with a microscopically positive resection margin with or without postoperative anastomosis related complications

Table 3

Patients with a microscopically positive resection margin with or without postoperative anastomosis-related complications

	NO anastomotic complications (*n* = 14)	**YES anastomotic complications (*n* = 5)**
Age	39.5 ± 17.1	47 ± 14.7
Sex (M/F)	6:8	2:3
BMI	23 ± 2.8	21 ± 7.1
Previous surgery	1 (7.1%)	0
Penetrating disease phenotype	2 (14.3%)	2 (40%)*
Operating time (minutes)	135 ± 46	270 ± 90.9*
LOS (days)	5 ± 1.7	8 ± 6.4

BMI body mass index, *F* female, *M* male, *AL* anastomotic leak, *IAC* intra-abdominal collection, *LOS* length of hospital stay

*$p < 0.0001$