



## Ileocecal Resections for Crohn's: Predictive Value of Resection Margins on the Risk of Re-Surgery in the Swiss IBD Cohort

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### Abstract

**Background:** Whether positive resection margins have an influence on surgical recurrence is still a matter of debate for Crohn's disease (CD) patients undergoing ileocecal resection. The aims of this study were to analyze whether the involvement of the resection margins had a negative impact on endoscopic or surgical recurrence after ileocecal resection for CD diseases in a national Swiss cohort.

**Methods:** Retrospective analysis of the prospective Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) database of patients with ileocecal resection in whom pathology reports could be retrieved (n=82). The primary outcome was surgical recurrence.

**Results:** The median follow-up was 8 years. Pathology reports were not standardized, did not mention the resection margins in 13%, and often did not include important features such as myenteric and submucosal plexitis. Positive small bowel margins were significantly associated with surgical recurrence (p=0.022) but not with endoscopic recurrence.

**Conclusion:** Positive small bowel margins are associated with surgical recurrence. Pathology reports in Switzerland are still lacking important information and should be standardized in order to stratify the postoperative risk of recurrence.

**Keywords:** Crohn disease, surgical recurrence, resection margins, pathology reports

### Introduction

The therapeutic options for treating Crohn's disease (CD) have been extended in recent years, allowing tailored and individualized treatments (1). The ileocecal segment is the most prevalent primary location of the disease (2) and up to 90% of patients will require ileocecal resection once in their lives (3,4). Well known factors associated with postoperative recurrence are smoking, prior intestinal surgery, absence of prophylactic treatment, penetrating disease at index surgery, perianal location, granulomas in the resection specimen and myenteric plexitis (4). In addition, transmural lesions at the ileal resection margin were found to be associated with endoscopic recurrence (p=0.022) (5). A recent meta-analysis also confirmed the predictive value of positive resection margins with surgical recurrence (relative risk 3.72) (6). These data were however contradicted by other studies (7,8). Furthermore, recent data indicated that not only the proximal margin, but also the distal colonic margin involvement could lead to higher recurrence rates.

The aims of this study were to analyze whether the involvement of the

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resection margins had a negative impact on endoscopic or surgical recurrence after ileocecal resection for CD disease in a national Swiss cohort.

## Material and Methods

This is a retrospective analysis of prospective data from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) (9) including all patients with ileocecal resection Crohn's disease (n=446). The study protocol was approved by the scientific committee of the SIBDCS (Project N°2019-06). The SIBDCS collects data of IBD patients in Switzerland from 2006-2020 and the aim was to improve the understanding of Crohn Disease (10). As the registry had no to very little surgical information and limited histopathological findings, all centers following-up the patients were contacted. Where available, review of the operation protocol and the histopathological report was performed. The retrospective retrieval of these reports was approved by the ethical committee of the canton de Vaud (CER-VD, Project-ID 2020-02426). For totally 82 patients, both operation protocol and histopathological report were available.

The following information was retrieved: gender, age at diagnosis and at ileocecal resection, smoking status, location of Crohn's disease, related surgery and other abdominal surgery prior to ileocecal resection. Information at last follow-up included median follow-up, current Crohn Disease Activity Index, smoking status, use of immunomodulators, time until surgical recurrence and type of first abdominal re-surgery. Surgical information included elective or emergency surgery, open or laparoscopic approach, type and configuration of anastomosis (stapled or hand-sewn, end-to-end, side-to-side, end-to-side or Kono-S), orientation of the anastomosis (isoperistaltic or anisoperistaltic), mesenteric defect closure, realization of a stoma and any additional associated operation. Histological findings included penetrating disease, stenosis, fistula, abscess, presence of positive small bowel or large bowel margins, plexitis, ulcer, granuloma, fissure, neural hypertrophy, cryptitis and total number of lymph nodes resected. Positive resection margins were defined by presence of inflammatory cells seen on histology.

Endoscopic recurrence was defined as lesion (Rutgeer's score) seen at the colonoscopy control. Surgical recurrence was defined as the need for bowel surgery after primary ileocecal resection.

## Statistical Analysis

Data were retrieved from the database of the SIBDCS at the Department of Epidemiology and Health Systems at the University Center for Primary Care and Public Health (Unisanté) in Lausanne, Switzerland. All statistical analyses were performed by the cohort statistician using Stata (version 18.0, College Station, Texas, USA). Quantitative data

distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented either as median plus interquartile ranges (for data with non-Gaussian distribution) or mean  $\pm$  SD and range (for normally distributed data). Categorical data were summarized as the percentage of the group total. For quantitative data, differences in distribution between two groups were evaluated using either the Wilcoxon-Mann-Whitney rank test (for data with non-Gaussian distribution) or the Student's t-test (for normally-distributed data). For categorical outcomes, differences in observed frequencies between groups were compared using the chi-squared test or using the exact Fisher test for groups with a small number of observations (n<20). For the present study, a p-value < 0.05 was considered as statistically significant. A Bonferroni correction was performed in case of multiple testing.

## Results

Patient demographics of the 82 patients are shown in Table 1.

79 patients (96%) were operated electively and 64 (78%) had a laparoscopic approach. For the 3 patients undergoing emergency surgery, 2 of them had a laparoscopic resection. Conversion to open surgery occurred in 20 patients (31%), with 15 (75%) in a reactive way (due to complication) and 5 (25%) in a preventive way. Surgical and pathology data of the ileocecal resection specimen are shown in table 2 and 3. Small and large bowel margins were not mentioned in 13% of pathology reports, and plexitis was never reported in the histologic description. The median follow-up was 8 years (1-13 years). The mean Crohn Disease Activity Index (CDAI) at last follow-up was 34.12 (0-410). Twenty-three patients (28%) were active smoker at last follow-up and thirty-seven (45%) were taking immunomodulators.

## Endoscopic recurrence

Positive bowel resections margins and type and configuration of anastomosis were not associated with endoscopic recurrence.

## Surgical recurrence

Seventy-four patients (90%) did not have any other surgery, while 8 (10%) were re-operated. Among them, 6 (75%) had had more than one re-surgery. Median time until first re-surgery was 2.9 years (1-19). In the 8 patients who had had re-surgery, 4 patients (50%) had ileal resection, 2 (25%) had strictureplasty, one (12%) had other small bowel resection and one (12%) needed an ileostomy. Some patients had other abdominal non-Crohn disease related surgery, including appendectomy (1 patient), cholecystectomy (1 patient) and adhesiolysis (4 patients). Positive small bowel margins were significantly associated with surgical recurrence, but not

positive large bowel margins (Table 5). Type ( $p=1.00$ ) and configuration of anastomosis ( $p=0.338$ ) were not associated with surgical recurrence.

**Table 1:** Patient demographics

|  | Patients<br>(n = 82) |
|--|----------------------|
| Male gender  | 41 (50%)             |
| Mean age at diagnosis of Crohn (years; range)        | 27 (8-64)            |
| Mean age at ileocecal resection (years; range)       | 33 (14-72)           |
| Active smoker  |                      |
| at baseline follow-up                                | 26 (32%)             |
| at latest follow-up                                  | 23 (28%)             |
| Location of Crohn's disease at baseline follow up    |                      |
| Other  | 5 (6%)               |
| L1: terminal ileum                                   | 24 (29%)             |
| L2: colon  | 10 (12%)             |
| L3: ileo-colon                                       | 43 (52%)             |
| Crohn's related surgery prior to ileocecal resection |                      |
| Segmental colectomy                                  | 1                    |
| Other small bowel resection                          | 1                    |
| Pre-operative therapy at time of ileocecal resection |                      |
| Unknown  | 62                   |
| Immunomodulators, 5-ASA, MTX, antibiotics, steroids  | 20                   |

**Table 2:** Surgical information of the ileocecal resection specimen

|                              | Patients<br>(n = 82) |
|------------------------------|----------------------|
| Type of anastomosis          |                      |
| Stapled                      | 36 (44%)             |
| Hand-sewn                    | 46 (56%)             |
| Configuration of anastomosis |                      |
| End-to-end                   | 19 (23%)             |
| Side-to-side                 | 48 (59%)             |
| End-to-side                  | 1 (1%)               |
| Kono-S                       | 3 (4%)               |
| Not mentioned                | 11 (13%)             |
| Orientation of anastomosis   |                      |
| Isoperistaltic               | 16 (20%)             |
| Anisoperistaltic             | 4 (5%)               |
| Not mentionned               | 62 (76%)             |
| Closure of mesenteric defect | 5 (6%)               |
| Stoma                        | 4 (5%)               |
| Additional operation         | 18 (22%)             |

**Table 3:** Pathology data of the ileocecal resection specimen

|                             | Patients<br>(n = 82) |
|-----------------------------|----------------------|
| Penetrating disease         | 21 (26%)             |
| Stenosis                    | 58 (71%)             |
| Fistula or Abscess          | 63 (77%)             |
| Not mentioned               | 0 (0%)               |
| Any positive margins        | 41 (50%)             |
| Positive small bowel margin | 31 (38%)             |
| Small margin not mentioned  | 11 (13%)             |
| Positive large bowel margin | 10 (12%)             |
| Large margin not mentioned  | 11 (13%)             |
| Myenteric plexitis          | 0 (0%)               |
| Not mentioned               | 82 (100%)            |
| Submucosal plexitis         | 0 (0%)               |
| Not mentioned               | 82 (100%)            |
| Ulceration                  | 66 (80%)             |
| Not mentioned               | 5 (6%)               |
| Granuloma                   | 26 (32%)             |
| Not mentioned               | 6 (7%)               |
| Fissure                     | 26 (32%)             |
| Not mentioned               | 6 (7%)               |
| Neural hypertrophy          | 5 (6%)               |
| Not mentioned               | 77 (94%)             |
| Lymph nodes resected        | 35 (43%)             |
| Not mentioned               | 43 (52%)             |
| Cryptitis                   | 23 (28%)             |
| Not mentioned               | 53 (65%)             |

**Table 4:** Endoscopic recurrence

|                                | No<br>endoscopic<br>recurrence<br>n = 45 (55%) | Endoscopic<br>recurrence<br>n = 37 (45%) | p-value      |
|--------------------------------|--|--|--------------|
| <b>Patient factors</b>         |  |  |              |
| Median Follow-up (years)       | 5 (0-13)                                       | 9 (0-13)                                 |              |
| Male gender                    | 18 (40%)                                       | 23 (62%)                                 | <b>0.047</b> |
| Mean age at diagnosis of Crohn | 27 (13-64)                                     | 28 (8-63)                                |              |
| Current smoker                 | 10 (22%)                                       | 10 (27%)                                 | 0.614        |
| Current biologics medication   | 22 (49%)                                       | 29 (78%)                                 | <b>0.006</b> |
| <b>Surgical factors</b>        |  |  |              |
| Laparoscopy                    | 34 (76%)                                       | 30 (81%)                                 | 0.547        |
| Conversion                     | 12 (27%)                                       | 8 (22%)                                  | 0.596        |
| <b>Type of anastomosis</b>     |  |  |              |
| Stapled                        | 24 (53%)                                       | 12 (32%)                                 | 0.532        |
| Hand-sewn                      | 21 (47%)                                       | 25 (68%)                                 |              |

| Configuration of anastomosis |          |          |       |
|------------------------------|----------|----------|-------|
| End-to-end                   | 10 (22%) | 9 (24%)  | 0.638 |
| Side-to-side                 | 29 (64%) | 19 (51%) |       |
| End-to-side                  | 0 (0%)   | 1 (27%)  |       |
| Kono-S                       | 1 (2%)   | 2 (54%)  |       |
| Not mentioned                | 5 (11%)  | 6 (16%)  |       |
| Pathology factors            |          |          |       |
| Penetrating disease          | 15 (33%) | 6 (16%)  | 0.077 |
| Positive small bowel margin  | 17 (38%) | 14 (38%) | 0.455 |
| Positive large bowel margin  | 4 (9%)   | 6 (16%)  | 0.313 |
| Fistula or Abscess           | 34 (76%) | 29 (78%) | 0.763 |

**Table 5:** Surgical recurrence

|  | No re-surgery<br>n = 74 (90%) | Re-surgery<br>n = 8 (10%) | p-value      |
|--|-------------------------------|---------------------------|--------------|
| Patient factors                                |                               |                           |              |
| Median Follow-up (years)                       | 8 years (1-13)                |                           |              |
| Male gender                                    | 38 (52%)                      | 3 (38%)                   | 0.456        |
| Mean age at diagnosis of Crohn                 | 27 (8-64)                     | 31 (18-63)                |              |
| Median time to first re-surgery (years, range) |                               | 2.9 (1-19)                |              |
| Current smoker                                 | 45 (61%)                      | 5 (62%)                   | 0.925        |
| Ever exposed to biologic medication            | 48 (65%)                      | 5 (62%)                   | 0.894        |
| Surgical factors                               |                               |                           |              |
| Laparoscopy                                    | 56 (76%)                      | 8 (100%)                  | 0.114        |
| Conversion                                     | 17 (23%)                      | 3 (37%)                   | 0.363        |
| Type of anastomosis                            |                               |                           |              |
| Stapled  | 33 (45%)                      | 3 (38%)                   | 1            |
| Hand-sewn                                      | 41 (55%)                      | 5 (62%)                   |              |
| Configuration of anastomosis                   |                               |                           |              |
| End-to-end                                     | 19 (26%)                      | 0 (0%)                    | 0.338        |
| Side-to-side                                   | 42 (57%)                      | 6 (75%)                   |              |
| End-to-side                                    | 1 (1%)                        | 0 (0%)                    |              |
| Kono-S   | 3 (4%)                        | 0 (0%)                    |              |
| Not mentioned                                  | 9 (12%)                       | 2 (25%)                   |              |
| Pathology factors                              |                               |                           |              |
| Penetrating disease                            | 19 (26%)                      | 2 (25%)                   | 0.966        |
| Positive small bowel margin                    | 25 (34%)                      | 6 (75%)                   | <b>0.022</b> |
| Positive large bowel margin                    | 8 (11%)                       | 2 (25%)                   | 0.244        |
| Fistula or Abscess                             | 55 (74%)                      | 8 (100%)                  | 0.102        |

## Discussion

In this study, pathological margins were missing in 13% and reports were not standardized. We found a significant association between positive small bowel margin and surgical recurrence but not with endoscopic recurrence. The extent of ileocecal resection is guided by macroscopic view of the inflammation. However, microscopic lesions at the proximal and distal margins seem to play an important role in the postoperative course of the disease. There is no clear consensus on the definition of positive margin, but it is defined in the literature as the presence of a transmural inflammation, granulomas, ulcerations, fibrosis, cryptitis, abscesses, and/or myenteric plexitis (11). K. Poredska et al. demonstrated a strong correlation between positive resection margins and endoscopic recurrence with a risk twenty-six times higher for early endoscopic recurrence in the presence of positive margins (12). A recent meta-analysis demonstrated that positive resection margins were also associated with a relative risk of 1.53 for clinical recurrence and 3.72 for surgical recurrence (6). These studies however did not specifically differentiate the proximal margin from the distal margin. As we know, local recurrence more often appears at the anastomosis with an extension towards the ileal side (13) which is why positive proximal margins are considered a risk factor for postoperative recurrence (5, 14). However, colonic margin may also play a role in the postoperative course of the disease as recently demonstrated with a significant association between a positive distal margin and endoscopic recurrence (15).

In regards to myenteric plexitis at the margin resection, their association with postoperative endoscopic recurrence was first reported by Ferrante et al in 2006 (16), with a correlation between severity of myenteric plexitis and severity of endoscopic recurrence at 1 year ( $p=0.001$ ). Several studies then supported this correlation (17, 6, 14). In 2019, a meta-analysis confirmed this correlation not only for endoscopic, but also for clinical and surgical recurrence (11). Presence of submucosal plexitis may also have an impact on the natural postoperative course of the disease, as shown in two retrospective studies (18, 19). However, these conclusions remain controversial (17). From a histological perspective, Crohn disease can be associated with non-caseous granulomas. A recent study demonstrated that mesenteric granulomas significantly increased the risk of surgical recurrence ( $p=0.037$ ) whereas intestinal granulomas did not (20), supporting once again the important role of the mesentery in the physiopathology of the disease. Postoperatively, patients should be closely monitored clinically, chemically (calprotectin) and endoscopically, so that any escalation of treatment can take place at an early stage (21). The aforementioned analysis illustrates the importance of a careful analysis of the ileocecal resected specimen in



order to identify the presence or absence of histopathological risk factors for recurrence. If all features were mentioned, patients at high risk of postoperative recurrence could be identified and others with low risk factors may benefit from a break in immunomodulator therapy. In our study, we noticed a vast heterogeneity in the information listed in the pathology reports. Important histopathological information was missing in most cases. Indeed, resection margins were missing in 13% of cases and none of the reports mentioned myenteric nor submucosal plexitis (table 3). We believe that a standardized pathology report with minimal required information should be established in Switzerland in order to help stratify the postoperative risk of recurrence. Such a report should list all items in table 3.

Today, the laparoscopic approach for ileocecal Crohn Disease is standard in most centers (4, 22), and is associated with lower postoperative complication rates compared to open surgery (23-25). Regarding postoperative recurrence after laparoscopy and open surgery, Bergamaschi's study (26) didn't show any differences for the five-year surgical recurrence rates, which was later supported by Unger et al in 2019 (20). Poredsa et al. also on showed no differences for endoscopic recurrence (12). In our cohort, a laparoscopic approach was used in 78% with a high conversion rate of 31%, mostly in a reactive way due to intraoperative complications. Abdominal wall access (laparoscopically or open) did not influence either endoscopic or surgical recurrence in our study. These findings are consistent with newer literature. With both approaches the entire macroscopically affected intestinal segment should be resected, which was the case in our study.

The main limitation of our study is due to the small number of patients due to the non-availability of both pathological and operating reports. However, it represents a national cohort with a complete and long-follow-up of 8 years. The findings are therefore generalizable and most likely reflect the current situation and especially ways of improvement in Switzerland.

In conclusion, involvement of the proximal resection margin is associated with surgical recurrence. Positive distal resection margin did not seem to have influence on surgical nor endoscopic recurrence. However, data on margins were missing in 13% and most histopathological reports did not include other important information such as plexitis. Pathologists should develop guidelines on standardized reporting of key data so clinicians can more carefully treat and follow their patients.

## Declarations

**Ethical approval:** This retrospective study complies with internationally accepted standards for research practice and reporting. Written informed consent was obtained from included patients, and all data were de-identified and

anonymized prior to analysis. The local institutional review board approved this study (Commission cantonale d'éthique de la recherche sur l'être humain CER-VD No. 2017-01971), which was conducted in accordance with the STROBE criteria (<https://strobe-statement.org>).

**Consent to participate:** Written informed consent was obtain from all included participants.

**Consent to publish:** Patients signed informed consent regarding publishing their data.

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**Competing interests:** All authors have no conflict of interest to declare.

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