The Predictive Value of Inflammation at Ileocecal Resection Margins for Postoperative Crohn’s Recurrence: A Cohort Study

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Background: Resections for Crohn’s disease should be limited and only resect macroscopically affected bowel. However, recent studies suggest microscopic inflammation at resection margins as a predictor for postoperative recurrence. The clinical impact remains unclear, as non-uniform pathological criteria have been used. The aim of this study was to assess the predictive value of pathological characteristics at ileocecal resection margins for recurrence.

Methods: Both resection margins of 106 consecutive patients undergoing ileocecal resection for Crohn’s disease between 2002 and 2009 were re-visited and scored for active inflammation, myenteric plexitis, and granulomas. Pathological findings were correlated to recurrence, defined as recurrent disease activity demonstrated by endoscopy (modified Rutgeerts score ≥i2) requiring upscaling medical treatment, using multivariate analysis.

Results: Active inflammation was found at the proximal and distal resection margin in 27% and 15% of patients, respectively, myenteric plexitis in 37% and 32%, respectively, and granulomas in 4% and 6%, respectively. In total, 47 out of 106 patients developed recurrence. Only active inflammation at the distal colonic resection margin was an independent significant predictor for recurrence (88% vs 43% vs 51% for distal, proximal, and no involved margins, respectively; P < 0.01).

Conclusion: Active inflammation at the distal colonic resection margin after ileocecal resection identifies a patient group at high risk for postoperative recurrence both at the anastomotic site and the colon because it identifies undiagnosed L3 disease. These patients have a different and more aggressive natural history and require more intensive medical treatment. Therefore, pathological evaluation of the distal resection margin should be implemented in daily practice.

Key Words: Geboes, ileocolonic resection, histological inflammation, postoperative recurrence

INTRODUCTION

Despite advances in medical treatment, the majority of Crohn’s disease (CD) patients with terminal ileitis still need surgical resection. A substantial proportion of patients will develop postoperative recurrence during the course of the disease.1 Smoking, prior intestinal surgery, penetrating disease at surgery, and perianal disease are established risk factors for clinical and surgical recurrence after ileocecal resection.2 Prophylactic treatment is recommended in patients with at least 1 of these risk factors. Current guidelines advise limited resection to avoid short bowel syndrome and do not specifically recommend performing a radical resection (ie, without involved resection margins).3 The only randomized evidence originates from 1996, reporting no reduced recurrence rates after a more extensive proximal (ileum) resection.3 However, recent cohort studies have identified inflammation at resection margins as a new independent risk factor for recurrence.4, 5 Furthermore, the presence of myenteric plexitis at the proximal resection margins and granulomas in the resection specimen was recently discussed in the guidelines as potential risk factors for recurrence. This concludes that new studies are needed to clarify the value of histological evaluation in daily clinical practice.6, 7 So far, it is difficult to draw clinical conclusions, as results are conflicting, and nonuniform pathological definitions have been used.

The aim of this study was to assess the predictive value of microscopic inflammation, including active inflammation, myenteric plexitis, and granulomas at the ileocecal resection margins for clinical and surgical recurrence in CD patients.

MATERIALS AND METHODS

Patients

All consecutive patients with terminal ileitis CD who underwent a primary ileocecal resection between January 2002
and September 2009 in the Amsterdam UMC, Amsterdam, the Netherlands, were included from a prospectively maintained database. Patients were excluded if histological sections of both margins were not available for examination.

In all patients, a limited close bowel resection of macroscopically affected bowel was performed as recommended by current guidelines. Patients were operated upon supervision of a dedicated colorectal surgeon specialized in inflammatory bowel disease. Reporting of the data adheres to the STROBE Statement.

Histological Features

After surgical resection, the specimen was handled by a pathologist according to standard operating procedure, which included collection of proximal and distal resection margin in paraffin blocks. For the purpose of this study, hematoxylin and eosin (H&E)–stained slides of the proximal ileal and distal colonic resection margins were reevaluated by a dedicated pathologist and a researcher, both blinded to clinical outcome. In case of interobserver variation, consensus was established by reevaluation of the slides using a multiheaded microscope.

Active inflammation at the margins was scored according to the validated Geboes grading system for ulcerative colitis (UC), as there is currently no validated histological score for CD. The Geboes score (GS) grades on a scale of 0 to 5. A higher score represents more severe histological inflammation (see Supplementary Table 1). Results of the GS have demonstrated to reliably distinguish between UC patients in histological remission and activity. Recently, a GS cutoff of >3 compared with the original cutoff of >2 seems to be more clinically relevant, as the presence of neutrophils in the epithelium is the main marker of histological activity (also in the context of the Robarts and Nancy score). Therefore, active inflammation at the resection margin was defined as a GS of >3.

Myenteric plexitis at the proximal or distal resection specimen margin was histologically defined as the presence of inflammatory cells per high power field (HPF), adjacent to or within an enteric ganglion or nerve bundle. It was based on the appearance of the most severely inflamed ganglion or nerve bundle in the resection margin slide. Myenteric plexitis was graded mild (1–3 inflammatory cells/HPF), moderate (4–9 inflammatory cells/HPF), or severe (>10 cells/HPF). Myenteric plexitis was recorded when moderate or severe plexitis was found.

The presence of granulomas at the resection margins was defined as a focal collection of macrophages at the proximal and distal resection margins. The presence of granulomas in the overall resection specimen was retrieved from the pathology report, as this was already part of standard histological evaluation during the study period.

Variables and Outcomes

Patient and disease characteristics were collected from the prospectively maintained ileocecal resection database. Disease location was subdivided into terminal ileitis (L1) and ileocolonic disease (L3). Ileocolonic disease was defined as (previous) involvement of the colon on endoscopy or MRE. In case of L3 disease, patients were generally treated until colonic disease was macroscopically in remission, except for patients in whom terminal ileum disease urged ileocecal resection (eg, therapy refractory disease, stenosis, and fistula).

Prophylactic therapy was scored if patients started Crohn’s medication directly postoperative, before endoscopic or clinical recurrence. It included immunomodulators (azathioprine [AZA], 6-mercaptopurine [6MP], methotrexate [MTX]), or biologicals (antitumor necrosis factor alpha [anti-TNF alpha]). During the study period, a “wait and see” policy regarding prophylactic therapy was conducted in our hospital. The follow-up protocol consisted of a routine surveillance colonoscopy within 6 to 12 months postoperatively, after which prophylactic therapy could be considered. Only during a multidisciplinary meeting could it be decided to start prophylaxis directly postoperatively, dependent on patients’ risk profiles. Afterward, colonoscopy was performed on indication, which means either suspicion of recurrent disease or to evaluate a new drug therapy.

The primary endpoint was recurrence, defined as reappearance of symptoms confirmed by endoscopy (modified Rutgeerts score ≥2) or other imaging, preferably MRE (MaRIA score ≥7), requiring upscaling of anti-inflammatory medical treatment.

Local recurrence (in the neoterminal ileum, above the anastomosis) was distinguished from colonic recurrence based on endoscopy or MRE results. The development of perianal activity was not considered as recurrence. The secondary endpoint was surgical recurrence, defined as disease recurrence with the need for a second intestinal resection or strictureplasty.

Statistical Analysis

Differences in baseline characteristics between patients with and without certain histological features were assessed using a χ² square test for categorical variables, or in case of low counts (<5), a Fisher exact test. The unpaired t test was used for numerical variables. Mean and standard deviation (SD) were reported in case of normally distributed variables; for non-normally distributed variables, median and interquartile range (IQR) were reported. Pearson correlation was assessed to test the correlation between histological features. Kaplan-Meier analysis with log rank test was used to compare recurrence free survival. Patients were categorized into proximal, distal, or no involved margins. Patient with inflammation at both margins were distributed to the resection margin with the strongest association to recurrence in univariate analysis. Independent factors associated with recurrence were identified using Cox regression. Variables with a P value of P ≤ 0.1 in the univariable analyses were included in the multivariable model after assessing multicollinearity.


**RESULTS**

**Patients and Histopathological Findings**

A total of 113 patients underwent primary ileocecal resection for CD in the terminal ileum between January 2002 and September 2009. Seven patients were excluded due to missing histologic resection sections, resulting in a total study cohort of 106 patients, 36 men, with a median age of 32 years. A total of 27 patients (26%) had been diagnosed with (previous) ileocolonic L3 disease. At time of resection, colonic disease was endoscopically in remission for most patients, except for 10 out of 27 patients, for whom terminal ileum disease activity necessitated ileocecal resection.

For 66 patients (62%), microscopic disease activity was found in at least 1 of the resection margins: active inflammation in 40 patients, myenteric plexitis in 58 patients, and granulomas in 7 patients (Table 1, Figs. 1 and 2). When looking at baseline characteristics, no association between clinical parameters and microscopic disease activity at the resection margins could be demonstrated (Table 2). When specifically looking at patients with L3 disease compared with patients with L1 disease, only active inflammation at the distal colonic resection margin was more frequently seen (30% vs 10%; \( P = 0.02 \)).

**Recurrences**

Median follow-up was 8.7 years (IQR, 5.9–11.3). Recurrence after 2, 5, and 10 years was 24%, 38%, and 53%, respectively (Fig. 3). A minority of patients (38%) received postoperative medical prophylaxis. Local recurrence was higher in patients with microscopic disease activity at resection margins compared with patients without involved margins; however, this was not significant (63% vs 47%, \( P = 0.08 \), respectively).

The association between recurrence and active inflammation, myenteric plexitis, or granulomas at the distal colonic margin was stronger compared with the occurrence of these features at the proximal ileal margin. Similar results were shown after excluding patients with a histologic features at both resection margins. Only active inflammation at the distal colonic resection margin was significantly associated with local recurrence: 14 out of 16 patients (88%) with active inflammation at the distal colonic resection margin developed local recurrence after a median of 2 years (IQR, 1.5–6.5). Local recurrence rates were comparable between patients with active inflammation at the proximal ileal resection margin (43%) and patients without active inflammation at resections margins (51%, \( P = 0.008 \), Fig. 4). Recurrence rates for myenteric plexitis were 67% when present at the distal (colon) margin, 55% at proximal (ileum) margin, and 50% for no involved margins (\( P = 0.64 \)). An increased recurrence rate was also observed for granulomas at the distal resection margin. However, the small numbers precluded statistical analyses: the corresponding rates were 83%, 0%, and 57%, respectively.

The correlation between active inflammation and myenteric plexitis or granulomas at resection margins was high. Myenteric plexitis was found at more than 85% of patients with active inflammation at the distal margin, while active inflammation was found at 5 of the 6 patients with granulomas distally.

Univariate analysis demonstrated increased local recurrence in patients with active inflammation or granulomas at the distal colonic resection margin and for smoking and nonpenetrating disease. Active inflammation and granulomas at the proximal ileal margins did not show to be risk factors, nor were myenteric plexitis at the resection margins (both distal and proximal) or granulomas in the overall resection specimen predictive in this series.

Due to multicollinearity, granulomas at distal resection margins were not included in the multivariate analyses. After multivariate analysis, active inflammation at the distal resection margin and smoking were the only independent prognostic parameters (hazard ratio [HR], 2.89; 95% CI, 1.4–5.8; \( P = 0.003 \); and HR, 2.60; 95% CI, 1.4–4.9; \( P = 0.004 \)) (Table 3).

In addition, results indicated that patients with active inflammation at the distal resection margin more frequently

| TABLE 1. Histologic Features |
|----------------------------------|----------------------------------|----------------------------------|
| **Active inflammation at resection margins** | **Myenteric plexitis at resection margins** | **Granulomas at resection margins** |
| (n: 40) n (%) | (n: 58) n (%) | (n: 7) n (%) |
| Proximal | 29 (27%) | 39 (37%) | 4 (4%) |
| Distal | 16 (16%) | 34 (32%) | 6 (6%) |
| Both | 5 (5%) | 15 (14%) | 3 (3%) |
developed postoperative colonic recurrence compared with patients with active inflammation at the proximal resection margin or no actively inflamed resection margins, (56% vs 9% vs 7%; \( P < 0.001 \), respectively). The incidence of surgical recurrence was 2% after 5 years, which was too low to perform statistical analyses.

Finally, excluding the 27 patients who were preoperatively known with colonic Crohn’s disease did not change the results. Active inflammation at the distal resection margin remained significantly associated with postoperative recurrence compared with patients with active inflammation at the proximal resection margin or no actively inflamed
resection margins (88% vs 49% vs 56%; \( P < 0.035 \), respectively, Supplementary fig. 1).

**DISCUSSION**

Active inflammation at the distal colonic resection margin after ileocecal resection for CD was associated with a significantly increased risk of local and colonic recurrence after surgical resection. The presence of myenteric plexitis and granulomas at the distal resection margin showed a trend toward higher recurrence. In contrast, none of these features tended to have predictive value at the proximal (ileum) resection margin.

The local recurrence rate in the patient group with active inflammation at the distal resection margin was 88%. This is much higher than currently known predictive parameters, whereas the HRs for most established clinical risk factors for CD recurrence were comparable to previous series. The relatively low HRs for ileocolonic L3 disease and penetrating B3 disease in this study are explained, as these patients were considered for prophylactic therapy according to protocol.

So far, the discussion regarding the predictive value of resection margins predominantly focused on the proximal resection margin, as length of ileum resection is at the surgeon’s discretion, whereas the colonic resection level is generally directly after the cecal base. This is the first study exploring the prognostic value of both proximal and distal margin separately with the use of the validated Geboes score while also assessing multiple histological features. The unexpected finding that active inflammation at the distal (colon) resection margin is an important predictor for recurrent disease, instead of the proximal...
(ileum) margins, might be the explanation for previous found discrepancies.

Prior studies used controversial definitions of inflammation, causing conflicting results. Both studies demonstrating a prognostic value of inflammation at the resection margins\(^5\)\(^{18-23}\) and studies showing no effect\(^24-30\) did not distinguish between proximal and distal resection margins—or analyzed the proximal margin only. The studies revealing an association consisted of remarkably larger cohorts (±300 patients vs ±100 patients), suggesting that the smaller studies were underpowered. In the absence of a validated score, most studies did not distinguish between histological chronic and active inflammation. This probably decreases validity of prior studies results, as the relevance of scoring chronic inflammation is not acknowledged. With regard to the proximal margin, current findings corroborate the results of the only randomised controlled

### TABLE 2. Baseline Patients and Disease Characteristics

<table>
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<tr>
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<th>Total (n = 106)</th>
<th>Any Inflammation at Resection Margins (n = 66)</th>
<th>No Inflammation at Resection Margins (n = 40)</th>
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<td></td>
<td>n</td>
<td>%</td>
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<td>33 (14)</td>
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<td>Mean (SD)</td>
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<td>Montreal L3</td>
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<td>Immunomodulators (AZA/6MP/MTX)</td>
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<tr>
<td>Resection length (cm)</td>
<td>Mean (SD)</td>
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<td></td>
<td>Immunomodulators</td>
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<tr>
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<td>Biologicals</td>
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None of the listed baseline patients characteristics were significantly differed between the 2 groups. Any inflammation at resection margins is microscopic disease activity, present when 1 of the variables, active inflammation, myenteric plexitis, and/or granulomas, was detected at 1 or both resection margins. Smoking was defined as daily smoking, independent of the number of units. Disease location and behavior were graded according to the Montreal classification.\(^14\) Perianal disease was scored using the fistula drainage assessment.\(^15\) Preoperative biological therapy included patients ever on biologic drugs (antitumor necrosis factor alpha). Perioperative CD medication was scored if patients used steroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), or biologicals within 12 weeks before surgery. Concomitant surgery included concomitant bowel resection for enter-enteral or entero-vesical fistula, stricuroplasty for small bowel lesions, or fistulotomy resection.
Ileocecal Resection Margins in Crohn’s Disease

In a trial (RCT) where no reduced recurrence rates were reported after more extensive ileum resection during ileocecal resection.\(^3\) Furthermore, a microscopically actively inflamed proximal resection margin having no prognostic value is intuitively supported by studies demonstrating good clinical results after stricturoplasty, leaving the affected bowel in situ.\(^3\) The RCT did not evaluate the distal margin.

Most studies describe myenteric plexitis at the proximal margin as an independent predictor for endoscopic,\(^6\) clinical,\(^2\) and surgical recurrence,\(^1\) which is in contrast to our findings. The difference can be understood because prior studies did not include other histological features as active inflammation and granulomas in the multivariate model, while the correlation between active inflammation and myenteric plexitis seems high. The role of granulomas in CD is not yet clarified.\(^2\),\(^3\) In the current series, granulomas in the overall resection specimen did not show any predictive value. In contrast, in these study results the presence of granulomas at the distal margin was suggested to have clinical relevance in univariate analyses; however, the numbers were small. In addition, granulomas and active inflammation distally had a strong correlation. Decreased lymphatic vessel density\(^3\) and increased Paneth cells\(^3\) are once described as potential associated features with recurrence. However, as these histological features are not easily implementable in daily clinical histological practice, the current value is debatable.

Because it is not common practice to assess the distal resection margins, results of presumed L1 ileocolic disease are confounded by L3 ileocolic disease.\(^1\) In general, the prognosis after ileocecal resection for terminal ileitis only (L1 disease) is good, with less than 20% recurrent surgery after 10 years.\(^3\) This contrasts the surgical outcome for colonic disease (L3 disease). A meta-analysis demonstrated that at least one third of these patients will need a re-resection within a few years, and a substantial proportion of patients will end with a permanent ileostomy due to refractory disease.\(^3\) Whether this hypothesis of a different prognostic colonic CD profile could be extrapolated to patients with histological inflammation at the colon resection margin remains speculative, but the data clearly suggest a different risk profile for both local and colonic recurrence when the colon is involved.

One of the drawbacks of this study is the relatively small number of patients with active inflammation. Although the results come from a large consecutive series, there are only 16 patients with active inflammation at the distal resection margin. Nevertheless, the observation that 14 of these patients developed local recurrence is striking and should not be considered coincidence. Whether the results could be influenced by a relatively high percentage of patients with a history of ileocolonic L3...
disease in this series (26%) is difficult to assess. However, overall recurrence rates are comparable to existing literature, and active inflammation at the distal resection margin was not confined to patients with a history of L3 disease. Excluding L3 patients from the analysis did not change results (Supplementary Fig. 1). Nonetheless, including these patients increases extrapolation of the results to daily clinical practice, particularly as it has been demonstrated that the preoperative differentiation between L1 and L3 disease is difficult with an interobserver variation of up to 50%. The results of this study are strengthened as a prospective database was used, in which the majority of patients did not start postoperative prophylaxis. Therefore, the results accurately reflect the natural postoperative course. Due to the strict endoscopic surveillance program (colonoscopy after 6–12 months) and because only 1 patient was lost to follow-up, it is unlikely that recurrences would have been missed.

Currently, systematic evaluation of disease activity at resection margins is not routine practice, as there is no advice in guidelines on standard pathology reporting. This is also reflected by the fact that there is only 1 (nonvalidated) pathological activity score for CD, whereas there are over 20 different histological scoring systems for UC. The use of the validated Geboes score known for scoring UC was chosen, as this score is most frequently used in literature and daily practice.

In conclusion, patients with active inflammation, myenteric plexitis, or granulomas at the proximal (ileum) resection margin had comparable recurrence rates as patients with no involved resection margins. Therefore, it is unlikely that in these patients a more extensive ileum resection or postoperative medical prophylaxis would lead to decreased recurrences. However, histological active inflammation at the distal colonic resection margin is associated with a significant increase of local and colonic recurrence.
Once the distal resection margin is actively inflamed, this points toward a different phenotype of CD (L3 disease) with an overall worse natural history. Active inflammation at the colonic part of the ileocecal specimen should be regarded as a risk factor for recurrence both at the anastomotic site and the colon, categorizing the patient having L3 disease, and prophylactic treatment should be considered for this high-risk patient group. Our findings suggest that histological evaluation of the colonic margin after ileocecal resection should be implemented in daily clinical practice.

SUPPLEMENTARY DATA
Supplementary data is available at Inflammatory Bowel Diseases online.

ACKNOWLEDGEMENTS
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DATA ACCESSIBILITY STATEMENT
Anonymized patient level data can be made available on reasonable request after approval from the study management committee and after signing a data access agreement. Proposals should be directed to the corresponding author. Consent was not obtained for data sharing, but the presented data are anonymized, and the risk of identification is low.

REFERENCES