High prevalence of ulcerative appendicitis in patients with ulcerative colitis

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Abstract

Background: Previous studies have indicated that the appendix may be a priming site of ulcerative colitis (UC). Appendectomy is inversely associated with the development of UC, and is suggested to have a beneficial effect on the disease course in patients with refractory disease.

Objective: The aim of the current study was to assess histological features of appendices from patients with UC and their clinical relevance.

Methods: Patients with UC in remission and active UC (therapy refractory) that underwent appendectomy between 2012 and 2019 were included. Histological features of UC appendices were compared to those of patients with acute appendicitis and colon carcinoma. The Robarts Histopathology Index (RHI) was used to assess appendiceal inflammation. In patients with active UC, histological and clinical characteristics were compared between patients with and without endoscopic response following appendectomy.

Results: In total, 140 appendix specimens were assessed (n = 35 UC remission, n = 35 active UC, n = 35 acute appendicitis, n = 35 colon carcinoma). Histological features of appendices from UC patients looked like UC rather than acute appendicitis. The presence of active appendiceal inflammation was comparable between patients in remission versus active disease (53.7% vs. 46.3%, \( p = 0.45 \)) and limited versus extensive disease (58.5% vs. 41.5%, \( p = 0.50 \)). Endoscopic response (Mayo 0–1) following appendectomy, assessed in 28 therapy refractory patients, was more frequently seen in patients with higher RHI scores (RHI > 6: 81.8% vs. RHI \( \leq 6 \): 9.1%, \( p = 0.03 \)) and limited disease (proctitis/left sided 63.6% vs. pancolitis 36.4%, \( p = 0.02 \)).

Conclusion: The presence of active appendiceal inflammation is common in UC and does not correlate with colonic disease activity. More than 50% of UC patients in remission showed active histological disease in the appendix. Favorable response to appendectomy for refractory UC was seen in cases with ulcerative

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The immunological role of the human appendix, which was previously considered a vestigial organ, is becoming increasingly apparent. The appendix contains abundant lymphoid follicles and is part of the gut associated lymphoid tissue, which plays an important role in the development and preservation of the mucosal immune system. Although the etiology of ulcerative colitis (UC) remains unsolved, several studies have suggested that the appendix may be a priming site in the pathogenesis of UC, because of the inverse relationship between prior appendectomy and the risk of UC development in humans and mice. The therapeutic effect of appendectomy was assessed in several studies, including two prospective cohort studies. Both studies suggested a beneficial effect of appendectomy in refractory UC patients. The first study included 30 patients with ulcerative proctitis and showed improvement of the Simple Clinical Colitis Activity Index score in 27 (90%) patients, with withdrawal of all medication in 12 (40%) patients. The second study, performed by our study group, included 28 patients with therapy refractory disease and showed long-term clinical response in 46% of the patients after appendectomy. Appendectomy for UC is currently only performed in clinical trials and not yet considered a standard surgical therapeutic approach in UC.

Several histological studies demonstrated appendiceal inflammation in colectomy resection specimens from patients with therapy refractory disease (ranging from 5%–88%). Appendiceal orifice inflammation or a peri-appendiceal red patch (PARP) is frequently described in patients with disease activity limited to the rectum or left-sided colon. It has been suggested that this PARP is reflective of inflammation of the appendix in UC which further contributes to the hypothesis that the appendix is involved in (maintaining) the disease.

However, previous studies always focused on patients with active (therapy refractory) disease and data on the prevalence of appendiceal inflammation in UC patients in complete clinical and endoscopic remission are lacking. Comparing histological findings in appendices from UC patients in remission and with active disease may provide more insight in the relationship between active UC in the appendix and colon. Therefore, the aim of this study was to assess histological features of appendices in both UC groups. In addition, endoscopic response was assessed in patients with active UC undergoing appendectomy with therapeutic intent.

**Key summary**

**Summarise the established knowledge on this subject**

- The appendix is an important part of the intestinal immune system.
- Previous reports suggest a protective effect of appendectomy on the risk to develop ulcerative colitis (UC).
- Appendiceal inflammation is commonly demonstrated in patients with active UC undergoing colectomy.

**What are the significant and/or new findings of this study?**

- The presence of active appendiceal inflammation is irrespective of disease activity in the colon.
- In patients undergoing appendectomy with therapeutic intent, favorable response is suggested in cases with appendiceal inflammation.

**METHODS**

**Study population**

Appendectomy specimens from patients of ≥18 years old with UC who underwent an appendectomy between 2012 and 2019 at the Amsterdam University Medical Center, location AMC were histologically assessed. Patients were categorized in two groups: patients with UC in remission undergoing appendectomy in a clinical trial to maintain remission (ACCURE-trial, NTR2883) and patients with active refractory disease undergoing appendectomy in an attempt to avoid proctocolectomy (PASSION-study, COSTA-study NCT03912714 or off-label appendectomy). Remission in the ACCURE-trial was defined as clinical (total Mayo score < 3) and endoscopic (endoscopic Mayo score 0 or 1) remission with a faecal calprotectin <150 u/g. Patients with active disease were therapy refractory patients with a total Mayo-score ≥ 5 and an endoscopic subscore of 2 or 3, despite standard step-up treatment including biological(s). Two additional non-UC groups were included from the Amsterdam University Center, location VUMC: patients with acute appendicitis (age matched with the UC population) and patients with colorectal cancer who underwent a right hemicolectomy. Ethical approval was obtained by the Institutional Review Boards. All patients with UC undergoing appendectomy provided informed consent.
consent. For patients with acute appendicitis and colon carcinoma, no consent was required as anonymized retrospective data was used. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Pathologic assessment

Haematoxylin and eosin-stained slides of the appendices were collected from the pathology tissue bank and were reviewed by an inflammatory bowel disease (IBD) specialized pathologist (AM). The following histopathological features were assessed in all specimens: Paneth cell metaplasia, crypt branching, crypt shortening, crypt loss, infiltration of neutrophil granulocytes in the epithelium, lamina propria, muscularis propria, and subserosa, erosion and ulceration, fibrous obliteration, presence of lymphoid follicles, and submucosal adipose tissue. Active appendiceal inflammation was defined as infiltration of neutrophil granulocytes in the mucosal submucosal adipose tissue. Active appendiceal inflammation was assessed in all specimens: Paneth cell metaplasia, crypt branching, crypt shortening, crypt loss, infiltration of neutrophil granulocytes in the epithelium, lamina propria, muscularis propria, and subserosa, erosion and ulceration, fibrous obliteration, presence of lymphoid follicles, and submucosal adipose tissue. Active appendiceal inflammation was defined as infiltration of neutrophil granulocytes in the mucosal layer. In case of total fibrous obliteration of the lumen with absence of the mucosa, appendiceal inflammation could not be assessed.

Appendiceal inflammation in UC patients was assessed using the Robarts Histopathology Index (RHI). Although the RHI has been developed and validated to assess histologic disease activity in the context of colonic biopsies of patients with UC, the RHI was used in this study to grade appendiceal resection specimen. Since appendices of patients with UC show mucosal inflammation with comparable characteristics. The RHI includes the following four categories that are scored from 0 to 3: (1) chronic inflammatory infiltrate, (2) lamina propria neutrophils, (3) neutrophils in the epithelium, and (4) erosions or ulcerations. According to the RHI formula with weighted scores per category, the total score ranges from 0 (no disease activity) to 33 (severe disease activity). Endoscopic or clinical remission was defined as an RHI ≤ 6.

Clinical assessment in UC patients

All study data were prospectively registered in the concerning trial databases and included patient demographics, disease duration, disease extent, preoperative endoscopic Mayo score, and medication use. The prevalence of a PARP was assessed in all patients who underwent a baseline colonoscopy with assessment of the peri-appendicular area. Endoscopic response following appendectomy was assessed in patients with active UC undergoing an off-label appendectomy or an appendectomy in context of the PASSION-study. Clinical outcome after appendectomy was not assessed in patients participating in ongoing studies (ACCURE-trial or COSTA-study) of which data are still locked. Endoscopic response was defined as Mayo score ≤ 1 at 1 year, without upscaling of baseline medical therapy. Patients were also considered responders if they underwent a colectomy for persistent clinical symptoms but showed complete mucosal healing in the resection specimen.

Statistical analysis

Categorical data were presented as frequencies with percentage and compared using the Chi-square test or Fisher’s exact test, as appropriate. Normally distributed continuous data were compared using a Students t-test and presented as means with standard errors. Non-normally distributed continuous data were compared using the Mann–Whitney U test for two subgroups or the Kruskal–Wallis test for three subgroups and presented as medians with interquartile ranges (IQR). In all patients with UC, clinical characteristics were compared between no appendiceal inflammation, active appendiceal inflammation, and total fibrous obliteration of the appendix. In patients with active UC treated with appendectomy, clinical characteristics and RHI scores were compared between endoscopic and non-endoscopic response. Two-sided p values of less than 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows version 25 (IBM corp.).

RESULTS

Baseline characteristics

A total of 140 appendix specimens were assessed, with four groups of 35 patients. Baseline characteristics are shown in Table 1. In the UC groups, patients with active disease had more often pancolitis (62.9% vs. 22.9%, p < 0.01) and intensive medical treatment when compared to patients in complete remission.

Histological features of appendiceal resection specimens

In patients with UC, histological features of both chronic and active inflammation were present (Table 2). The presence of neutrophils in the epithelium and the lamina propria representing "ulcerative appendicitis", was comparable between patients in remission and those with active disease (62.9% [22/35] versus 54.3% [19/35], p = 0.96). The severity of inflammation in the appendix according the RHI, was also not significantly different between both groups (remission median RHI score 7 (IQR 1.0–15.0) versus active disease median RHI score 10 (IQR 1.0–13.0), p = 0.67). Histological features indicative of chronic inflammation as crypt branching (31.4% vs. 57.1%, p < 0.01) and crypt shortening (2.9% vs. 25.7%, p < 0.01), were lower in the remission group compared to patients with active disease. Interestingly, a high percentage of total fibrous obliteration was found in both UC groups. This finding is generally considered as an age-related
## Table 1  Demographic and clinical baseline characteristics

|                      | UC remission N = 35 | UC active disease N = 35 | p value | Acute appendicitis N = 35 | Colon carcinoma N = 35 |
|----------------------|----------------------|--------------------------|---------|--------------------------|------------------------|
| Age years (median, IQR) | 35 (32.0–49.0)       | 39 (31.0–47.0)           | 0.57    | 36 (27.0–50.0)           | 62 (52.0–65.0)         |
| Sex, female (%)       | 19 (54.3)            | 20 (57.1)                | 1.00    | 22 (62.9)                | 12 (34.3)              |
| Disease duration in years (median, IQR) | 5 (2.0–12.0)       | 8 (4.0–15.0)             | 0.20    | -                        | -                      |
| Smoking (% yes)       | 5 (14.3)             | 6 (17.1)                 | 1.00    | -                        | -                      |
| PSC (% yes)           | 0 (0.0)              | 3 (8.6)                  | 0.24    | -                        | -                      |
| Family history of IBD (% yes) | 7 (20.0)       | 5 (14.3)                 | 0.75    | -                        | -                      |
| Disease location      | -                    | -                        | <0.01   | -                        | -                      |
| Proctitis             | 14 (40.0)            | 5 (14.3)                 | -       | -                        | -                      |
| Left-sided            | 13 (37.1)            | 8 (22.9)                 | -       | -                        | -                      |
| Pancolitis            | 8 (22.9)             | 22 (62.9)                | -       | -                        | -                      |
| Medication            |                      |                          |         |                          |                        |
| None                  | 4 (11.4)             | 1 (2.9)                  | 0.36    | -                        | -                      |
| 5-ASA                 | 31 (88.6)            | 18 (51.4)                | <0.01   | -                        | -                      |
| Systemic steroids     | 0 (0.0)              | 10 (28.6)                | <0.01   | -                        | -                      |
| Immunomodulators      | 0 (0.0)              | 12 (34.3)                | <0.001  | -                        | -                      |
| Biologicals           | 0 (0.0)              | 12 (34.3)                | <0.001  | -                        | -                      |
| Trial medication      | 0 (0.0)              | 4 (11.4)                 | 0.11    | -                        | -                      |

Abbreviations: 5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

aComparison between UC remission and UC active disease.

## Table 2  Comparison of histological features of appendices derived from patients with UC in remission and with active disease

| Appendiceal histology | UC remission N = 35 (%) | UC active disease N = 35 (%) | p value |
|-----------------------|--------------------------|-----------------------------|---------|
| Paneth cell metaplasia| 24 (68.6)                | 17 (48.6)                   | 0.23    |
| Crypt branching       | 11 (31.4)                | 20 (57.1)                   | <0.01   |
| Crypt shortening      | 1 (2.9)                  | 9 (25.7)                    | <0.01   |
| Crypt loss            | 1 (2.9)                  | 0 (0.0)                     | 0.35    |
| NGs epithelium        | 22 (62.9)                | 19 (54.3)                   | 0.96    |
| NGs lamina propria    | 20 (57.1)                | 19 (54.3)                   | 0.64    |
| NGs submucosa         | 0 (0.0)                  | 0 (0.0)                     | NA      |
| NGs muscularis propia | 0 (0.0)                  | 1 (2.9)                     | 0.30    |
| NGs subserosa         | 1 (2.9)                  | 0 (0.0)                     | 0.33    |
| Crypt abscess         | 17 (48.6)                | 17 (48.6)                   | 0.53    |
| Erosion or ulceration | 5 (14.2)                 | 1 (2.9)                     | 0.12    |
| Total fibrous obliteration | 4 (11.4)        | 8 (22.9)                    | 0.21    |
| Partial fibrous obliteration | 12 (34.3)   | 6 (17.1)                    | 0.10    |
| Lymphoid follicles    | 33 (94.3)                | 33 (94.3)                   | 1.00    |
| Submucosal adipose tissue | 30 (85.7)       | 32 (91.4)                   | 0.45    |
| RHI score, median (IQR) | 7 (1.0-15.0)     | 10 (1.0-13.0)                | 0.67    |

Abbreviations: IQR, interquartile range; NGs, neutrophil granulocytes; RHI, Robarts Histopathology Index; UC, ulcerative colitis.
involution of the appendix, but is also frequently seen in chronic inflammation and it was observed twice as frequently in the therapy refractory group. All other histological features were not statistically different between both UC groups (Table 2).

Histological features of both UC groups together were compared to appendices from patients with acute appendicitis and colon carcinoma (Tables S1 and S2; Figure 1). In all patients with UC with active appendiceal inflammation, neutrophilic infiltration was limited to the mucosa (i.e., ulcerative appendicitis). This was in contrast with the transmural infiltration of neutrophils that was seen in acute appendicitis. Appendices of patients with UC were more likely to have Paneth cell metaplasia, crypt branching, crypt shortening, and total fibrous obliteration of the appendiceal lumen when compared to appendices derived from patients with acute appendicitis (58.8% vs. 40.0%, p < 0.02; 44.3% vs. 22.9%, p < 0.02; 14.3% vs. 2.9%, p < 0.05; 17.1% vs. 2.9%, p = 0.05, respectively) and colon carcinoma (58.8% vs. 37.1%, p < 0.01; 44.3% vs. 20.0%, p < 0.01; 14.3% vs. 0.0%, p < 0.01; 17.1% vs. 0.0%, p < 0.02, respectively).

### Appendiceal histology and clinical characteristics in UC patients

Pathologic assessment of UC appendices showed absence of inflammation in 24.3% (17/70), ulcerative appendicitis in 58.6% (41/70) and total fibrous obliteration of the appendiceal lumen in 17.1% (12/70) (Table 3). The presence of active appendiceal inflammation was not different between UC patients in remission or active disease (53.7% [22/41] versus 46.3% [19/41], p = 0.45) and proctitis/ left-sided or pancolitis (58.5% [24/41] versus 41.5% [17/41], p = 0.50).

The presence of a PARP at the orifice of the appendix during endoscopy before appendectomy was assessed in 34 patients, of which 23 patients were in remission and 11 patients had active disease. A PARP was identified in 14.7% (5/34) of patients and microscopic analysis showed severe appendiceal inflammation in all five appendices, with RHI scores of 15, 16, 19, 25, and 25 respectively. The median RHI score was significantly higher in patients with a PARP compared to patients without a PARP (median RHI score 19 [15.5–25.0] versus median RHI score 6 [1.0–11.0], p < 0.001). All patients with a PARP belonged to the remission group, with original disease extent limited to the left-side of the colon (n = 3) or the rectum (n = 2). Patients with a fibrotic appendix had a significantly longer median disease duration compared to patients with normal histology (13 years [6.3–18.3] versus 4 years [3.0–9.0], p < 0.05).

### Patients with active UC undergoing appendectomy for refractory disease

Endoscopic response was assessed in 28 of 35 patients. Endoscopic response could not be assessed in two patients who deteriorated following appendectomy and needed to undergo colectomy within four weeks of appendectomy. Five patients underwent an appendectomy in the ongoing COSTA-study and were also excluded (Figure 2). Eleven patients were classified as responders, of which eight patients were in endoscopic remission at least one year after appendectomy. Three patients who underwent a planned colectomy within one year of appendectomy for other reasons than ongoing disease activity (e.g., patient preference), who had complete mucosal healing in the resection specimen were also considered responders. Seventeen patients were non-responders of appendectomy, of which 13 had endoscopic disease activity (Mayo 2/3) requiring intensified medical treatment. Four patients underwent a colectomy, with signs of active inflammation in the colectomy specimen.

Endoscopic response after appendectomy was more frequently seen in patients with active appendiceal inflammation (RHI > 6, 81.8% vs. RHI ≤ 6, 9.1%, p = 0.03) and patients with proctitis/left-sided disease (proctitis/left-sided 63.6% vs. pancolitis 36.4%, p = 0.02) (Table 4). Patients with total fibrous obliteration of the appendix showed low response (9.1%). Appendectomy was not beneficial in all three patients with primary sclerosing cholangitis (PSC), of which one had an RHI score of 24.
The results of this study demonstrated active appendiceal inflammation in almost 60% of all patients with UC. Inflammation of the appendix was not related to disease activity in the colon or the extent of UC. Histological features of appendiceal inflammation in UC patients were different from those observed in acute appendicitis. All UC patients with a PARP at endoscopy had severe inflammation of the appendix with RHI scores ≥15. In patients with active disease undergoing appendectomy with therapeutic intent, the response rate was higher in patients with active appendiceal inflammation (RHI score > 6) and those with proctitis and left-sided disease. Patients
with total fibrous obliteration of the appendiceal lumen showed limited endoscopic response.

The histological findings of the current study are in line with previous studies that demonstrated appendiceal involvement in patients with active UC.13,16 Traditionally, UC was considered a disease of continuous mucosal inflammation extending proximally from the rectum. In this context, it was assumed that appendiceal inflammation was always involved in continuity with pancolitis. In 1974, Cohen and colleagues introduced the term "ulcerative appendicitis" in a case report describing a patient with appendiceal involvement of UC, without inflammation of the cecum.18 Thereafter, several studies reported the prevalence of appendiceal inflammation found in colectomy specimens (ranging from 5%–88%) and appendiceal orifice inflammation assessed during colonoscopy (ranging from 8%–75%).13 The current findings confirm the presence of appendiceal inflammation in over 50% of UC patients, but for the first time demonstrated a high prevalence (62.9%) of "ulcerative appendicitis" in patients with colonic quiescent UC. The high prevalence of fibrosis suggests that an even larger proportion of patients had suffered from ulcerative appendicitis. Fibrosis is generally considered a normal involution of the appendix with age,19 but it has also been described secondary to (chronic) inflammation of the appendix.20

Although the pathogenesis of UC has not been resolved, cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells are considered important factors in the development of UC.1 The mucosal lymphoid tissue in the appendix is predominantly composed of B-cells and CD4+ T-helper cells.1 The release of inflammatory mediators in the appendiceal lumen are proposed to trigger an immunological cascade in the colon and rectum, causing active inflammation.21,22 Cheluvappa et al. found in a murine model that appendectomy for appendicitis was associated with autophagy suppression in the colon.23 The authors suggest that autophagy suppression, may induce lesser antigen processing, leading to diminished cross-reactive immunity between microbes and self-antigens, and thus having an anti-inflammatory effect on colitis.23 In addition, Harney et al. demonstrated in a similar murine

| TABLE 4 | Comparison of patient characteristics and RHI of therapy refractory patients according endoscopic response after appendectomy |
|---------|-------------------------------------------------|
|         | Responder N = 11 (%) | Non-responder N = 17 (%) | p value |
| Age years (median IQR) | 42 (31.0–47.0) | 39 (30.5–48.50) | 1.00 |
| Sex | | | |
| Male | 5 (45.5) | 9 (52.9) | 0.70 |
| Female | 6 (54.5) | 8 (47.1) | - |
| Disease duration in years (median, IQR) | 8 (3.0–15.0) | 8 (3.5–17.0) | 0.72 |
| Smoking (% yes) | 0 (0.0) | 3 (17.6) | 0.14 |
| PSC (% yes) | 0 (0.0) | 3 (17.6) | 0.26 |
| Family history of IBD (% yes) | 3 (27.3) | 2 (11.8) | 0.35 |
| Disease location | | | |
| Proctitis/left-sided | 7 (63.6) | 3 (17.6) | 0.02 |
| Pancolitis | 11 (36.4) | 14 (82.4) | - |
| Medication | | | |
| None | 0 (0.0) | 1 (5.9) | 1.00 |
| 5-ASA | 6 (54.5) | 9 (52.9) | 0.93 |
| Systemic steroids | 3 (27.3) | 5 (29.4) | 1.00 |
| Immunomodulators | 3 (27.3) | 6 (35.3) | 1.00 |
| Biologicals | 4 (36.4) | 5 (29.4) | 1.00 |
| Trial medication | 1 (9.1) | 2 (11.8) | 1.00 |
| Robarts Histopathology Index (n = 22) | | | |
| RHI ≤ 6 | 1 (9.1) | 7 (41.2) | 0.03 |
| RHI > 6 | 9 (81.8) | 5 (29.4) | - |
| Total fibrous obliteration | 1 (9.1) | 5 (29.4) | 0.36 |

Abbreviations: 5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; RHI, Robarts Histopathology Index.

*RHI could not be assessed in appendices with total fibrous obliteration of the appendiceal lumen with absence of the mucosa (n = 6).
model that appendectomy for appendicitis ameliorated experimental colitis, which was more pronounced in young mice. The potential immunological mechanisms responsible for the effect of appendiceal inflammation on UC in humans requires further investigation.

The finding of the current study that the appendix is inflamed irrespective of the disease activity of the colon, might support the role of the appendix as driving force rather than a merely reactive bystander. The appendix could be less susceptible for (topical) medical therapy, allowing the inflamed appendix to reactivate disease activity in the colon at a later stage. In addition to an immunological function, the appendix with its shape and location is also considered a reservoir for commensal flora. The rich biofilms of the appendix contain diverse microbiota, from which the gut can be recolonized with healthy flora after a gastrointestinal infection. It is hypothesized that bacteria from the appendix that are shed into the intestinal lumen, affect the microbiome in the colon and may cause an aberrant immunological response in patients with UC. In both theories, an appendectomy might prevent activation of disease activity in the colon.

In this study, favorable response to appendectomy for refractory UC was more frequently seen in cases with ulcerative appendicitis compared to those without active inflammation or fibrous obliteration. These observations were discordant from those of Bolin et al., who found comparable response rates between these three histology groups. However, Bolin et al. assessed treatment effect in terms of clinical response in contrast to endoscopic response in the current study. Several studies have shown that clinical and endoscopic response do not always correlate, which may explain these contrasting outcomes. In the current study, little treatment effect of appendectomy was seen in patients with appendiceal fibrosis. This could be explained by the absence of lymphoid tissue observed in degenerative fibrotic appendices, which is more frequently seen in UC patients with a long (>10 years) disease duration. In these patients, the role of the appendix in remission maintenance has likely become limited, since removal of the appendix may not impact disease course anymore. Intriguingly, appendectomy did not lead to endoscopic response in all three patients with concomitant PSC. The inverse relation between appendectomy and the prevalence of UC does not relate to PSC-UC, and the idea that PSC-UC is a different UC phenotype may explain why PSC-UC is less responsive to appendectomy.

Our results suggest that ulcerative appendicitis might be a good indication for appendectomy. To identify patients with appendiceal inflammation in clinical practice, it would be compelling if appendiceal inflammation could be assessed during colonoscopy or ultrasound. The current study demonstrated that endoscopic identification of a PARP might be a potential marker for appendiceal inflammation, as all patients with a PARP (14.7%) had ulcerative appendicitis (RHI > 15). Similar results were found in the study of Bolin and colleagues, in which 10% (3/30) had a PARP, of which histology showed ulcerative appendicitis. Despite the relation between a PARP and appendiceal inflammation, only a minority of patients responding to appendectomy will have a PARP. Therefore, it cannot be concluded that patients with a PARP are more likely to benefit from appendectomy. Data on the clinical significance of a PARP on the disease course are still conflicting and require further assessment.

In this study, several limitations were encountered. Treatment effect of appendectomy could only be assessed in patients with active disease. This resulted in a relatively small series, although it is currently the largest series in literature. In addition, the response rate after appendectomy might be confounded by concomitant medication use or placebo effect. However, the patients in the PASSION study were classified as therapy refractory disease and were initially referred for colectomy. With respect to the placebo effect, we have previously demonstrated that the results remained stable over a median follow-up of almost 4 years, with the accompanying improvement in quality of life remaining stable over time. Therefore, a long-term (endoscopic) placebo effect should be considered unlikely. The main strength of this study was the assessment of histological features in the appendix resection specimen of patients with UC in complete clinical and endoscopic remission. Furthermore, all slides were analyzed by an IBD specialist pathologist.

In conclusion, this study demonstrated that ulcerative appendicitis is common in UC, with no difference in the prevalence of appendiceal inflammation between patients with UC in remission and active disease. Patients with ulcerative appendicitis showed a more favorable response to appendectomy, supporting the hypothesis that the appendix should be seen as a pivotal organ in UC. Results of currently ongoing clinical studies should be awaited before an appendectomy can be offered as an alternative surgical therapy for UC. Future studies should focus on the mechanistic link between the appendix, the pathogenesis of UC, and the clinical significance of appendiceal (orifice) inflammation.

CONFLICT OF INTEREST
The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTION
Lianne Heuthorst, Aart Mookhoek, Christianne J. Buskens: study concept and design. Lianne Heuthorst and Aart Mookhoek data extraction. Lianne Heuthorst, Aart Mookhoek, Christianne J. Buskens: data analysis and interpretation. Lianne Heuthorst: drafting of manuscript. Lianne Heuthorst, Aart Mookhoek, Manon E. Wildenberg, Geert R. D’Haens, Willem A. Bemelman, Christianne J. Buskens participated in the critical revision of the manuscript for intellectual content. All authors approved the final version.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.
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SUPPORTING INFORMATION

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