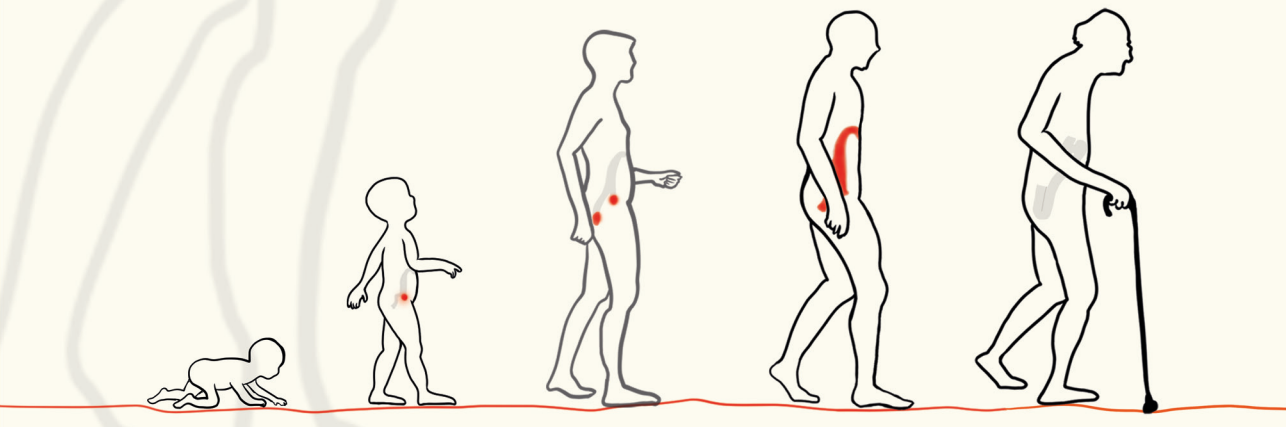
EVA VISSER

NEW INSIGHTS INTO THE MANAGEMENT OF ULCERATIVE COLITIS



New insights into the management of ulcerative colitis

Eva Visser

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New insights into the management of ulcerative colitis

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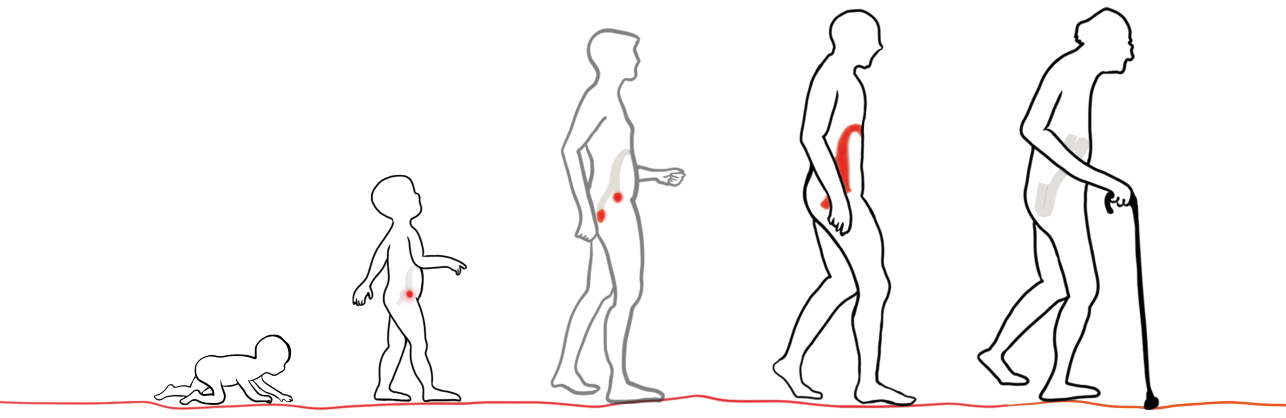
Chapter 1

General introduction and thesis outline



General introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) and the most prevalent form of IBD, affecting approximately five million individuals worldwide.[1] Although UC can present at any age, the peak incidence occurs between 15 and 30 years. The disease is particularly common in Western countries, with Europe reporting the highest prevalence, affecting one in every 200 persons. While the incidence of UC in Western regions has stabilised or even slightly declined, a significant rise in cases has been observed in newly industrialised countries in Africa, Asia, and South America since the 1990s. This trend is likely associated with urbanisation, dietary changes, and the adoption of Western lifestyles, emphasising the influence of environmental factors in disease pathogenesis.[2]

Pathogenesis

The pathogenesis of UC is multifactorial, involving a complex interplay of genetic, environmental, immunological, and dietary factors.[3,4] These factors interact to disrupt the intestinal immune response, leading to chronic inflammation that predominantly affects the colonic mucosa. Genetic susceptibility is estimated to account for 8.2% of UC risk, with several genetic loci linked to immune regulation, epithelial barrier function, and microbial interactions. Environmental factors, such as the use of oral contraceptives and dietary habits, have also been associated with the onset and progression of UC.[4] Notably, smoking appears to have a protective effect against UC, as current smokers exhibit a lower risk of developing UC than non-smokers or former smokers. Furthermore, appendectomy, particularly when performed before the age of 20, has demonstrated a strong protective effect against disease development.[4-7]

Clinical symptoms and diagnosis

The inflammatory process in UC primarily affects the mucosa of the colon and rectum, with its clinical course marked by alternating periods of remission and relapse (i.e. flare-up; Figure 1). The disease typically begins in the rectum (proctitis) and may extend proximally in a continuous manner, affecting the left side of the colon (left-sided colitis), or the entire colon (pancolitis; Figure 2). The formation of mucosal inflammation disrupts the epithelial barrier, resulting in the hallmark symptoms of UC, including increased stool frequency, rectal bleeding, urgency, abdominal pain and fatigue. These symptoms not only impair the patient's quality of life, but also place a substantial burden on healthcare systems.[8,9]

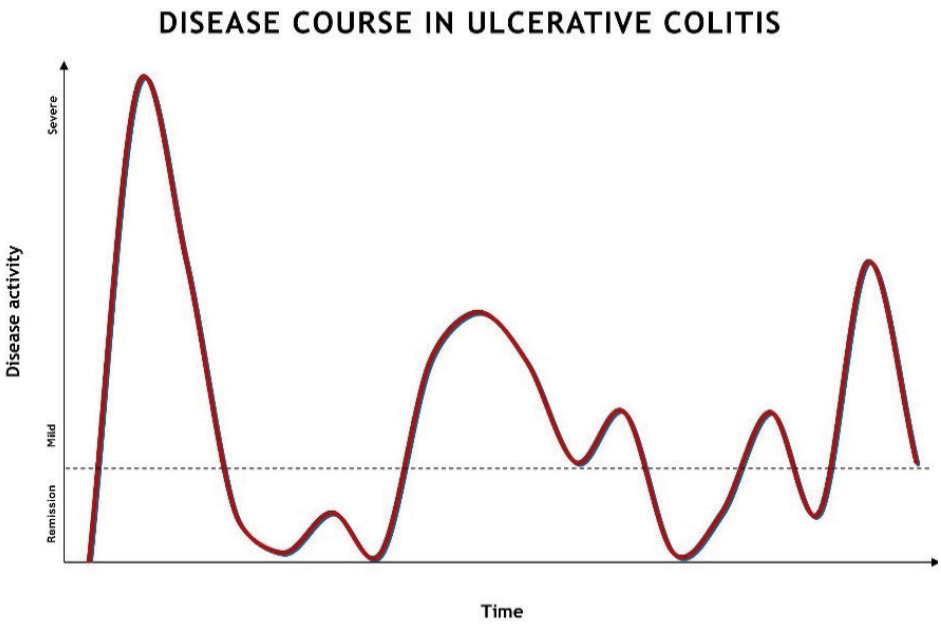


Figure 1. Disease course in ulcerative colitis

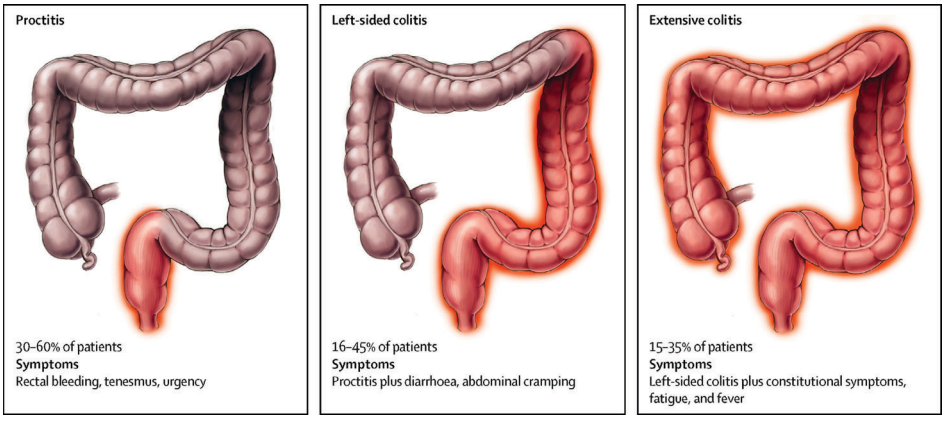


Figure 2. Disease extent[10]

The diagnosis is established based on a combination of clinical presentation, endoscopic findings, and histopathological examination, as no single diagnostic gold standard exists.[11,12] Laboratory markers such as C-reactive protein and faecal calprotectin are indicative of active inflammation and are valuable for disease monitoring. Endoscopic assessment via colonoscopy allows for direct visualisation

of mucosal inflammation and biopsy collection for histological evaluation. Histopathological findings typically include crypt abscesses, goblet cell depletion, and diffuse mucosal inflammation with erosions and ulcerations.

To standardise the disease severity assessment, validated scoring systems are employed. The Mayo score is a widely used index in clinical practice and research to assess disease activity, stratify severity, and monitor therapeutic response. It comprises four subscores evaluating stool frequency, rectal bleeding, endoscopic findings, and the physician's global assessment (PGA) (Table 1). The total Mayo score is calculated as the sum of these 4-point components, yielding scores ranging from 0 to 12, with higher scores indicating more severe disease activity.[13,14] In more recent clinical trials, a modified Mayo score has been adopted that excludes the PGA to reduce subjectivity, resulting in a maximum score of 9.[15] For histopathology assessment, the Robarts Histopathology index, Nancy index, and Geboes score are utilised.[16]

Table 1. Mayo score[13]

Score	Component
	Rectal bleeding
0	Normal number of stools for patient
1	1 to 2 stools per day more than normal
2	3 to 4 stools more than normal
3	≥5 stools more than normal
	Endoscopic finding
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
	Physician's global assessment
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

Management and treatment:

Medical

The management of UC is aimed to induce and maintain remission, prevent complications, and improve patients' quality of life.[17] Medical therapy is stratified based on disease extent (proctitis; left-sided colitis; pancolitis) and severity (mild; moderate; severe), with treatment regimens tailored accordingly[11,18] Figure 3

illustrates how therapeutic strategies alternate between induction and maintenance phases in response to changes in disease activity. For mild to moderate disease, approved medical therapies include 5-aminosalicylic acid (5-ASA), (topical) corticosteroids, and immunomodulators. In cases of moderate to severe disease activity, corticosteroids are also used to induce remission, while advanced medical therapies consist of biologic agents (anti-tumour necrosis factor; anti-integrin) and small molecules such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators.

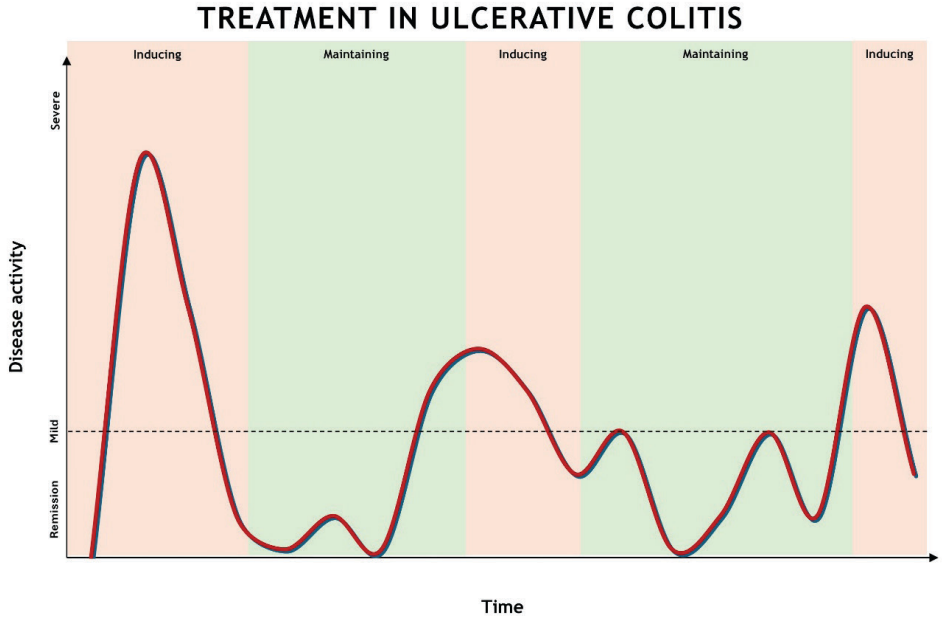


Figure 3. Treatment in ulcerative colitis
Illustrates the relapsing-remitting course of UC and the corresponding therapeutic strategy of alternating induction and maintenance therapy.

Surgery

Despite the expanding therapeutic armamentarium, surgical intervention remains necessary for approximately 10–30% of UC patients, particularly those with refractory disease, severe colitis, or colorectal neoplasia (CRN).[19] The standard surgical procedure in UC is proctocolectomy with ileal pouch-anal anastomosis, which removes the inflamed colon and rectum while preserving bowel continuity and function.[20] Beyond refractory colitis, surgery has an important role in managing CRN in UC. Chronic inflammation is a well-established risk factor for colorectal

cancer (CRC) in UC, particularly in patients with extensive colitis, concomitant primary sclerosing cholangitis, or a family history of CRC.[21,22]

Appendix and appendectomy in UC

Once described as a vestigial organ by Darwin in his seminal work *The Descent of Man* (1871), the appendix has, in recent decades, attracted increasing scientific interest for its potential immunomodulatory role in the pathogenesis of UC.[5,23,24] The observed association between appendectomy and a reduced risk of developing UC has further stimulated interest in the immunological function of the appendix.[5,25] This finding challenges the traditional view of the appendix as a redundant organ and instead suggests a contributory role in intestinal immune regulation. The hypothesis that appendectomy might alter disease course introduces a novel and potentially paradigm-shifting therapeutic concept for patients with established UC.

Recent studies have explored the impact of appendectomy on disease course and clinical outcomes. In a case series of 30 patients with ulcerative proctitis, 40% (12 of 30) achieved complete remission following appendectomy.[26] Furthermore, a pilot study conducted by our research group demonstrated a clinical response in approximately one-third of patients with treatment-refractory colitis who were initially referred for colectomy.[27,28] After a median follow-up of eight years, 24% (6 of 25) of these patients exhibited endoscopic improvement, and only 36% (9 of 25) ultimately underwent colectomy.[29]

Thesis outline

This thesis examines the surgical management of UC, with particular focus on the therapeutic potential of appendectomy and CRC outcomes in UC patients undergoing colectomy. The thesis is structured into four parts:

Part I establishes a baseline for the efficacy of currently approved advanced medical therapies in moderate to severe UC, serving as a reference point for evaluation of appendectomy. This is addressed in **Chapter 2,** which presents a systematic review and meta-analysis evaluating the absolute efficacy (Δ)—defined here as the measurable difference in efficacy outcomes between treatment and control groups—of biologic agents and small molecules in inducing and maintaining remission in UC, compared with placebo or active comparators.

Part II explores the surgical role of appendectomy in maintaining remission in UC patients. This section is based on data from the ACCURE trial, a pragmatic international randomised controlled trial (RCT) assessing the clinical effectiveness of laparoscopic appendectomy in addition to standard medical therapy, compared with standard therapy alone. **Chapter 3** outlines the clinical statistical analysis plan for the trial. **Chapter 4** presents the primary results of the ACCURE trial, comparing relapse rates between treatment arms at one year. **Chapter 5** investigates clinical and demographic predictors of maintained remission post-appendectomy, aiming to refine patient selection criteria for appendectomy. **Chapter 6** examines histopathological characteristics of resected appendix specimens and their association with postoperative clinical outcomes in patients with quiescent UC.

Part III shifts the focus to appendectomy as a therapeutic strategy for inducing remission in biologic-refractory UC patients. **Chapter 7** presents the primary outcomes of the COSTA trial, a pragmatic multicentre, patient-preference, interventional cohort trial comparing the efficacy of appendectomy versus JAK inhibitors in achieving remission at one year. **Chapter 8** assesses the predictive value of preoperative appendiceal intestinal ultrasound in identifying patients likely to respond to appendectomy, proposing potential sonographic markers for treatment stratification. **Chapter 9** investigates the biological activity and phenotypic characteristics of the appendix in responders and non-responders to appendectomy, examining their association with response to appendectomy and informing future patient selection strategies.

Part IV transitions from appendectomy to colectomy and reports oncological outcomes in the surgical management of UC. **Chapter 10** analyses the impact of advanced medical therapies on time to surgery and oncological outcomes in patients undergoing colectomy.

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Part I

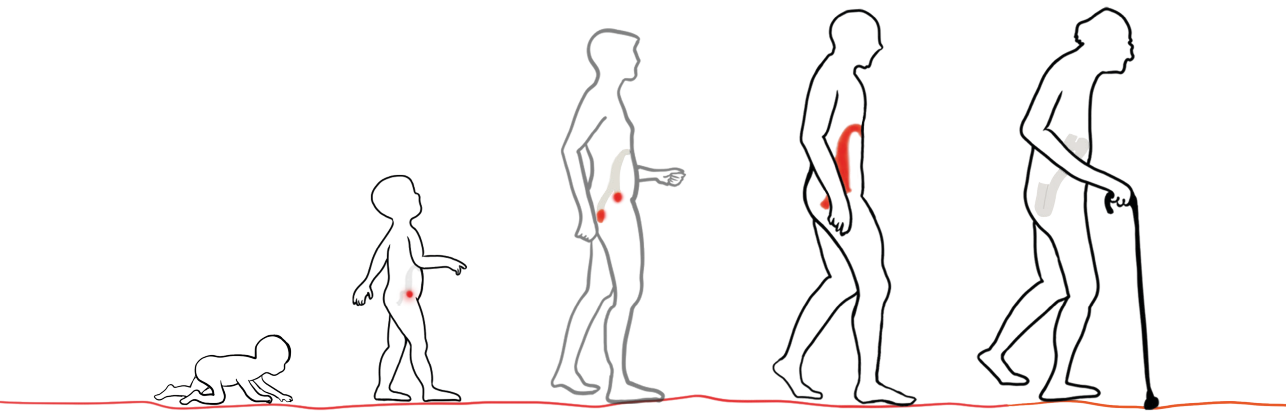
Efficacy of medical therapy in ulcerative colitis

2

Chapter 2

Efficacy of advanced medical therapies in patients with moderately to severely active ulcerative colitis: a systematic review and meta-analysis

Eva Visser, Isabelle D van Dijk, George L Burchell, Willem A Bemelman, Geert R D'Haens, Christianne J Buskens



Submitted (under review)

Abstract

Background

To evaluate the absolute efficacy of approved advanced medical therapies (biologicals or small molecules) in adults with moderately to severely active ulcerative colitis (UC), compared with placebo or active comparators.

Methods

We included phase 3 and 4 randomised controlled trials (RCTs) evaluating FDA- or EMA-approved advanced therapies in adults with moderately to severely active UC. PubMed, EMBASE, Cochrane, and major congress abstracts were searched through October, 2024. Eligible RCTs compared these therapies to placebo or an active comparator and reported clinical remission, clinical response, endoscopic remission, and/or histological remission. Our primary outcome was clinical remission after induction (defined as a Mayo score ≤2 with no individual subscore >1, including the endoscopic subscore). Random-effects models estimated pooled absolute differences in outcome rates (risk differences; RDs) for induction and maintenance. Certainty of evidence was assessed using GRADE.

Results

The search yielded 7,712 records, of which 25 RCTs (38 cohorts; 15,460 patients) met inclusion criteria. Of these, 20 RCTs (25 cohorts; 11,476 patients) reported induction outcomes, and 18 RCTs (19 cohorts; 6,692 patients) reported maintenance outcomes. The pooled absolute difference (RD) for clinical remission after induction was +13.1% (95% CI 10.3-16.0), increasing to +21.1% (95% CI 16.4-25.7) for maintenance. Clinical response also favoured intervention, with RDs of +24.2% (95% CI 19.7-28.6) for induction and +26.6% (95% CI 20.3-33.0) for maintenance. Endoscopic remission was less frequently reported, and showed smaller but significant effects (induction RD +8.2%, 95% CI 4.7-11.8; maintenance +13.6%, 95% CI 8.5-18.7). Histological remission RDs were +12.5% (95% CI 6.6-18.4) and +15.5% (95% CI 9.0-22.0), respectively. Certainty of evidence was high for clinical remission and moderate-to-low for other outcomes due to limited reporting and heterogeneity.

Conclusions

Advanced therapies favoured significant absolute benefits in inducing and maintaining remission in moderate-to-severe UC. These results provide a benchmark for future trials and non-pharmacological interventions.

What is already known?

Advanced therapies (biologics and small molecules) are effective in treating moderate-to-severe ulcerative colitis, but existing systematic reviews and meta-analysis often report only relative effect sizes.

What is new here?

This study provides pooled absolute efficacy estimates across all advanced therapies approved up to October 2024, offering direct measures of clinical, endoscopic, and histological outcomes.

How can this study help patient care?

By establishing absolute, evidence-based benchmarks, this study supports informed decision-making, helps set patient expectations, and provides a reference for evaluating new or alternative treatment strategies.

Introduction

Ulcerative colitis (UC) is a chronic relapsing-remitting inflammatory bowel disease that affects the rectum and colon, substantial impacting patient's quality of life and healthcare systems.[1,2] Over the past two decades, the therapeutic landscape of UC has expanded considerably, driven by the development and approval of advanced medical therapies. These include biological agents, such as anti-tumour necrosis factor (anti-TNF) therapies (i.e., infliximab, adalimumab, golimumab), integrin receptor antagonists (vedolizumab), interleukin-12/23 inhibitors (i.e., ustekinumab, risankizumab, mirikizumab, guselkumab), as well as small molecules, including Janus Kinase (JAK) inhibitors (i.e., tofacitinib, filgotinib, upadacitinib), and sphingosine-1-phosphate (S1P) receptor modulators (i.e., ozanimod, etrasimod). These agents effectively induce and maintain remission in patients with moderately to severely active UC, contributing to improvements in quality of life and a reduction in colectomy rates over recent decades.[3,4]

Despite these advances, clinical decision-making remains challenging due to the growing number of therapeutic options. Direct head-to-head trials are limited, and in their absence, clinicians often rely on indirect comparisons and network meta-analyses.[5-8] While these analyses are informative, they typically report relative efficacy measures (relative risk, odds ratio), which may not translate clearly into the absolute clinical benefit of a treatment. In contrast, absolute treatment effects (risk differences) are important metrics for benchmarking efficacy across diverse therapies and informative for real-world decisions. Therapeutic efficacy may also vary across disease phenotypes, severity, and/or underlying pathophysiological mechanisms. The concept of a "therapeutic ceiling", the maximum achievable benefit with current medical therapies, has emerged, but unfortunately, it has not yet been broken.[9] This is particularly relevant in the context of the evaluating of emerging interventions, including non-medical treatment such as hyperbaric oxygen therapy, faecal microbiota transplantation or surgical interventions like appendicectomy,[10-12] which are difficult to assess against current medical benchmarks without a clearly defined efficacy baseline for existing therapies.

To address these gaps, we aimed to perform a systematic review and meta-analysis of phase 3 and 4 randomised controlled trials (RCTs) evaluating the absolute efficacy of approved advanced medical therapies in adults with moderately to severely active UC, compared with placebo or active comparators. Our comprehensive and updated synthesis will not only serve to guide clinical practice but can also be used in the context of emerging non-pharmacological therapeutic approaches.

Methods

Search strategy and selection criteria

The protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42024599272) prior to the start of screening. This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines.[13] Relevant databases systematically searched were PubMed, EMBASE, and the Cochrane Library, for articles published from database inception to October 25, 2024 without language restrictions. In addition, congress abstract databases (European Crohn's and Colitis Organisation, Digestive Disease Week, and United European Gastroenterology Week) were manually searched from January 1, 2021 and October 25, 2024 for unpublished studies.

A comprehensive search strategy was developed by the medical information specialist GLB. The final search included keywords and free text terms for (synonyms of) 'remission induction' combined with (synonyms of) 'ulcerative colitis' combined with (synonyms of) 'drug therapy' combined with (synonyms of) 'controlled clinical trial'. The full search strategy is available in the Supplementary Material (pp 2-4). Eligible studies were phase 3 or 4 RCTs that met the following inclusion criteria: (1) studies including adult patients (≥16 years) with moderately to severely active UC (defined as a total Mayo score of 6 to 12 with an endoscopic Mayo subscore of 2 or 3); (2) studies evaluating therapies approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) in their approved dosing regimens; (3) studies including comparison groups of placebo, or an active comparator group (another approved therapy, standard-care therapy); (4) studies reporting at least one of the following outcomes: clinical remission (defined as a Mayo score ≤2 with no individual subscore >1, including the endoscopic subscore), clinical response (defined as a decrease from baseline Mayo score by ≥3 points and ≥30%, plus a ≥1-point decrease in rectal bleeding subscore or a rectal bleeding subscore 0-1), endoscopic remission (defined as a Mayo endoscopic score of 0), histological remission (defined as a Nancy score of 0, Geboes score ≤2.0 or Robarts Histopathology Index (RHI) score ≤3). Alternative disease activity indices were accepted if they could be mapped to Mayo-equivalent definitions. This included the modified or adapted Mayo score (i.e., the Mayo score without the Physician's Global Assessment), as well as other indices such as the Ulcerative Colitis Disease Activity Index, Disease Activity Index, and Sutherland score). In addition, studies

using stricter criteria than those defined above, such as requiring a rectal bleeding subscore of 0, were also eligible. Studies were excluded if they: (1) did not specify or stratify disease severity into mild-to-moderate (Mayo score 3-5) and moderate-to-severe (Mayo score 6-12) UC; (2) evaluated therapies or combinations not approved by FDA or EMA at the time of this review; (3) were not phase 3 of 4 RCTs; (4) reported study outcomes that did not match the predefined criteria for this review.

Approved biological and small molecule agents at the time of conducting this review included: infliximab (induction: 5mg/kg intravenous [IV] infusion at weeks 0, 2 and 6; maintenance: 5 mg/mg IV every 8 weeks or 120 mg subcutaneous (SC) injection every 2 weeks), adalimumab (induction: 160 mg SC at week 0, 80 mg at week 2; maintenance: 40 mg SC every other week starting at week 4), golimumab (induction: 200 mg SC at week 0, 100 mg at week 2; maintenance: 100 mg SC every 4 weeks); vedolizumab (induction: 300 mg IV at weeks 0, 2 and 6; maintenance: 300 mg IV every 8 weeks or 108 mg SC every 2 weeks), ustekinumab (induction: single weight-based IV infusion ~6 mg/kg; maintenance: 90 mg IV every 8 weeks), risankizumab (induction: 1,200 mg IV at weeks 0, 4 and 8; maintenance: 360 mg SC every 8 weeks), mirikizumab (induction: 300 mg IV at weeks 0, 4 and 8; maintenance: 200 mg SC every 4 weeks), guselkumab (induction 200 mg SC at weeks 0, 4 and 8; maintenance: 200 mg SC every 8 weeks), tofacitinib (induction: 10 mg orally twice daily for 8 weeks; maintenance: 5 or 10 mg orally twice daily), filgotinib (induction: 200 mg orally once daily for 10 weeks; maintenance: 200 mg orally once daily), upadacitinib (induction: 45 mg orally once daily for 8 weeks; maintenance: 15 of 30 mg orally once daily), ozanimod (induction: 0.23 mg orally once daily on days 1-4, 0.46 mg on days 5-7, then 0.92 mg one daily thereafter; maintenance: 0.92 mg orally once daily), and etrasimod (induction and maintenance: 2 mg orally once daily).

Selection and data collection

Title and abstracts were independently screened by two reviewers (EV and IDvD) using Rayyan systematic review tool.[14] Full-text reviews of potentially eligible studies were performed in duplicate and discrepancies were resolved by discussion or, if necessary, a third reviewer (CJB).

Data were independently extracted by two reviewers (EV and IDvD) using a standardised extraction form. Extracted information included study identifiers (first author's last name, publication year, country, trial registration number, and DOI), design characteristics (aim, blinding, follow-up duration, and outcome assessment

timepoints), population demographics (sample size, inclusion and exclusion criteria, baseline demographics including age, sex, disease duration, prior exposure to advanced therapy, total Mayo score, and use of concomitant corticosteroids), details on the intervention and comparator group (drug type, dosage, route of administration, frequency, and duration), and reported outcomes. For studies reporting maintenance outcomes, trial designs and corresponding cohorts were classified as either "randomised responder cohorts", which re-randomised only patients who responded during induction, or "treat-through cohorts", which evaluated both induction and maintenance phases in all initially randomised patients. If necessary, median and interquartile range (IQR) were converted to mean and standard deviation (SD) using established statistical methods.[15] Outcomes were stratified into induction (defined per each therapy's approved dosing regimen, typically 8-12 weeks) and maintenance (52-60 weeks) phases. Discrepancies during extraction were resolved through discussion or, if unresolved, through consultation with the supervisor (CJB). If multiple cohorts were described within a study (e.g., varying patient populations, doses, or outcome periods) data were analysed separately to maintain accuracy and consistency across treatment arms. Separate cohorts within each study were labeled according to the cohort names provided by the study. If no predefined name was specified, cohorts were labeled using the terms "induction" or "maintenance" as appropriate based on the outcome period reported. Summary data from intention-to-treat analyses were retrieved from the published reports, and data from the most comprehensive report were selected if multiple publications of a trial were available.

Outcomes

The primary outcome was clinical remission after induction therapy. Secondary outcomes included clinical response, endoscopic remission, histological remission, and the frequency and types of primary outcomes reported across included studies.

Study risk of bias assessment

The quality of the included trials was independently assessed by two reviewers (EV and IDvD) using the Cochrane risk of Bias tool, version 2.0.[16]

Data synthesis and statistical analysis

Efficacy outcomes were reported as absolute differences in outcome rates (risk differences; RDs) with 95% confidence intervals (CI). A random-effects meta-analysis

was conducted to pool outcome data across studies, accounting for anticipated heterogeneity in study populations, interventions, and trial designs. Data were synthesised separately for the induction and maintenance phases. Heterogeneity was quantified using the I^2 statistic, with values above 50% indicating considerable heterogeneity. Separate cohorts within studies (e.g., different populations, such as biological-naïve and biological-exposed), were analysed independently. Meta-analyses were conducted using STATA software version 17.0, with results presented in forest plots. Predefined subgroup analyses evaluated potential efficacy differences across therapeutic subclasses (anti-TNF agents, integrin receptor antagonists, IL-12/23 inhibitors, JAK-inhibitors, S1P receptor modulators), conducted when five or more studies were available within a subclass and stratified by treatment phase (induction, maintenance).

Assessment of reporting bias

Publication bias was assessed using funnel plots and Egger's test, with $p<0.05$ considered suggestive of small-study effects.

Certainty of evidence

Certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[17], evaluating risk of bias, inconsistency, indirectness, imprecision and publication bias. Results were presented in a GRADE 'Summary of Findings' table, indicating the GRADE certainty for each outcome.

Role of the funding source

This study was self-funded.

Results

Study selection

The search yielded a total of 7,712 records. After title and abstract screening, 198 full-text articles were assessed for eligibility. Of these, 25 studies comprising 38 relevant cohorts met the inclusion criteria and were included in the review (Figure 1). Among these, 19 were induction cohorts and 19 maintenance cohorts (13 randomised responders to induction therapy; 6 treat-through cohorts). A total of 15,460 adults with moderately to severely active UC were enrolled in the corresponding cohorts across all included studies. Reasons for exclusion are provided in Figure 1.

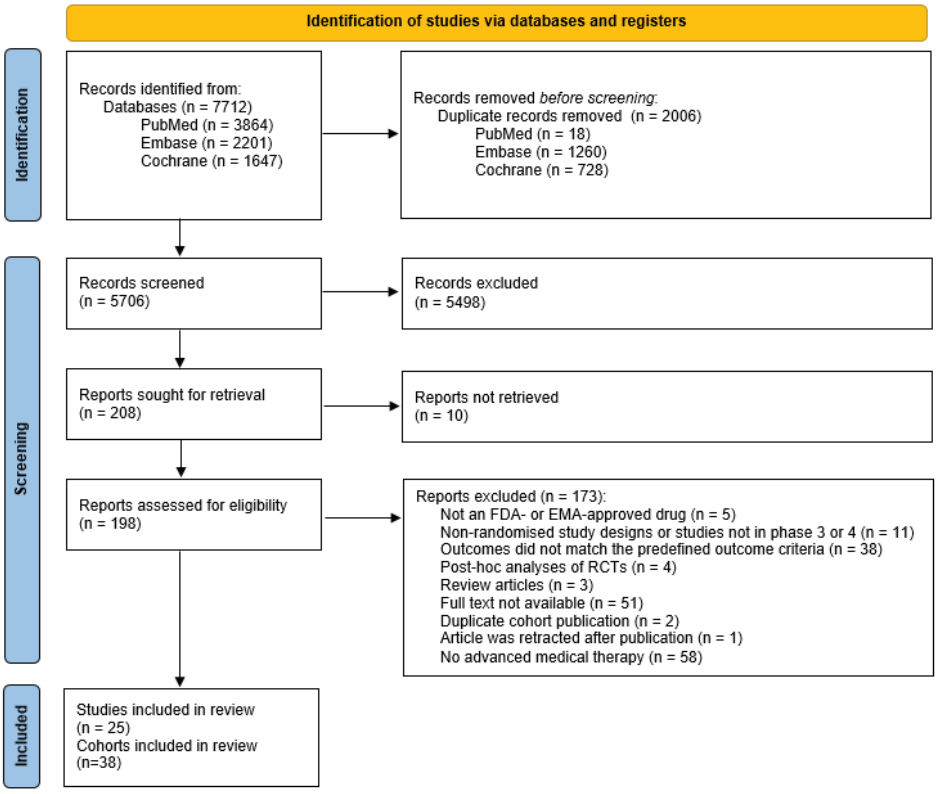


Figure 1. Study selection

Abbreviations: FDA: U.S. Food and Drug Administration; EMA: European Medicines agency; RCT: randomised controlled trial. Advanced medical therapy are biologics or small molecules.

Study characteristics

Study characteristics are summarised in Supplementary Table 1 (pp 8-10), and baseline patient characteristics per cohort are provided in Supplementary Table 2 (pp 11-13). There were four studies of infliximab (ACT-1 and ACT-2[18]; UC SUCCESS[19]; Jiang at al.[20]; LIBERTY UC[21]), three studies of adalimumab (ULTRA 1 induction[22]; ULTRA 2[23]; Suzuki et al.[24]), three studies of golimumab (PURSUIT-SC induction[25]; PURSUIT-M[26]; PURSUIT-J maintenance[27]), four studies of vedolizumab (GEMINI 1[28]; NCT02039505[29]; VARSITY[30]; VISIBLE 1[31]), one study of ustekinumab (UNIFI[32]), one study of risankizumab (INSPIRE and COMMAND[33]) one study of mirikizumab (LUCENT 1 and LUCENT 2[34]), one study of guselkumab (QUASAR[35]), two studies of tofacitinib (OCTAVE[36]; CTRI/2021/10/037641[37]), one study of filgotinib (SELECTION[38]), two studies of upadacitinib (U-ACHIEVE induction and U-ACCOMPLISH[39]; U-ACHIEVE maintenance[40]), one study of ozanimod (True North[41]), and one study of etrasimod (ELEVATE UC[42]).

Twenty studies (25 cohorts; 11,476 patients) reported induction outcomes[18-20,22-25,28-30,32-39,41,42] and 18 studies (19 cohorts; 6,692 patients) reported maintenance outcomes.[18,21,23,24,26-34,36,38,40-42] Among the latter, 12 studies followed a randomised responders design (13 cohorts; 3,981 patients),[21,26-29,31-34,36,38,40] and 6 used a treat-trough approach (6 cohorts; 2,771 patients).[18,23,24,30,41,42]

Most trials (22 studies; 14,453 patients) were placebo-controlled,[18,20-29,31-36,38-42] three used active comparators: tofacitinib versus prednisolone[37], vedolizumab versus adalimumab[30], and infliximab combination versus infliximab monotherapy.[19]

Additionally, 12 studies (14 cohorts), had a third comparator arm, typically evaluating alternative dosing strategies or formulations.[18-20,22,24-26,31-33,38,40] These arms were therefore excluded from the meta-analyses, further details are available in Supplementary Table 1 (pp 8-10).

Primary outcomes reported

One study (Suzuki et al.[24]) did not report a clearly defined primary outcome. Among the remaining studies, six distinct primary outcomes were reported. Clinical remission was most the common, designated as the primary outcome in 14 studies.[21,23,30-36,38-42] Clinical response was the primary outcome in five studies.[18,20,25,28,29]. Two studies used maintenance of clinical response.[26,27] Other primary outcomes included composite remission (n=1),[37] corticosteroid-free remission (n=1),[19], and remission (n=1).[22] Details are shown in Figure 2.

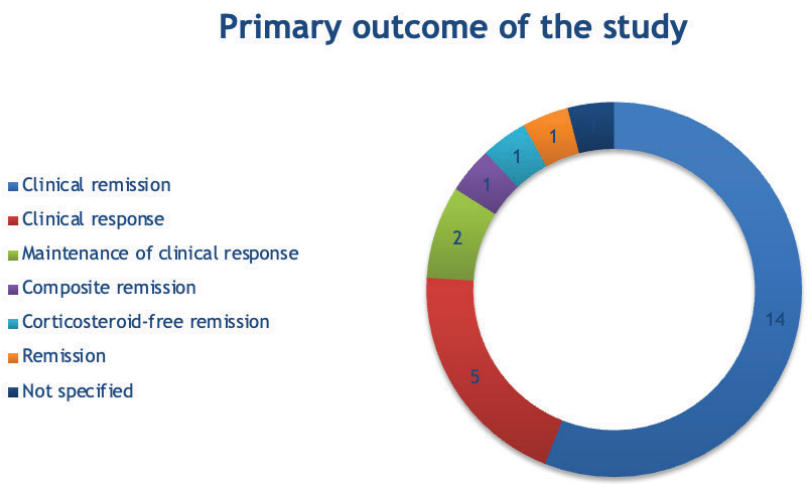


Figure 2. Primary outcome of the study

Risk of bias in studies

Risk of bias was generally low across included studies (Supplementary Figure 1; p 5). Visual inspection of the funnel plot (Supplementary Figure 2; p 5) and Egger's test (p=0.387) did not indicate evidence of publication bias or small-study effects. A summary of the risk of bias for secondary outcomes is provided in Supplementary Table 4 (p 14).

Results of individual studies

Outcomes of interest were variably reported across studies. A full overview is described in Supplementary Table 3 (pp 13-14). Baseline characteristics varied substantially, particularly in prior biological exposure (range: 0% to 100%), and baseline concomitant corticosteroid use (range: 13.41% to 65.29%). Clinical remission after induction was reported in 18 RCTs, with remission rates in intervention arms ranging from 9.5% to 53.7% after a treatment period of 8-16 weeks. Among maintenance cohorts, clinical remission rates ranged from 6.5% to 56.1% in re-randomised responder, and 6.7% to 37% in treat-through cohorts after 52-60 weeks.

Primary outcome

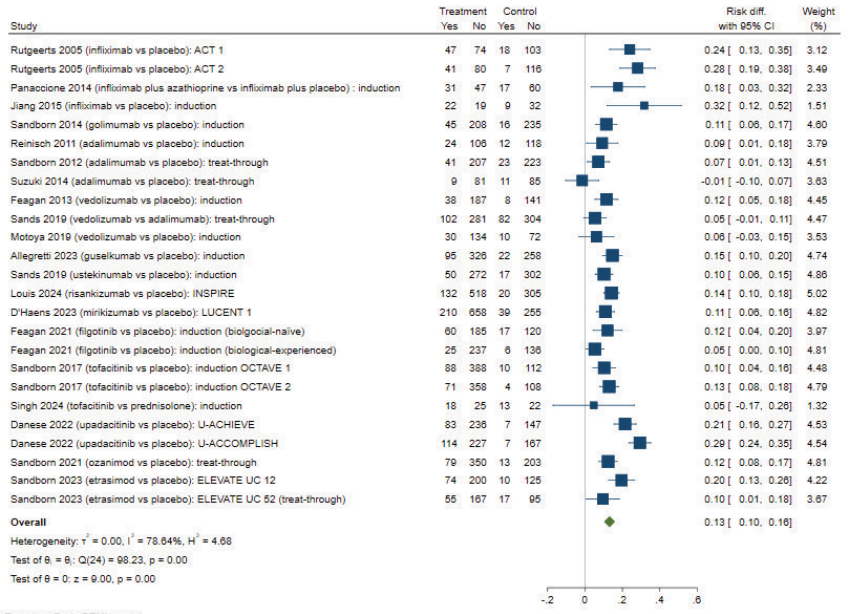
Clinical remission after induction

Clinical remission after induction was achieved in 1584 of 7154 patients (22.1%) in the intervention group, compared to 415 of 4259 (9.7%) in the comparator arm. Meta-analysis of 25 cohorts to evaluate clinical remission after induction therapy demonstrated a significant benefit of advanced medical therapies over placebo or active comparator, with a pooled RD of +13.1% (95% CI +10.3% to +16.0%, $p<0.001$; $I^2 = 78.64\%$; Figure 3A). This corresponds to a number needed to treat of 8 patients (95% CI, 7 to 9). Subgroup analyses (Figure 3B) showed similar efficacy among anti-TNF agents (RD: +14.6%, 95% CI +7.9 to +21.3, $p<0.001$; $I^2=77.88\%$) and JAK-inhibitors (pooled RD: +14.6%, 95% CI +7.9 to +21.3, $p<0.001$; $I^2=92.25$).

Secondary outcomes

An overview of the primary and all secondary outcomes from the pooled meta-analyses is presented in Figure 4.

A.



B. Subgroup analyses

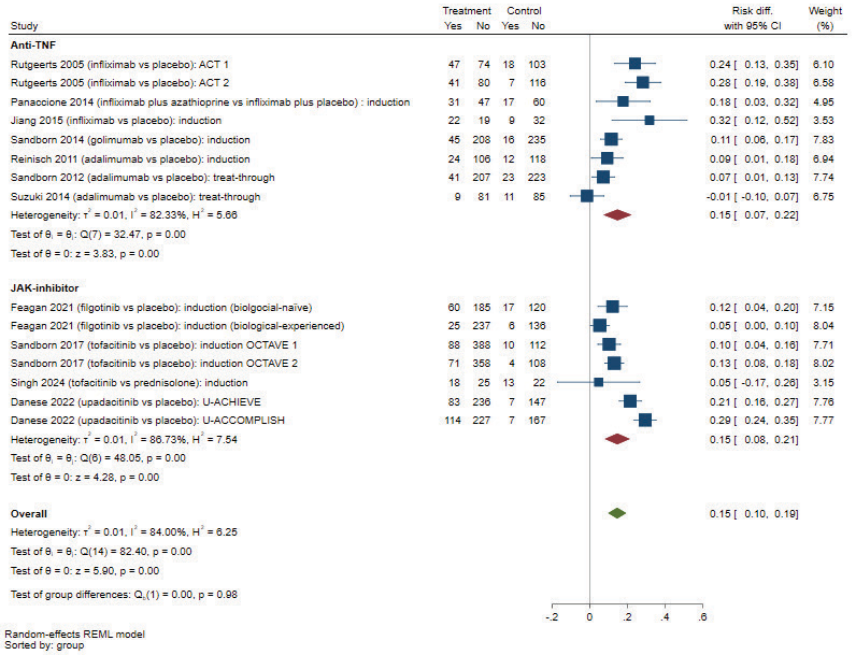


Figure 3. Meta-analysis on clinical remission after induction

Outcome	No. Cohorts (RCTs)	Intervention No. Events/No. Participants (%)	Comparator No. Events/No. Participants (%)	RD (95% CI)	Heterogeneity
Clinical remission					
Induction	25 (18)	1584/7155 (22.1)	415/4259 (9.7)	13.1 (10.3-16.0)	τ^2=0.00 I^2=79%
Maintenance	19 (18)	1310/3570 (36.7)	463/2788 (16.6)	21.1 (16.4-25.7)	τ^2=0.01 I^2=80%
Clinical response					
Induction	25 (20)	4330/7155 (60.5)	1494/4259 (35.1)	24.2 (19.7-28.6)	τ^2=0.01 I^2=82%
Maintenance	16 (14)	1618/2803 (57.7)	765/2329 (32.9)	26.6 (20.3-33.0)	τ^2=0.01 I^2=84%
Endoscopic remission					
Induction	10 (8)	342/837 (12.1)	67/1724 (3.9)	8.2 (4.7-11.8)	τ^2=0.00 I^2=83%
Maintenance	7 (6)	290/1162 (25.0)	113/929 (12.2)	13.6 (8.5-18.7)	τ^2=0.00 I^2=61%
Histological remission					
Induction	6 (5)	508/2035 (25.0)	179/1458 (12.3)	12.5 (6.6-18.4)	τ^2=0.00 I^2=85%
Maintenance	6 (5)	357/1257 (28.4)	136/1023 (13.3)	15.5 (9.0-22.0)	τ^2=0.00 I^2=76%

Abbreviations: RD: risk difference

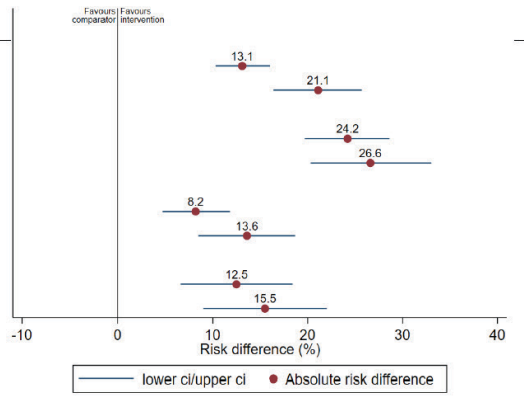


Figure 4. Results of primary outcome and secondary outcomes of interest
Abbreviation: RCT: randomized controlled trial; RD: risk difference.

Clinical remission (maintenance)

Nineteen cohorts reported on clinical remission during maintenance phase, showing a benefit in favour of advanced therapy with a pooled RD of +21.1% (95% CI +16.4 to +25.7, $p<0.001$; $I^2 = 80.46\%$).

Clinical response

Clinical response following induction was reported in 25 cohorts, with a pooled RD of +24.2% (95% CI +19.7 to +28.6, $p<0.001$; $I^2=82.48\%$). For maintenance therapy, 16 cohorts were included, yielding a pooled RD of **+**26.6% (95% CI +20.3 to +33.0, $p<0.001$; $I^2=83.77\%$).

Endoscopic remission

Endoscopic remission after induction therapy was assessed in 10 cohorts, showing a significant treatment benefit of advanced therapies with a RD of +8.2% (95% CI +4.7 to +11.8, $p<0.001$; $I^2=82.74\%$). For the maintenance phase, only 6 cohorts were included, with a pooled RD of + 13.6% (95% CI+ 8.5 to +18.7, $p<0.001$; $I^2 =60.70\%$).

Histological remission

Six cohorts evaluated histological remission after induction therapy, demonstrating a pooled RD of +12.5% (95% CI +6.6 to +18.4, $p<0.001$). Heterogeneity was considerable $I^2 = 84.93\%$. During maintenance, six studies reported a pooled RD of +15.5% (95% CI +9.0 to +22.0, $p<0.001$; $I^2=76.06\%$).

All meta-analyses of secondary outcome of interests are detailed in Supplementary Figure 3 (pp 6-7).

Certainty of evidence

The certainty of evidence of each outcome was evaluated using the GRADE framework. Overall, the certainty was rated high for clinical remission and moderate for clinical response, with downgrades primarily due to inconsistency across studies. Evidence certainty for endoscopic and histological remission ranged from moderate to low, largely due to a limited number of studies and imprecision. A detailed GRADE Summary of Findings table is presented in Supplementary Table 4 (p 14).

Discussion

This systematic review and meta-analysis provide a comprehensive synthesis of absolute efficacy outcomes from phase 3 and 4 RCTs of approved biologicals and small molecule therapies for both induction and maintenance treatment in adults with moderately to severely active UC. Across 25 studies encompassing 38 cohorts and over 15,000 patients, advanced therapies, including biologics and small molecules, demonstrated significant improvements in clinical, endoscopic, and histological outcomes when compared to placebo or active comparators.

The pooled RD for clinical remission after induction therapy was +13.1%, increasing to 21.1% during maintenance, reflecting a durable therapeutic effect across disease phases. These findings update and extend prior meta-analyses by integrating data from recently approved agents, including risankizumab, upadacitinib and etrasimod. Importantly, this study reports *absolute* effect sizes rather than relative measures alone, offering a more tangible framework for clinicians, patients, and policymakers to assess real-world treatment value and therapeutic expectations. The consistency of benefit across clinical and mucosal healing outcomes supports the multidimensional efficacy of modern UC therapies in reducing inflammation and improving disease control.

This study also highlights a consistent treatment benefit across therapeutic classes. Subgroup analyses indicated comparable efficacy for anti-TNF agents and JAK-inhibitors during induction, both demonstrating RDs of approximately +15%. This aligns with the growing recognition of a 'plateau' in efficacy across current pharmacological mechanisms, called "therapeutic ceiling". Although the highest observed RD for induction remission reached +32%, reported in a study of infliximab in a Chinese cohort,[20] most therapies demonstrated more modest yet clinically relevant effects. The similarity in efficacy across classes suggests that further gains in outcomes may not stem from existing drug mechanisms alone, but from individualised strategies, combination approaches, or entirely novel therapeutic paradigms.

Endoscopic and histological remission—reflecting objective levels of mucosal healing—were less frequently reported and achieved lower absolute effect sizes after induction (RDs +8.2% and +12.5%, respectively). Given the emerging importance of these endpoints in prognostication and treatment de-escalation strategies, their limited reporting and moderate-to-low certainty of evidence warrant emphasis.[43,44]

A key strength of this study is its inclusion of different trials encompassing various disease phenotypes, patient background, treatment histories, and trial designs. Although statistical heterogeneity across studies was, as expected, considerable (e.g., I^2=78% for the primary outcome), this should not be interpreted as a limitation. On the contrary, this heterogeneity reflects the real-world variability in moderate-to-severe UC populations, such as differences in prior biologic exposure, corticosteroid use, disease duration and regional practices. Rather than undermining the findings, this variability enhances their external validity and supports a generalizable estimate of efficacy across the full spectrum of patients encountered in clinical practice. The consistent direction and magnitude of treatment benefit across diverse settings strengthen the robustness of our findings.

While placebo-controlled trials remain the backbone of regulatory approval, only three studies included active comparators, highlighting an existing gap in head-to-head efficacy data. This reinforces the need for high-quality comparative effectiveness research to directly inform treatment sequencing, particularly in light of multiple agents now being used as first- or second-line therapy. Furthermore, novel non-pharmacological treatments such as appendicectomy or hyperbaric oxygen therapy require benchmarking against an established efficacy baseline, precisely what this review sought to establish.

This study also has several limitations. First, older trials or those using alternative outcome definitions that could not be harmonised with current endpoints were excluded. Second, certain therapeutic subclasses, such as IL-12/23 inhibitors, anti-integrin agents, and S1P receptor modulators, had an insufficient number of studies to permit subgroup meta-analysis. Third, most maintenance-phase data originated from randomised responder designs, which selectively analyse patients who responded to induction therapy. This design may overestimate long-term efficacy and limits the generalisability of maintenance outcomes to broader UC populations. Lastly, some studies had a stricter definition of clinical remission, with a rectal bleeding subscore of 0, which might influence remission rates. This was specially the case in more recent RCTs.[41,42]

Despite these limitations, this review offers an up-to-date, high-certainty benchmark for evaluating the absolute efficacy of advanced therapies in UC. Our findings can help inform treatment expectations, guide shared decision-making, and be applied in the context of emerging interventions—whether pharmacological or non-pharmacological—against a realistic and clinically meaningful efficacy baseline.

In conclusion, advanced therapies for moderate-to-severe UC deliver significant absolute benefits in inducing and maintaining clinical, endoscopic and histological remission. The consistency of effect across diverse populations and pharmacological classes suggests a plateau in efficacy with current therapeutic options, reinforcing the concept of a therapeutic ceiling. These results provide a benchmark for future trials and are especially relevant for appraising the value of novel agents and non-drug interventions.

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Supplementary materials

Part II

Appendectomy for maintenance of remission in ulcerative colitis

3

Chapter 3

Clinical statistical analysis plan for the ACCURE trial: the effect of appendectomy on the clinical course of ulcerative colitis, a randomised international multicentre trial

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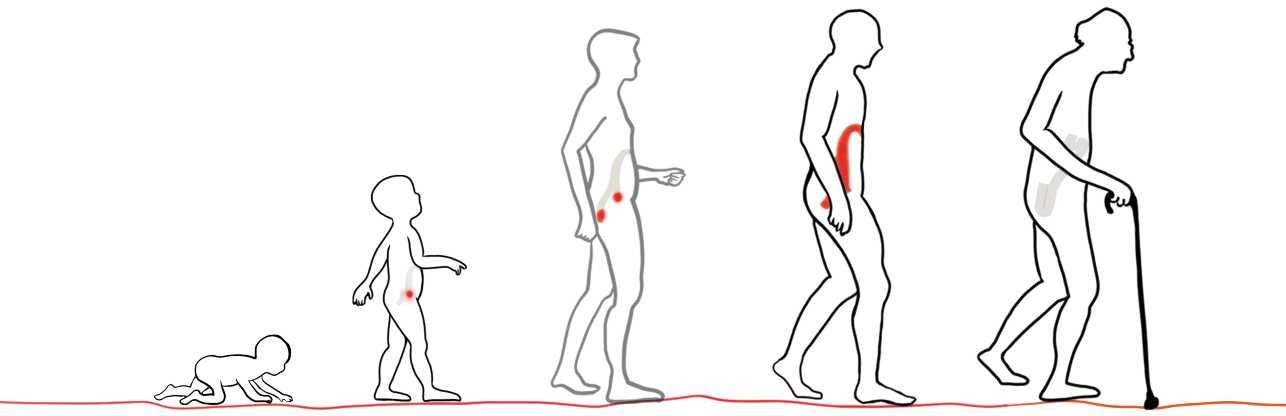

Trials, 2024

Abstract

Background

The primary treatment of ulcerative colitis (UC) is medical therapy using a standard step-up approach. An appendectomy might modulate the clinical course of UC, decreasing the incidence of relapses and reducing need for medication. The objective of the ACCURE trial is to assess the efficacy of laparoscopic appendectomy in addition to standard medical treatment in maintaining remission in UC patients. This article presents the statistical analysis plan to evaluate the outcomes of the ACCURE trial.

Design and methods

The ACCURE trial was designed as a multicentre, randomised controlled trial. UC patients with a new diagnosis or a disease relapse within the past 12 months, treated with 5-ASA, corticosteroids, or immunomodulators until complete clinical and endoscopic remission (defined as total Mayo score < 3 with endoscopic subscore of 0 or 1), were counselled for inclusion. Also, patients previously treated with biologicals who had a washout period of at least 3 months were considered for inclusion. Patients were randomised (1:1) to laparoscopic appendectomy plus maintenance treatment or a control group (maintenance therapy only). The primary outcome is the 1-year UC relapse rate (defined as a total Mayo-score ≥ 5 with endoscopic subscore of 2 or 3, or clinically as an exacerbation of symptoms and rectal bleeding or FCP > 150 or intensified medical therapy other than 5-ASA therapy). Secondary outcomes include number of relapses per patient, time to first relapse, disease activity, number of colectomies, medication usage, and health-related quality of life.

Discussion

The ACCURE trial will provide comprehensive evidence whether adding an appendectomy to maintenance treatment is superior to maintenance treatment only in maintaining remission in UC patients.

Trial registration

Dutch Trial Register (NTR) NTR2883. Registered May 3, 2011. ISRCTN, ISRCTN60945764. Registered August 12, 2019.

Introduction

Background and rationale

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the mucosa of the colon and rectum, with an annual incidence of 6–8 new cases per 100,000.[1] The primary treatment is medical therapy consisting of step-up approach starting with 5-aminosalicylic acids (5-ASA), followed by immunomodulators, biologicals, small molecules, and trial medication. Most patients will remain on long-term medication to prevent exacerbations and preserve quality of life. Despite the expanding medical armamentarium and declining emergent UC colectomy rates, the overall incidence of (procto)colectomy in UC patients has remained unchanged over the years.[2] Nevertheless, up to 20% of the patients require surgery.[3,4]

There is increasing evidence suggesting an immunomodulatory role of the appendix in patients with UC.[5,6] We hypothesise that an appendectomy has a beneficial effect on the UC disease course: decreasing the number of relapses and reducing the need for (upscaling) medication. The ACCURE trial is a randomised, international, multicentre trial to assess the efficacy of appendectomy to maintain remission in patients with UC.[7] From September 2012 to September 2022, 201 patients were randomised. Analyses will commence in 2023 following completion of 1-year follow-up for the last patient, data cleaning checks, and data lock.

Objectives

The objective of the ACCURE trial was to determine the efficacy of appendectomy in addition to standard medical treatment to maintain remission in patients with UC and to establish the acceptability of the intervention compared to standard treatment only. The trial protocol was previously published.[7] The present manuscript is the proposed statistical analysis plan (SAP), which follows the JAMA Guidelines for the content of statistical analysis plans in clinical trials (Supplementary Material 1).[8]

Study methods

Trial design

The ACCURE trial was an investigator-initiated two-arm, multicentre, randomised controlled superiority trial. UC patients in complete clinical and endoscopic remission (defined as Mayo score < 3 with endoscopic subscore 0 or 1) who were treated for a relapse within the past 12 months (with 5-ASA, corticosteroids, immunomodulators

or after a washout period of at least 3 months after treatment with biologicals) were randomised into two groups. The intervention group underwent laparoscopic appendectomy in day care setting plus maintenance medical therapy. The appendix was removed including the cecal base to include the orifice of the appendix using a laparoscopic endostapler. The control group continued maintenance therapy at the discretion of the treating gastroenterologist.

The ACCURE trial included two trial registrations. The ACCURE trial (NL) was registered at the Dutch National Trial Register (NTR2883) on May 3, 2011. Ten centres were involved in the trial in the Netherlands (NL) and Ireland. The ACCURE-UK-2 (ISRCTN60945764) is the UK arm of the ACCURE trial (NL) and was registered on August 12, 2019. The study was conducted in 10 hospitals in the United Kingdom (UK). The ACCURE trial (NL) and ACCURE-UK-2 shared a matched overall study design and form the definitive trial (the ACCURE trial) for the final analysis.

Randomisation

Eligible patients were randomly assigned (1:1 ratio) by the research team with ALEA randomisation software. Randomisation was stratified by disease localisation (rectum, left-sided colitis, pancolitis). Patients and physicians were not blinded during treatment.

Sample size

The ACCURE trial (NL) was powered on a clinically relevant reduction in relapse rate from an expected 40% in the control group to 20% in the intervention group.[7] With a 5% two-sided significance level, 82 patients per study arm were needed to achieve 80% power to detect such a difference using chi-square test. Considering 10% patient dropouts, we aimed to include 184 patients in order to analyse 164 patients.

In September 2019, the ACCURE trial was started in the United Kingdom (ACCURE-UK-2) to improve recruitment and increase statistical power. The aim was to include 244 patients intending to analyse 218 patients (109 per study arm) to reach 90% power in demonstrating superiority of appendectomy. However, the study was closed after the inclusion of 201 patients in September 2022 due to prolonged accrual (related to the COVID-19 pandemic).

Framework

The ACCURE trial was a superiority trial. The hypotheses for the primary analysis were as follows:

Null hypothesis: there is no difference in the 1-year cumulative relapse rate between laparoscopic appendectomy plus maintenance therapy versus maintenance therapy only.

Alternative hypothesis: there is a difference in the 1-year cumulative relapse rate between laparoscopic appendectomy plus maintenance therapy versus maintenance therapy only.

Statistical interim analysis and stopping guidance

According to the protocol, no planned interim analysis was scheduled. However, during the inclusion period, a few manuscripts were published suggesting a relation between appendectomy and the development of high-grade dysplasia (HGD) and colorectal cancer (CRC) in UC patients.[9] Therefore, an interim analysis for safety was performed at the discretion of the Data Monitoring and Safety Committee (DSMC) after inclusion of 153 patients in March 2021. In addition to the number of (serious) adverse events in both groups at 1 year, the interim analysis for confirmation of safety also addressed the number of patients with HGD and CRC in both groups during long-term follow-up. For safety regarding neoplasia, the following rules were defined: when the absolute number of patients with HGD/CRC in the intervention group was higher by 1: continuation of the trial; higher by 2: assessment of potential underlying risk factors for HGD/CRC (i.e. onset before adulthood, disease duration > 10 years, concomitant PSC); higher by 3: continuation of the trial was at the discretion of the DSMC. When the absolute number of patients with HGD/CRC was higher in the control group (standard care), assessment of cases could be conducted at the discretion of the DSMC. Conditional on appendectomy being considered safe, the interim analysis was proceeded with a stopping rule for superiority (Haijbittle-Peto boundary $P < 0.001$). In this analysis, no overwhelming efficacy could be demonstrated. The DSMC did not share the outcome results with the research group but communicated that there was no need for early termination of the trial.

Timing of final analysis

The analyses will be performed when the last patient has reached 1 year follow-up, data entry has been completed, the collected patient data have been monitored, and after this SAP has been accepted for publication.

Timing of outcome assessments

Outpatient clinic visits or telephone consults were performed at 6 weeks and 3, 6, 9, and 12 months after appendectomy or in the control group after randomisation. During these contacts, the partial Mayo score (pMS), medication use, complications, readmissions, hospital stay, and visits to outpatient clinic were assessed.[10] Health-related quality of life (HRQL) questionnaires (EQ-5D, EORTC-QLQ-C30, and IBDQ)[11-13] were completed at inclusion and every 3 months thereafter during the first year. In the Netherlands, the questionnaires were sent via the MyIBDcoach application or could be completed online. In the UK, hard copies of the questionnaires were completed by the participant on site at the baseline visit or at home and returned by post if an in-person visit was not possible, and at all subsequent time points, the questionnaires were posted out by the central trial team. An endoscopy was performed at the time of suspected relapse or at the end of the 12-month study period (12 months after appendectomy in the intervention group and after randomisation in the control group) to objectively assess mucosal appearance and determine the full Mayo score.

Statistical principles

Confidence intervals and P values

All statistical tests will be two-sided. P values of less than 0.05 will be considered statistically significant. The presented confidence intervals will be 95% and two-sided.

Adherence and protocol violation

Protocol violation in eligibility was defined as randomisation of a patient who did not qualify for inclusion or who met an exclusion criterion. These patients were excluded from intervention and further follow-up.

Predefined as a major protocol violation with a direct impact on the primary outcome was UC relapse during the waiting period for appendectomy in the intervention group. These patients were not excluded, but the number (and percentage) of patients with a protocol violation will be summarised by group with details of the type of deviation provided and reported in a patient flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT, Figure 1).

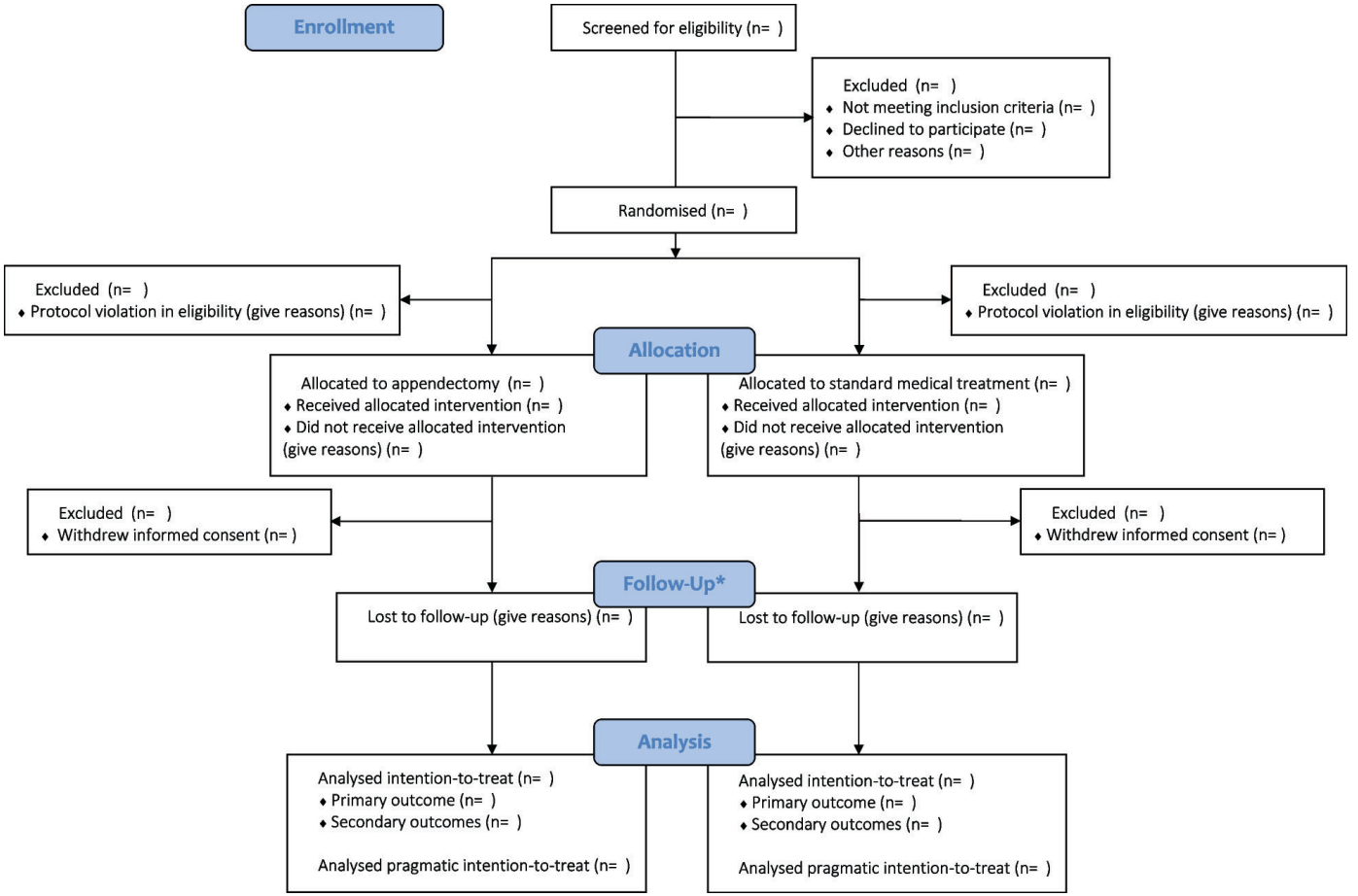

Figure 1. CONSORT

Analysis populations

All primary analyses (primary and secondary outcomes) will be based on the intention-to-treat (ITT) principle. All randomised patients will be included in the analyses according to their initially assigned study arm at baseline, regardless of whether they actually received the allocated intervention or not. Patients with a protocol violation concerning eligibility will be excluded from analysis. Safety data will be reported by treatment arm, and an as-treated (AT) analysis will be performed. In the AT analysis, patients will be analysed according to the treatment they actually received, rather than the study arm they were initially assigned.

Trial population

Screening and eligibility

Patients were screened for eligibility using the inclusion and exclusion criteria according to the most recent version of the study protocol. The number of excluded patients after randomisation and reasons for ineligibility will be reported and illustrated in the CONSORT flow diagram (Figure 1).

Inclusion criteria:

- Aged ≥ 18 years
- Established diagnosis of UC according to ECCO guideline[14]
- Disease relapse within 12 months prior to randomisation medically treated until remission
- Clinically confirmed remission at time of randomisation, with pMS < 3 and presumptive endoscopic Mayo subscore of 0 or 1, identified by either:
- Colonoscopy (within 3 months) examining the full length of the colon and rectum
- Sigmoidoscopy (within 3 months) examining the last part of the colon (sigmoid and rectum) with faecal calprotectin (FCP) < 150 µg/g
- FCP < 150 µg/g with a personal history of raised FCP levels (> 500 µg/g) during a previous disease flare-up at any stage
- Obtained informed consent

Exclusion criteria:

- Prior appendectomy or major abdominal surgery precluding safe appendectomy
- (Suspicion of) Crohn's disease
- Disease recently treated with biologicals (within 3 months prior to inclusion)
- pMS ≥ 3 or endoscopic Mayo score > 1
- Medical comorbidity that increases perioperative morbidity

Recruitment

Informed consent was obtained from the patients according to the ACCURE trial protocol. For both treatment arms, the numbers of patients who were randomised, received the intended treatment, and were analysed for the primary outcome will be presented in the CONSORT flow diagram (Figure 1).

Withdrawal/follow-up

For each group, withdrawal and loss to follow-up will be reported and specified with reasons at each time point (Figure 1). These outcomes will be explored as per other missing responses.

Baseline patient characteristics

The baseline characteristics of the included patients will be reported per randomisation group and shown in a baseline table (Table 1). Categorical variables will be summarised by numbers and percentages in each category. Continuous variables will be summarised by mean and standard deviation or median and interquartile range, as appropriate. Tests of statistical significance will not be undertaken, nor will confidence intervals be presented.[15]

Table 1. Baseline characteristics of the patients included in the trial (intention to treat)

Characteristic	*Appendectomy (N=)*	*Control (N=)*
Age (years)		
Age at diagnosis (years)		
Gender, female, *n (% n/N)*		
Disease duration (years)		
Smoking status, *n (% n/N)*		
Current		
Former		
BMI (kg/m2)		
ASA physical status classification grade > II, *n (% n/N)*		
PSC, n (% n/N)		
Family history of IBD, *n (% n/N)*		
Medication at baseline		
No medication, *n (% n/N)*		
Topical therapy, *n (% n/N)*		
5-ASA, *n (% n/N)*		
Systemic steroids, *n (% n/N)*		
Immunomodulators, *n (% n/N)*		

Table 1. Continued

Characteristic	*Appendectomy (N=)*	*Control (N=)*
Extent of disease		
Proctitis, *n (% n/N)*		
Left-sided colitis, *n (% n/N)*		
Pancolitis, *n (% n/N)*		
Start of most recent exacerbation UC before randomisation (weeks)		

Abbreviations: BMI body mass index, ASA American Society of Anaesthesiologists, PSC primary sclerosing cholangitis, IBD inflammatory bowel disease, 5-ASA 5-aminosalicylic acid, UC ulcerative colitis.

Analysis

Outcome definitions

Primary outcome

The primary outcome measure is the 1-year total UC relapse rate, defined as:

- Both clinically and endoscopically with a total Mayo score ≥ 5 and endoscopic subscore of 2 or 3
- OR clinically in absence of endoscopy, based on review by an independent critical event committee (see below)

Relapse data was collected at the 3-, 6-, 9-, and 12-month follow-up forms and the end of study form. Clinically suspected relapses without endoscopic confirmation were evaluated by a critical event committee (CEC), consisting of an independent IBD surgeon and gastroenterologist blinded to the allocation group. The CEC members were the same for both the NL and the UK. The decision will be based on clinical information suggesting relapse (exacerbation of abdominal symptoms, increased bowel frequency and rectal bleeding) or FCP > 150 (> 4 weeks after surgery) or intensified medical therapy other than 5-ASA therapy.

Secondary outcomes

Secondary outcomes include:

1. Number of relapses per patient after 12 months
2. Time to first relapse defined as the time between randomisation in the control group or laparoscopic appendectomy in the intervention group and the first day of clinical symptoms of an endoscopically or clinically confirmed relapse

3. Disease activity measured with the total Mayo score at baseline and 12 months and the pMS assessed at 3, 6, and 9 months.[10] The total Mayo score consists of four components stool frequency, rectal bleeding, endoscopic appearance, and physician's global assessment (Table 2). These items are rated from 0 to 3, resulting in a total Mayo score ranging from 0 to 12 and a pMS without endoscopic assessment ranging from 0 to 9. In the Mayo score, clinical remission is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing is defined as an absolute subscore for endoscopy of 0 or 1
4. Number of colectomies at the 1-year follow-up
5. Medication usage (no medication, topical therapy, 5-ASA, systemic steroids, immunomodulators, biologicals, small molecules, trial medication) at baseline, 3, 6, 9, and 12 months
6. HRQL measured by the EQ-5D health status questionnaire[12], the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30[11], and the Inflammatory Bowel Disease Questionnaire (IBDQ), at baseline, 3, 6, 9, and 12 months.[13,16] The EQ-5D is a generic standardised measure of HRQL at the day of completion consisting of the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ-VAS). The EQ-5D comprises 5 problem areas (mobility, self-care, daily activities, pain/discomfort, mood) with patients indicating whether they experience no, some, or extreme problems. The EQ-VAS is a vertical scale grading overall health status, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Global quality of life (QoL) is assessed using two items of the global QoL dimension (items 29 and 30 in version 3.0) of the EORTC-QLQ-C30 that reflect overall health and QoL on the day of completion. These two items are 7-point response scales, ranging from 1 (very poor) to 7 (excellent). The average of these two items is estimated, which is the raw score (RS). The global QoL is scored by transforming the RS to a standardised 0–100 final scale score. If one or both items are missing, the global QoL is scored as missing. The IBDQ is a disease-specific questionnaire measuring QoL in 4 domains (bowel symptoms, systemic symptoms, social function and emotional function) over 2 weeks preceding completion. The IBDQ consists of 32 questions rated on a scale of 1–7, resulting in a total score ranging from 32 to 224. The score per domain is also estimated. If one or more items are missing, a domain and the total IBDQ are scored as missing. After inclusion of 79 patients, the protocol was amended to include a 'global change question' after 12 months: 'Since the start of the study, have your UC symptoms improved overall?'

Table 2. Components of the Mayo score

Stool frequency	0 = Normal no. of stools for this patient
	1 = 1 to 2 stools per day more than normal
	2 = 3 to 4 stools per day more than normal
	3 = ⩾5 stools per day more than normal
Rectal bleeding	0 = No blood seen
	1 = Streaks of blood with stool less than half the time
	2 = Obvious blood with stool most of the time
	3 = Blood alone passes
Mucosal appearance at endoscopy[a]	0 = Normal or inactive disease
	1 = Mild disease (erythema, decreased vascular pattern, mild friability)
	2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
	3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity	0 = Normal
	1 = Mild disease
	2 = Moderate disease
	3 = Severe disease

[a]*Not included in the partial Mayo score.*

Handling missing items

If one or more items are missing to determine the outcome score (e.g. stool frequency to determine the partial and total Mayo score), the outcome (e.g. pMS) is scored as missing.

Analysis methods

Primary outcome analysis

The 1-year UC relapse rate will be compared between the intervention and control groups with chi-square testing (Table 3).

Table 3. Primary outcome results

	Appendectomy N=	**Control group N=**	**P value[1]**	**Adjusted P value[2]**
Total relapse rate, *n (% n/N)*				

[1]*Chi-square test.*
[2]*Logistic regression.*

Additional analysis primary outcome

Stratified analysis, covariate adjustment, subgroup analysis

Logistic regression on the 1-year UC relapse rate will be used to (i) explore the interaction between treatment and disease location as stratification factor

during randomisation and (ii) adjust for the following covariates: age at time of randomisation, gender, smoking status, extent of disease, and time between start of most recent exacerbation of UC and randomisation.[17] In addition, the interaction between treatment and country (UK vs. NL) will be exploratively addressed (Table 4).

Table 4. Subgroup analysis for primary outcome

	Appendectomy N=	**Control group N=**	**P value for interaction**
NL total relapse rate, *n (%) n/N)*			
UK total relapse rate, *n (%), n/N)*			

Abbreviations: NL the Netherlands, UK United Kingdom.

Pragmatic ITT analysis

As described in the published study protocol, T0 lies at different time points in both groups (i.e. intervention group: T0 date of appendectomy; control group: T0 date of randomisation). To provide a pragmatic worst-case scenario for daily clinical practice, we will perform an additional analysis in which relapses occurring between dates of randomisation and appendectomy will be included as well. In this 'pragmatic' ITT analysis, T0 will be the randomisation date in both groups. Consequently, the follow-up time in the intervention group will be longer compared to the control group (i.e. time between randomisation date and appendectomy plus 1 year follow-up versus 1 year follow-up only).

Secondary outcome analysis

The number of relapses per patient will be compared between groups with Poisson regression (Table 5), time to first relapse with Kaplan–Meier survival analysis including log-rank testing, and number of colectomies with chi-square testing (Table 5). If covariate adjustment substantially affected the primary outcome contrast, covariate adjustment will also be applied for these secondary outcomes with Poisson regression, Cox-regression, and logistic regression, respectively. If the assumption of proportional hazards seems invalid given the data, the time to first relapse will be analysed in distinct strata. Use of medication over time and by group will be descriptively reported by number and percentages (Table 6). General estimation equation will be utilised to examine the impact of intervention on medication use over time within treatment, time and the interaction between treatment, and time as model parameters.

Table 5. Secondary outcome results

	Baseline		3 months		6 months		9 months		12 months	
	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*
Number of relapses per patient, median (IQR)										
Time to first relapse, median, (IQR)										
HRQL, median (IQR)										
EQ-5D score										
Global QoL score										
Total IBDQ score										
IBDQ: bowel symptoms										
IBDQ: systemic symptoms										
IBDQ: social function										
IBDQ: emotional function										
Mayo score, median (IQR)										
Total Mayo score										
Partial Mayo score										
Number of colectomies at one year, *n (% n/N)*										

Abbreviations: A: appendectomy, C: control, IQR: interquartile range, HRQL: health-related quality of life, QoL: quality of life, IBDQ: Inflammatory Bowel Disease Questionnaire.
Results will be marked with one asterisk (*) if P < 0.05.

Table 6. Medication usage (general estimation equation)

	Baseline		3 months		6 months		9 months		12 months	
	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*	A *N=*	C *N=*
No medication, *n (% n/N)*										
Topical therapy, *n (% n/N)*										
5-ASA, *n (% n/N)*										
Systemic steroids, *n (% n/N)*										
Immunomodulators, *n (% n/N)*										
Biologicals, *n (% n/N)*										
Trial medication, *n (% n/N)*										

Abbreviations: A appendectomy, C control, 5-ASA 5-aminosalicylic acid.

Additional generalised linear mixed models will be applied to investigate whether a different pattern of change over time exists between the two study arms in the Mayo score and the IBDQ, EQ-5D, EQ-VAS, and EORTC QLQ-C30.[18] Best fitting covariance structures among repeated data will be based on visual inspection and Akaike's information criterion. Baseline scores will be included as covariates in the models of repeated data.

To assess the clinical relevance of changes in the IBDQ, a clinical minimally important difference in IBDQ will be determined using a clinical anchor-based method. The minimally important difference will be calculated from the difference in IBDQ change scores of the patients answering 'yes' and 'no' to the 'global change question'. Furthermore, the correlation coefficient between the IBDQ score and the global change question will be calculated by Pearson's correlation method; a minimum correlation of at least 0.30 will be regarded as acceptable.

The critical P value of 0.05 will not be adjusted for multiple testing and all analyses of secondary outcomes should be considered exploratory. Additional analyses not mentioned in this analysis plan but performed in response to journal reviewers will explicitly be qualified as post hoc.

Missing data

Missing data on outcome data will not be imputed. Based on the sample size calculation, a total of 164 evaluable patients (82 per study arm) are needed. Patients are evaluable if they were not excluded due to protocol violation in eligibility or consent and if the primary outcome is available. To reach the appropriate sample size and target power in the study, patients not fulfilling these evaluability criteria were replaced. Generalised linear mixed modelling of repeated data allows for missing data. Patients without any follow-up data for an outcome will not be included in the analysis of that outcome, with the reasons for this missingness counted by group and overall.

Harms

The number and percentage of participants experiencing any adverse events (AEs) or serious adverse events (SAEs) will be presented by treatment group, and safety AT analysis will be performed (Table 7). AEs and SAEs between randomisation/surgery and 3-month follow-up will be registered. SAEs will be followed up at least until the final consequences have become clear, even if it implies that the follow-up continues beyond the planned follow-up period. For patients undergoing appendectomy, in-hospital stay (N nights), postoperative complications, and reinterventions will be reported. Complications of laparoscopic appendectomy will be classified according the Clavien-Dindo classification.[19]

Table 7. Safety (reported as-treated)

	Arm A *N*=	Arm B *N*=	P value[1]
Total SAE, *n (% n/N)*			
Total AE, *n (% n/N)*			

Abbreviations: A: appendectomy plus maintenance therapy, B: maintenance therapy, SAE: serious adverse event, AE: adverse event
[1]*Chi-square test*

Statistical software

Analyses will be carried out using the latest version of SPSS statistics (IBM Corp.) at the time of analysis.

Manuscript and authorship

The steering committee of the ACCURE trial will share the results irrespective of the outcomes. The manuscript will be submitted on behalf of the ACCURE study group in alphabetical order. The coordinating investigator and principal investigator will be first and senior authors, respectively. The steering committee, other local principal investigators, physician assistants, and research nurses who were responsible for significant patient recruitment and data collection will be listed in the ACCURE study group.

Discussion

The ACCURE trial is an investigator-initiated two-arm, multicentre, non-blinded, randomised controlled superiority trial in UC patients in complete clinical and endoscopic remission with the aim to assess whether the efficacy of laparoscopic appendectomy in addition to standard medical treatment is beneficial in maintaining remission in UC patients.

Challenges

In the design of the trial, we faced several challenges mostly regarding accrual of the trial, which was slower than anticipated. First, accrual might have been challenging due to the narrow eligibility criteria of the trial; originally, only patients in remission treated with 5-ASA were eligible. To improve inclusion rates, the criteria were amended in 2018, by also including patients who were in remission on immunomodulators and patients who were previously treated with biologicals (> 3 months prior to inclusion). Second, when including patients in remission, the

motivation for patients to participate in a trial is probably lower compared to patients with active UC. Furthermore, in daily practice, surgeons and gastroenterologists might also be less encouraged to counsel/include patients without active disease in a trial. Third, when comparing a surgical intervention with standard therapy in a randomised controlled setting, the majority of patients participating in the trial might opt for an appendectomy because they are already receiving the standard treatment. Randomised controlled trials are still seen as the gold standard. However, to increase accrual and prevent selection bias, a patient preference model might have been more suitable when comparing a surgical intervention versus medical therapy. Fourth, during the COVID pandemic the trial was paused for almost a year.

Another problem was that not all patients underwent endoscopy after 1 year of follow-up. According to the published protocol, the primary outcome is the 1-year UC relapse rate, defined both clinically and endoscopically as a Mayo-score ≥ 5 with an endoscopy score of 2 or 3. This issue was especially pronounced in patients without symptoms, making it difficult to persuade them to undergo colonoscopy. However, for patients presenting symptoms of a flare, it was not always possible to perform a colonoscopy. In the meeting on November 20, 2018, the DSMC advised to install a CEC to evaluate clinically suspected relapses without endoscopic confirmation. The advice was submitted to the Medical Ethics Review Committee for permission and granted on November 13, 2019. In addition to endoscopically proven relapses, the CEC also evaluated all clinically suspected relapses based on clinical information. To qualify as relapse, an exacerbation of symptoms and rectal bleeding or FCP >150 (>4 weeks after surgery) had to be observed, or medical therapy other than 5-ASA therapy had to be intensified. Finally, as the trial ran for a long period of time, daily clinical practice might have changed during the years. However, most developments were in the field of biologics, and these patients were not eligible for this trial.

Future perspectives

This update contains the predefined SAP for the ACCURE trial. By publishing the SAP, we aim to increase the transparency of data analyses. The outcomes of this study will provide insight into the role of appendectomy in the clinical course of UC. For this study, an IBD team was identified in every participating hospital, which could lead to improved communication and collaboration between different hospitals in future research. This will facilitate future research projects, and we have learned during this project that close collaborations are indispensable to carry out large projects aiming to improve the treatment of UC.

Trial status

Recruitment and randomisation concluded in September 2022. The final follow-up of participants is scheduled for completion in November 2023.

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Supplementary materials

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4

Chapter 4

Appendicectomy plus standard medical therapy versus standard medical therapy alone for maintenance of remission in ulcerative colitis (ACCURE): a pragmatic, open-label, international, randomised trial

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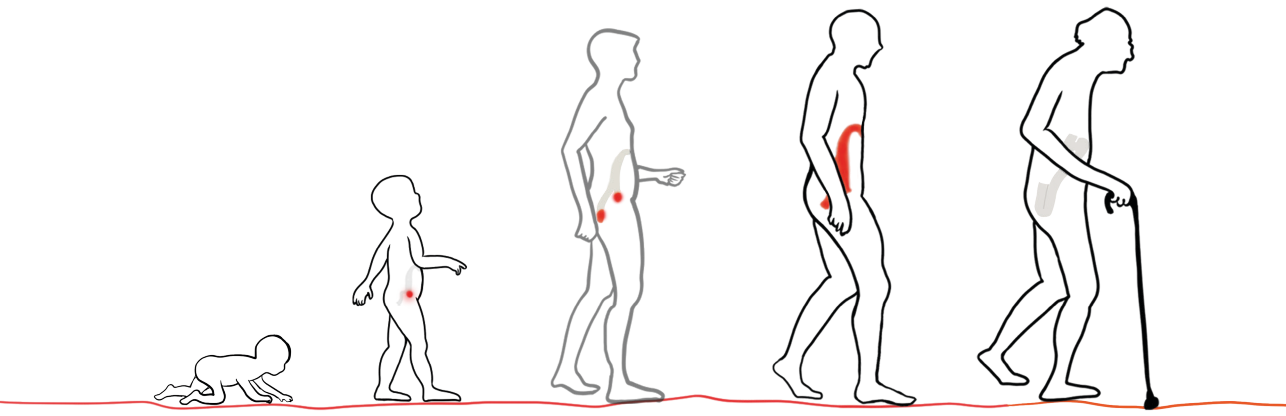

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Summary

Background

The appendix might have an immunomodulatory role in ulcerative colitis. Appendicectomy has been suggested as a potentially therapeutic intervention to maintain remission in ulcerative colitis. We aimed to evaluate the clinical effectiveness of laparoscopic appendicectomy in maintaining remission in patients with ulcerative colitis.

Methods

We did a pragmatic, open-label, international, randomised controlled superiority trial in 22 centres across the Netherlands, Ireland, and the UK. Patients with established ulcerative colitis who were in remission but had been treated for disease relapse within the preceding 12 months were randomly assigned (1:1) to undergo appendicectomy plus continued maintenance medical therapy (intervention group) or to continue maintenance medical therapy alone (control group). Randomisation was done with a central, computer-generated allocation concealment, stratified by disease extent. Patients and treating physicians were unmasked to group allocation. The prespecified primary outcome was the proportion of patients with a disease relapse within 1 year, predefined as a total Mayo score of 5 or higher with an endoscopic subscore of 2 or 3, or, in absence of endoscopy, based on a centrally independent masked review by a critical event committee as an exacerbation of abdominal symptoms (eg, elevated stool frequency subscore of ≥1 point from baseline) with a rectal bleeding subscore of ≥1 or faecal calprotectin level above 150 µg/g or necessitating treatment intensification other than mesalazine. Analyses were done on an intention-to-treat principle. This trial is complete and was registered with the Netherlands Trial Register (NTR2883) and ISRCTN (ISRCTN60945764).

Findings

Between Sept 20, 2012, and Sept 21, 2022, 1386 patients were screened. 201 patients were randomly assigned to the appendicectomy group (n=101) or the control group (n=100). After exclusion of four patients due to eligibility violations (three had active disease and one received biological agents at time of randomisation), 99 patients in the appendicectomy group and 98 patients in the control group were included in the intention-to-treat analyses. The 1-year relapse rate was significantly lower in the appendicectomy group than in the control group (36 [36%] of 99 patients vs

55 [56%] of 98 patients; relative risk 0.65 [95% CI 0.47–0.89]; p=0.005; adjusted p=0.002). Adverse events occurred in 11 (11%) of 96 patients in the appendicectomy group and 10 (10%) of 101 patients in the control group. The most frequently reported adverse events were postoperative temporary self-limiting abdominal pain in the appendicectomy group (three [3%] patients) and skin rash in the control group (three [3%] patients). Two cases (2%) of low-grade appendiceal mucinous neoplasm were incidentally found in resected appendix specimens in the appendicectomy group. Serious adverse events occurred in two (2%) of 96 patients who underwent appendicectomy and none in the control group. There were no deaths.

Interpretation

Appendicectomy is superior to standard medical therapy alone in maintaining remission in patients with ulcerative colitis.

Funding

Fonds Nuts-Ohra, Dr. Falk and National Institute for Health Research Efficacy and Mechanism Evaluation.

Research in context

Evidence before this study

An inverse association between appendicectomy and the development of ulcerative colitis was first reported in 1987, with subsequent case-control studies confirming this observation, and suggesting a possible role of the appendix in ulcerative colitis. In 2016, our research group did a systematic review and meta-analysis of available (case-control) studies. This analysis showed that previous appendicectomy was associated with a significantly reduced risk of developing ulcerative colitis, with an overall odds ratio of 0.39 (95% CI 0.29–0.52). Additionally, in 2012, our group published a systematic review assessing the effect of appendicectomy on the clinical course of ulcerative colitis. This review included six observational studies (five case-control studies and one cohort study) comprising 2532 patients. Although the heterogeneity among these studies precluded a formal meta-analysis, and data were scarce and conflicting, most studies suggested a beneficial effect of appendicectomy on the disease course in ulcerative colitis. We searched PubMed for literature published between Jan 1, 1998, and Oct 31, 2024, using the terms ("appendectomy"[MeSH Terms] OR "append*"[Title/Abstract]) AND ("colitis, ulcerative"[MeSH Terms] OR "ulcerative colitis"[Title/Abstract] OR "ulcerous colitis"[Title/Abstract] OR "colitis ulcerativa"[Title/Abstract] OR "colitis ulcerosa"[Title/Abstract] OR "ulcerative proctocolitis"[Title/Abstract]) AND ("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "random*"[Title/Abstract] OR "crossover*"[Title/Abstract] OR "cross over*"[Title/Abstract] OR ("doubl*"[Title/Abstract] AND "blind*"[Title/Abstract]) OR ("singl*"[Title/Abstract] AND "blind*"[Title/Abstract]) OR "trial*"[Title/Abstract] OR "intervention stud*"[Title/Abstract]). This searched confirmed that no randomised controlled trial of appendicectomy as an intervention in ulcerative colitis has been done to date.

Added value of this study

The ACCURE trial is the first randomised controlled trial evaluating the clinical effectiveness of appendicectomy in maintaining remission in patients with ulcerative colitis without advanced medical therapy (ie, biologicals or small molecules). This trial shows that laparoscopic appendicectomy, in addition to standard medical therapy, significantly reduces the relapse rates within 1 year.

Implications of all the available evidence

Appendicectomy might be an effective and safe option for reducing the relapse rate within 1 year in patients with ulcerative colitis in addition to standard medical therapy, offering a potential addition to standard medical therapies.

Introduction

Ulcerative colitis is a chronic inflammatory bowel disease affecting an estimated 5 million individuals globally as of 2023, with a rising incidence worldwide.[1-3] This disease affects the mucosal layer of the colon and rectum, and is characterised by a relapsing-remitting course. The inflammation typically starts in the rectum (proctitis) and with subsequent relapses it might extend proximally, involving the entire colon (pancolitis). Clinical symptoms of active colitis include frequent and urgent bowel movements, rectal bleeding, abdominal pain, and fatigue, and the condition is associated with an impaired health-related quality of life.[4-6]

The therapeutic goal in ulcerative colitis is to maintain health and related quality of life and avoid disability by adequately inducing and maintaining clinical and endoscopic remission.[7] Therefore, current medical therapy follows a step-up strategy to reduce inflammation until remission is reached, thereby preventing disease-related complications, such as colectomy, and development of colorectal neoplasia.[8]

The cause of ulcerative colitis is multifactorial, encompassing genetic predispositions, environmental triggers, microbial composition, and dysregulated immune responses. Recent studies[9,10] have highlighted the potential immunomodulatory role of the appendix in ulcerative colitis. The appendix is thought to have an important role by producing inflammatory cytokines, triggering cascade responses and thereby contributing to disease progression.[9,10] Preliminary case-control and small-scale cohort studies have indicated the potential beneficial effects of appendicectomy and suggested it as a therapeutic strategy supplementing medical treatments, which form the mainstay of modern ulcerative colitis management.[11,12] No randomised controlled trial of this intervention has been done to date. We aimed to evaluate the clinical effectiveness of laparoscopic appendicectomy in maintaining remission in patients with ulcerative colitis.

Methods

Study design

We did this investigator-initiated, two-arm, pragmatic, open-label, international, randomised controlled superiority trial at 22 sites across the Netherlands, Ireland, and the UK. The central ethics committee and institutional review board at each participating Dutch and Irish site, and the Research Ethical Committee in the UK approved the trial protocol and any amendments. The final versions of the protocol and statistical analysis plan were completed on May 18, 2021, and Aug 28, 2023,

respectively.[13,14] Patient enrolment was completed on Sept 29, 2022, with database closure on Jan 26, 2024. The trial adhered to Good Clinical Practice guidelines and the Declaration of Helsinki.[15] Written informed consent was obtained from all patients before trial-related procedures. This trial is registered with the Netherlands Trial Register (NTR2883) and ISRCTN (ISRCTN60945764).

Patients

Eligible patients were aged 18 years or older, had established ulcerative colitis and were in remission, but had required treatment for an episode of active disease within the preceding 12 months. Remission was defined as a Mayo score of 2 or lower, with stool frequency, rectal bleeding, and physician's global assessment subscores of 0 or 1, confirmed by a Mayo endoscopic score of 0 or 1 within 3 months before randomisation.[16] In cases in which endoscopy could not be done due to restrictions during the COVID-19 pandemic, a protocol amendment in 2020 allowed remission to be confirmed by a faecal calprotectin level of below 150 µg/g in patients with a previously documented history of raised faecal calprotectin levels (>500 µg/g) during a previous disease flare. Patients were excluded if they had previous appendicectomy or major abdominal surgery that would preclude a safe procedure; suspicion of Crohn's disease; received any biological agents within 3 months before randomisation; a partial Mayo score of 3 or more; an endoscopic Mayo score of more than 1; or medical comorbidities that increase perioperative morbidity. All endoscopy and faecal calprotectin assessments were done locally, with calprotectin used only when endoscopy could not be done, such as during COVID-19 restrictions. Complete enrolment criteria are detailed in the appendix (p 5).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to either undergo laparoscopic appendicectomy and continue standard medical therapy (appendicectomy group) or to continue standard medical treatment alone (control group). Randomisation was done by the research team using the computer-generated randomisation software ALEA and was stratified according to disease extent based on the Montreal classification (proctitis, left-sided colitis, pancolitis).[17] Patients and treating physicians were not masked to allocation during the trial. Group allocation was concealed from the critical event committee, which remained masked to ensure unbiased assessment of clinical relapses.

Procedures

Patients in the appendicectomy group underwent laparoscopic appendicectomy within 9 weeks of randomisation. The appendix, including the cuff of caecal pole surrounding the appendiceal orifice, was removed using a laparoscopic endostapler by or under direct supervision of a senior colorectal surgeon; a detailed standard operating procedure is listed in the appendix (p 6). Standard day-care procedures were followed across sites, similar to those used for typical day-case laparoscopic colorectal operations. Patients were typically discharged on the same day, provided they met standard discharge criteria: being afebrile and clinically stable, tolerating oral intake, mobilising independently, having adequate pain control with oral analgesia, and showing no signs of complications. No standard additional postoperative antibiotics were prescribed. Both groups continued their medical therapy at the discretion of the treating gastroenterologist.

Follow-up included outpatient clinic visits or telephone consultations at 3, 6, 9, and 12 months after appendicectomy or after randomisation for the control group. Postoperative complications and surgical morbidity were assessed at 6 weeks after appendicectomy. Relapse data, disease activity, outpatient clinic visits, hospital admission, and medication use were assessed quarterly. Disease activity was measured using the total Mayo score at baseline and 12 months, and the non-invasive partial Mayo score at 3, 6, and 9 months.[16] An endoscopy was done at the time of clinical suspicion of a relapse or at the end of the 12-month trial period to objectively assess mucosal appearance and determine the total Mayo score. Health-related quality of life was measured with the EQ-5D 3-level utility score (EQ-5D-3L; range −0.33 to 1.00, with higher scores indicating better health status),[18] the European Organisation for Research and Treatment of Cancer quality of life core score (EORTC QLQ-C30; range 0 to 100, with higher scores indicating better global quality of life),[19] and Inflammatory Bowel Disease Questionnaire (IBDQ; range 32 to 224, with higher scores indicating better quality of life),[20] and questionnaires were completed at baseline and quarterly throughout the 12-month follow-up period. The protocol was amended after 79 patients had been enrolled to remove concomitant immunomodulators as an exclusion criterion (to increase the trial's generalisability and external validity, and to enhance recruitment rates) and to include a dichotomous patient-reported global change assessment at 12 months follow-up, to assess the clinical relevance of IBDQ changes. The trial design and procedures are detailed in the appendix (p 11).

Outcomes

The primary outcome was the proportion of patients with a disease relapse within 1 year. Relapse was predefined as a total Mayo score of 5 or higher with an endoscopic subscore of 2 or 3. During the COVID-19 pandemic, the protocol was amended to overcome logistical challenges related to the restricted availability of endoscopic procedures. To ensure the study's continuity and maintain data integrity, the relapse definition was expanded to include, in cases of no endoscopy, an exacerbation of abdominal symptoms (elevated stool frequency subscore of ≥1 point from baseline) with a rectal bleeding subscore of 1 or more, or faecal calprotectin level above 150 µg/g, or necessitating treatment intensification other than mesalazine. This clinical definition was assessed in a centrally independent review by a critical event committee, comprising an inflammatory bowel disease gastroenterologist and surgeon, who were masked to group allocation. The comprehensive relapse definition is available in the appendix (p 7).

Secondary outcomes included number of relapses per patient at 12 months; time to first relapse (defined as the time from the date of randomisation to the first day of clinical symptoms of an endoscopically or clinically confirmed relapse; patients who did not relapse during follow-up were censored at the time of their last available follow up assessment); disease activity (as measured using the partial Mayo score at 3, 6, and 9 months, and the total Mayo score at 12 months); total number of colectomies at 1 year; medication use (none, topical therapy, oral mesalazine, systemic steroid, immunomodulators, and biologic agents; for each category, use was documented as a binary outcome [yes or no] at each time point) at 3, 6, 9, and 12 months; and health-related quality of life (EQ-5D-3L, EORTC-QLQ-C30, IBDQ at 3, 6, 9, and 12 months, and the global change assessment at 12 months).

Safety assessments were based on adverse events or serious adverse events that occurred between appendicectomy or randomisation and the 3-month follow-up (appendix pp 78–79). Intraoperative and postoperative complications were reported using the Clavien–Dindo grade.[21] Major complications were defined as Clavien–Dindo grade of III or more.

Data on sex were reported based on medical records, which were documented according to the individual's national identification documents. No planned interim efficacy analysis was scheduled. However, an interim safety analysis was conducted by the data monitoring and safety committee in March, 2021, following published research suggesting a relation between appendicectomy and development

of colorectal neoplasia in ulcerative colitis.[22] The trial continued without recommendation for early termination.

Statistical analysis

We assumed that the relapse rate at 12 months would be reduced by 50%, from 40% in the control group to 20% in the appendicectomy group. To detect this clinically relevant difference in relapse, with 80% power at a 5% two-sided significant level, we calculated that 82 participants per group were needed to evaluate whether appendicectomy plus medical therapy was superior to medical therapy alone. Accounting for a 10% dropout rate, we aimed to enrol 92 patients per group. In Sept 4, 2019, the trial started in the UK as the ACCURE-UK 2 trial with an identical protocol to improve recruitment and increase the statistical power to 90%. The recruitment target was revised to 244 patients, with the aim of analysing 218 patients (109 per study group). However, owing to the COVID-19 pandemic pressures, the trial required a prolonged recruitment period and enrolment was closed in Sept 29, 2022.

Prespecified outcomes[14] and analyses are provided in the appendix (pp 72–80). The demographic and clinical characteristics of the patients at baseline were summarised descriptively. All primary analyses (primary and secondary outcomes) were done on an intention-to-treat principle. χ^2 test of two proportions was used to compare relapse rates between the appendicectomy and control group, reported with relative risk (RR) and corresponding 95% CIs. Logistic regression on the 1-year relapse rate was used to adjust for disease extent as the stratification factor during randomisation to obtain correct variance estimates and explore the interaction between treatment and disease extent, and to adjust for age at time of randomisation, sex, current smoker, disease extent, time between start of most recent disease exacerbation and randomisation. In addition, the interaction between treatment and country (the Netherlands *vs* the UK) was exploratively addressed. A pragmatic intention-to-treat analysis was done for the primary endpoint only and included relapses during the appendicectomy waiting period. Poisson regression was done to compare the number of relapses per patient reported with RR and 95% CIs, and Kaplan–Meier survival analysis with log-rank testing to compare the time to first relapse between the groups. Medication use over time was descriptively reported by number and percentages, and generalised estimating equation was used to analyse the effect of appendicectomy on medication use over time within treatment, time and the interaction between treatment, and time as model parameters, reported with odds ratios (ORs) and 95% CIs.

Additional generalised linear mixed models were applied to investigate whether a different pattern of change over time existed between the groups in the Mayo score and health-related quality of life, and were reported with mean differences (MD) and 95% CIs. The optimal covariance structure for the repeated measures data were determined based on visual assessment and Akaike's information criterion values. Covariance structures evaluated included unstructured, autoregressive 1, Toeplitz matrix, and compound symmetry. The cohort-specific minimum clinically important difference in the IBDQ was determined to assess the clinical relevance of differences in the IBDQ, by using a clinical anchor-based method calculating the difference in IBDQ change scores from baseline between patients responding yes or no to the global change question. The correlation coefficient between the IBDQ change score and the global change question was calculated by Pearson's correlation method, with a minimum correlation of at least 0.30 regarded as acceptable.[23-25]

Safety data were reported by treatment group and analysed based on the treatment actually received (as-treated analysis), with absolute risk differences (ARD) and corresponding 95% CIs.

No adjustments were made for multiplicity in secondary outcome analyses, and these should be considered exploratory. Missing outcome data were not imputed (appendix p 16). All statistical tests were two-sided and p values less than 0.05 were considered statistically significant. Additional details of the statistical methods were published and listed in the appendix (pp 8–9).[14] Data were analysed with SPSS (version 28.0.1.1) and Stata (version 17.0). All outcomes and statistical methods presented in this Article were prespecified in the study protocol and corresponding statistical analysis plan. Additionally, a post-hoc sensitivity analysis of the primary outcome was done, limited to patients with available endoscopic follow-up data.

The patient safety and trial evaluation were monitored by an independent data monitoring and safety committee (appendix p 5).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report.

Results

Between Sept 20, 2012, and Sept 21, 2022, 1386 patients were assessed for eligibility, of whom 201 were randomly assigned to the appendicectomy group (n=101) or the control group (n=100). After exclusion of four patients due to protocol violation in eligibility (three had active disease and one received biological agents at time of randomisation), 99 patients in the appendicectomy group and 98 patients in the control group were included in the intention-to-treat and pragmatic intention-to-treat analyses (figure 1). Of the total participants, 168 were enrolled in the Dutch trial arm (which also included two participants from the Irish site) and 29 in the ACCURE-UK trial 2 arm. The demographics and clinical characteristics of the patients were similar across the groups at baseline (Table 1). Mean age was 42.2 years (SD 12.5) in the appendicectomy group and 43.2 years (SD 13.0) in the control group. 56 (57%) of 99 participants in the in the appendicectomy group and 55 (56%) of 98 in the control group were women. Most patients (76 [77%] of 99 in the appendicectomy group and 81 [83%] of 98 in the control group) were using oral mesalazine as maintenance therapy. Seven (7%) patients in the appendicectomy group and two (2%) patients in the control group had previously used biological therapy for their most recent exacerbation, but only more than 3 months before randomisation; median time to appendicectomy was 2.0 months (IQR 1.0–3.0). Six (6%) patients in the appendicectomy group had a relapse during the waiting period for appendicectomy. Among these, four patients were treated to complete remission (ie, re-baselined) and subsequently underwent appendicectomy, one patient achieved remission but opted to not have an appendicectomy, and one patient started a biological agent and therefore met the trial's exclusion criteria and became ineligible for appendicectomy. Additionally, one patient declined appendicectomy after randomisation. Thus, three patients in the appendicectomy group ultimately did not undergo appendicectomy.

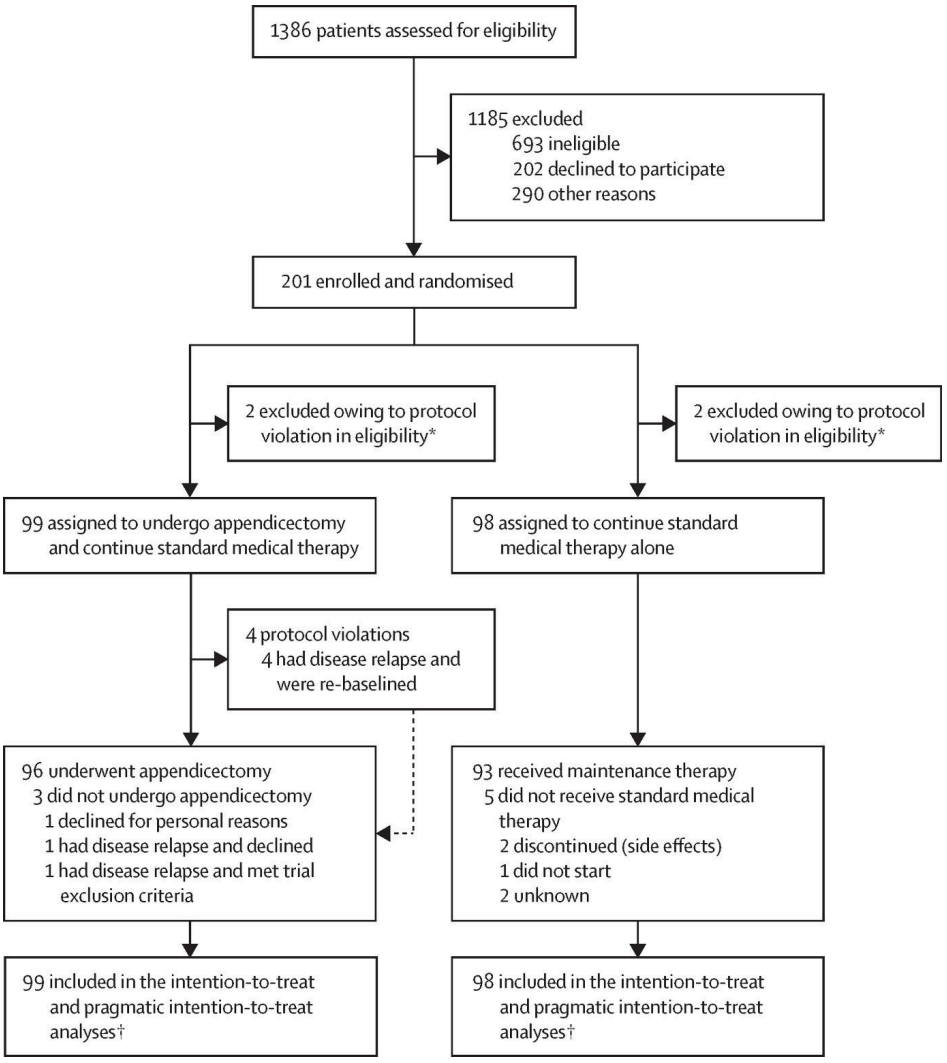

Figure 1. Trial profile

Table 1. Baseline demographic and disease characteristics (intention-to-treat population)

	Appendicectomy group (n=99)	*Control group (n=98)*
Age, years	42.2 (12.5)	43.2 (13.0)
Age at diagnosis, years	33.7 (11.0)	35.5 (12.6)
Sex		
Female	56 (57%)	55 (56%)
Male	43 (43%)	43 (44%)
Disease duration, years*	5.1 (1.8–11.6)	5.3 (1.8–11.3)
Smoking status		
Current smoker	14 (14%)	12 (12%)
Former smoker	39 (39%)	47 (48%)
BMI, kg/m^2†	24.3 (3.4)	24.8 (3.7)
Classification of physical status‡ of more than category ASAII	0	1 (1%)
Primary sclerosing cholangitis†	1 (1%)	0
Family history of inflammatory bowel disease†	24 (24%)	30 (31%)
Medication at baseline		
No medication	9 (9%)	4 (4%)
Topical therapy	23 (23%)	22 (22%)
Oral mesalazine	76 (77%)	81 (83%)
Systemic steroids	1 (1%)	1 (1%)
Immunomodulators	6 (6%)	12 (12%)
Extent of disease§		
Proctitis, E1	38 (38%)	39 (40%)
Left-sided colitis, E2	34 (34%)	36 (37%)
Pancolitis, E3	27 (27%)	23 (23%)
Time from start of most recent exacerbation ulcerative colitis before randomisation, weeks†	30.7 (17.9)	32.0 (19.4)
Partial Mayo score		
0	73 (74%)	77 (79%)
1	24 (24%)	17 (17%)
2	4 (4%)	2 (2%)
Total Mayo score		
0	32 (41%), n=79	44 (51%), n=86
1	38 (48%), n=79	31 (36%), n=86
2	9 (11%), n=79	11 (13%), n=86
Endoscopic subscore=1	33 (42%), n=79	31 (36%), n=86

**Disease duration is the time since diagnosis of ulcerative colitis to randomisation.*
†Data were missing for one patient in the control group for BMI; for 27 patients in the appendicectomy group and 32 in the control group for primary sclerosing cholangitis; for one patient in the appendicectomy group for family history of inflammatory bowel disease; and for five patients in the appendicectomy group and two in the control group for most recent exacerbation of ulcerative colitis.
‡Classification of physical status according to the American Society of Anesthesiologists.
§According to Montreal classification.

At 1 year, the relapse rate was significantly lower in the appendicectomy group than in the control group (36 [36%] of 99 patients *vs* 55 [56%] of 98 patients; RR 0.65 [95% CI 0.47–0.89]; p=0.005; adjusted p=0.002; figure 2). Two of the 63 patients who remained in remission after appendicectomy had a relapse during the waiting period and were re-baselined. When considering these two patients as relapses in the pragmatic intention-to-treat analysis, the results were similar (38 [38%] of 99 patients *vs* 55 [56%] of 98 patients; RR 0.68 [95% CI 0.50–0.93]; p=0.01). For details of other prespecified analysis for the primary outcome and for the post-hoc sensitivity analysis see the appendix (pp 12, 17).

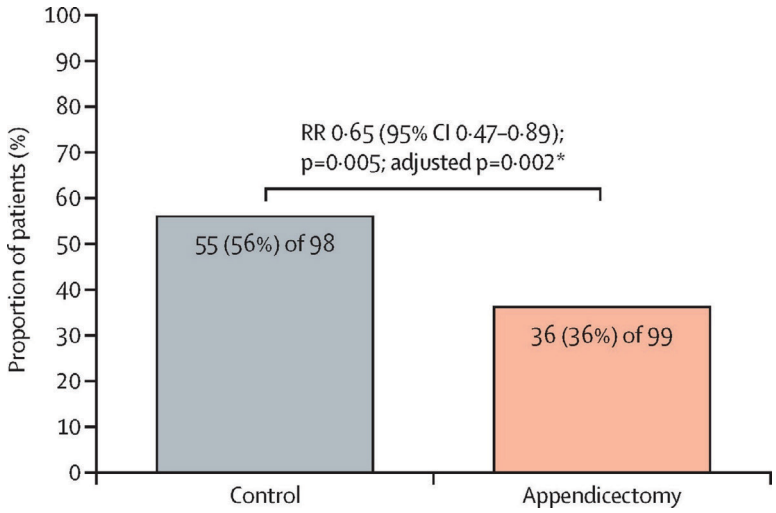

Figure 2. Primary outcome result
**Adjusted for age, sex, current smoking, disease extent, and weeks since most recent exacerbation.*

In the appendicectomy group, 29 (81%) of 36 relapsed patients had one relapse each and seven (19%) had two relapses each, whereas in the control group, 38 (69%) of 55 relapsed patients had one relapse each, 12 (22%) patients had two relapses each, and five (9%) patients had three relapses each (RR 0.85 [95% CI 0.59–1.24]; p=0.40). Median time-to-first relapse was not reached in the appendicectomy group and was 50.57 weeks (95% CI 37.59–63.56) in the control group (hazard ratio for relapse 0.54 [95% CI 0.36–0.82]; p=0.003; figure 3A). Disease activity over the trial period showed increases in the total and partial Mayo scored in both groups, with the appendicectomy group showing a lower total mayo score at 12 months (mean 1.2 points [SD 1.8]) compared with the control group (1.8 points [SD 2.3]; MD 0.70 [95% CI 0.11–1.29]; p=0.02). There were no colectomies done during the 12-month follow-up period.

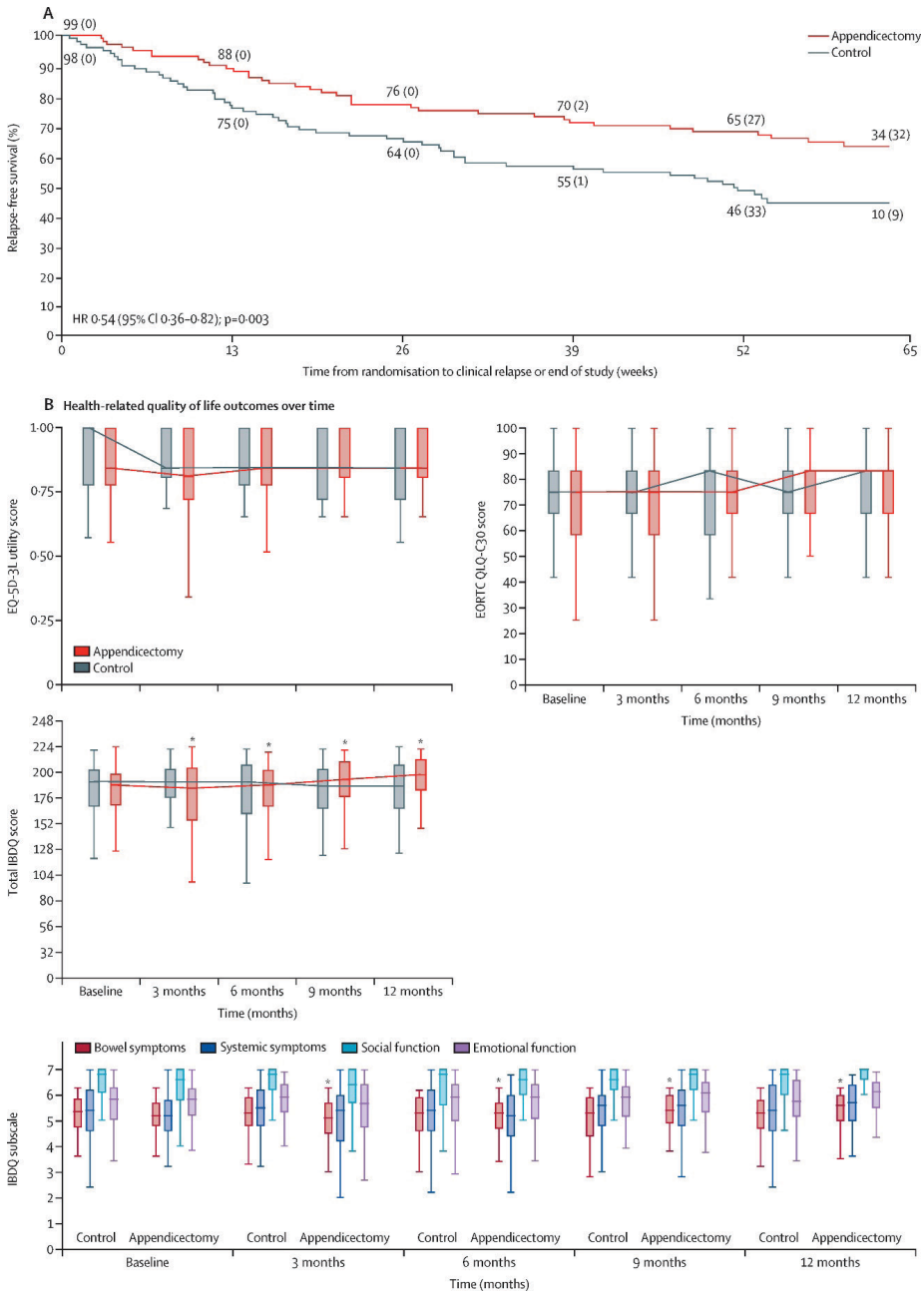

Figure 3. Secondary outcome results

*(A) Kaplan–Meier survival analysis with log-rank testing. Kaplan–Meier plot with log-rank testing comparing the time-to-first-relapse following randomisation between the appendicectomy and control groups. Hazard rate is unadjusted for age, sex, current smoking, disease extent, and weeks since most recent exacerbation. Data at each timepoint are number at risk (number censored). (B) Health-related quality-of-life outcomes over time.*p<0.05 in generalised linear mixed models. EQ-5D-3L=EQ-5D 3-level. IBDQ=Inflammatory Bowel Disease Questionnaire.*

Medication use during the trial period is shown in figure 4. Biological agents were initiated less frequently in the appendicectomy group than in the control group over the trial follow-up period (OR 0.003 [95% CI 0.00–0.27]; p=0.01). Both groups showed significantly decreasing use of oral mesalazine (OR 0.82 [95% CI 0.69–0.97]; p=0.02) over the trial period. At 12 months, for those with available data, 58 (62%) of 94 patients in the appendicectomy group and 73 (80%) of 91 patients in the control group used mesalazine that there were no other significant changes in medication use in the study.

The EQ-5D-3L utility score and the EORTC QLQ-C30 scores showed no significant between-group differences over time. The total IBDQ score and IBDQ bowel symptoms domain score significantly differed over time between the groups in favour of the appendicectomy group (total IBDQ score: MD 3.80 [95% CI 1.20–6.40], p=0.005; IBDQ bowel symptoms domain score: MD 0.16 [95% CI 0.06–0.25], p=0.002), with, at 12 months, a mean total IBDQ score difference between the groups of 6.4 points (95% CI 2.3–15.0). The mean total IBDQ score change between the groups was in favour of the appendicectomy group, with a mean difference between the groups of 11 points (95% CI 2.6–19.6; p=0.01). There were no significant differences in the other IBDQ subdomains. The minimum clinically important difference was calculated as 17.8 point change in IBDQ score (95% CI 5.8–29.9). Comprehensive analyses of secondary outcomes and missing secondary endpoint data are summarised in the appendix (pp 13–16).

Postoperative complications occurred in five (5%) of 96 patients who underwent appendicectomy, of which two (2%) were classified as major and reported as serious adverse event. One patient had an internal herniation requiring laparotomy and another had an intra-abdominal haematoma that was successfully drained. Both patients remained in remission during follow-up. No serious adverse events were reported in the control group (ARD 2.1% [95% CI −0.77 to 4.9]; p=0.24). Adverse events were reported in 11 (11%) of 96 patients in the appendicectomy group and in 10 (10%) of 101 patients in the control group (ARD 1.6% [95% CI −7.1 to 10.2]; p=0.72). The most frequently reported adverse events were postoperative temporary self-limiting abdominal pain, which occurred in three (3%) patients in the appendicectomy group, and skin rash, reported in three (3%) patients in the control group. Two cases (2%) of low-grade appendiceal mucinous neoplasm were incidentally found in resected appendix specimens in the appendicectomy group and did not require further treatment. Safety and postoperative complication

outcomes are listed in the appendix (p 17). There were no deaths reported in either group.

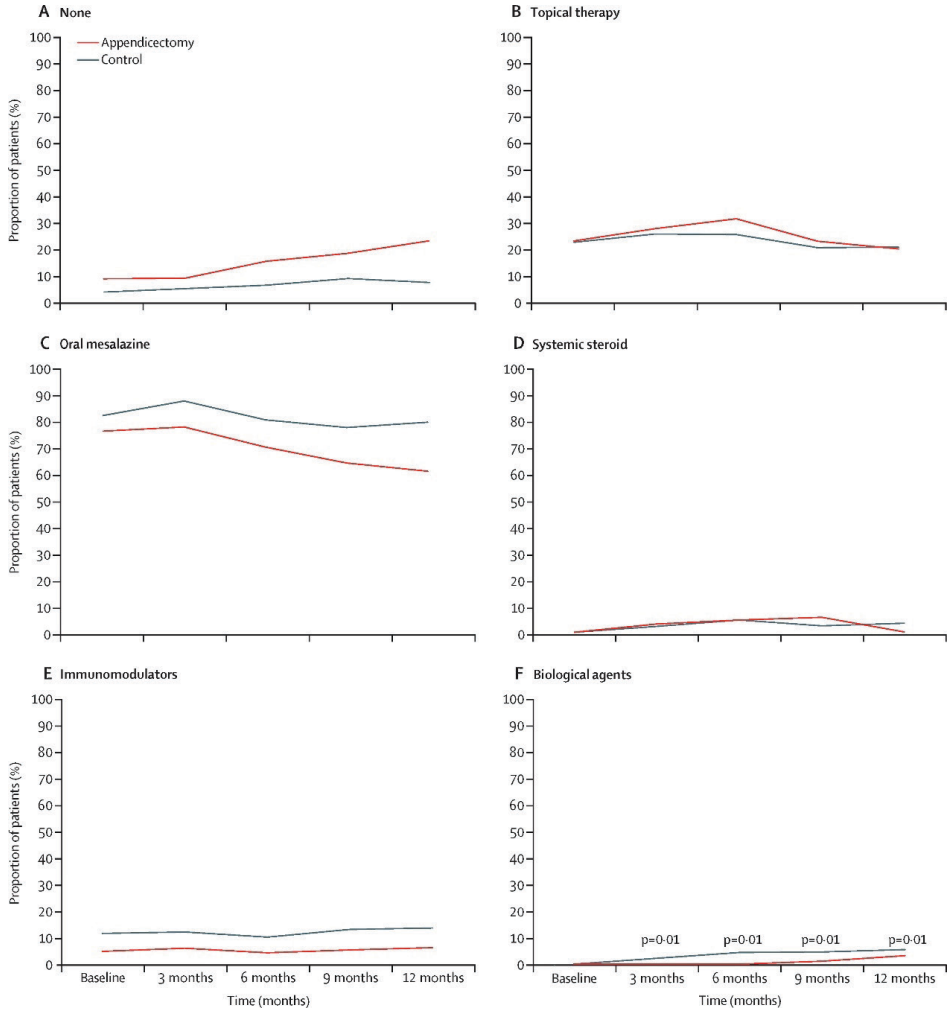

Figure 4. Medication use

(A) None. (B) Topical therapy, defined as rectal enemas or suppositories. (C) Oral mesalazine. (D) Systemic steroid, as oral corticosteroids (prednisone or equivalents or budesonide). (E) Immunomodulators (ie, azathioprine, methotrexate, thioguanine). (F) Biological agents, such as biological medication (anti-TNF, integrin antibody, or small molecules such as JAK inhibitors). In the generalised estimating equation, the baseline measurement was included as a fixed effect to adjust for initial differences between groups. Data for medication use were available for 97 patients in the appendicectomy group and 93 in the control group at 3 months; 89 and 90, respectively, at 6 months; 91 and 87, respectively, at 9 months; and 94 and 91, respectively, at 12 months.

Discussion

This randomised controlled trial showed that appendicectomy was superior to medical therapy alone in maintaining remission in patients with ulcerative colitis within 1 year. At 12 months, around a third of the patients in the appendicectomy group had a relapse compared with more than half of those in the control group. This significant relative risk reduction (RR 0.65 [95% CI 0.47–0.89]) suggests that appendicectomy might be a viable additional therapeutic option for maintaining remission in ulcerative colitis. Furthermore, patients who underwent appendicectomy were significantly more likely to maintain lower disease activity, reduce the initiation of biological agents, and improve health-related quality of life compared with patients who received standard medical therapy alone at 1 year.

The relapse rates in the trial were higher in both groups than initially expected, and several factors might have contributed to this difference. First, the protocol was amended to include patients on immunomodulators, who exhibit higher relapse rates[26] than the reported 37% in patients on oral mesalazine within 1 year.[27] Second, the efficacy–effectiveness gap, reflecting differences between outcomes in clinical trials and real-world practice, might also have had an effect on these relapse rates. This pragmatic trial more closely resembles real-world practice, by maintaining standard medical therapy at the discretion of the treating gastroenterologist in both groups, rather than enforcing standardised medication. This approach, combined with the potential issue of non-adherence to maintenance therapy, a known risk factor for relapse,[28,29] might consequently explain the higher relapse rates observed.

Previous studies on the role of appendicectomy in ulcerative colitis have suggested a potential beneficial effect on the disease course, but were limited by their observational, uncontrolled designs.[11,12] The current randomised controlled trial provides more solid evidence confirming these preliminary observations, and supports the theory that the appendix has an immunomodulatory role in ulcerative colitis.[9,10] The appendix is known to be a reservoir for commensal gut bacteria and gut-associated lymphoid tissue, both having an important role in the gastrointestinal tract's immune response. In ulcerative colitis, the dysregulated immune system leads to chronic colonic inflammation. One possible mechanism is that the appendix contributes to the maintenance and activation of immune cells, especially CD4 T helper cells, that drive the inflammatory process. By removing the appendix, these immune cells might be diminished, thereby reducing the inflammatory mucosal activation and leading to a reduced relapse rate. Nevertheless,

this trial primarily focused on clinical outcomes, and did not evaluate the appendix's immunomodulatory mechanism, so no further causal conclusions can be drawn. Further studies are needed to elucidate the immunological mechanisms of the appendix in ulcerative colitis and ongoing follow-up of this trial will inform longer term outcomes. Further research should also focus on identifying patients who are most likely to benefit.

The appendicectomy group not only had lower relapse rates but also showed favourable trends in medication use. Biological agents were initiated less frequently in the appendicectomy group than in the control group, with the largest difference observed at 6 months (0.0% *vs* 4.4%, respectively). By 12 months, however, this difference had narrowed (3.2% *vs* 5.5%), suggesting that appendicectomy may delay the need for biologic therapy. If this trend were to persist beyond 12 months, even a modest reduction in biologic use could be clinically and economically meaningful. These findings should be interpreted with caution, as these patient numbers are small.[30] Pillai and colleagues reported a 10% annual increase in health-care costs for ulcerative colitis, primarily driven by the increased use of biological agents.[31] Another advantage of a surgical procedure as therapeutic intervention is that non-adherence is not a factor, making it a more attractive alternative to medication or maintenance medication for a subset of patients.

Moreover, the appendicectomy group showed a beneficial effect on some health-related quality-of-life outcomes. This might be a result of the lower relapse rates in this group, as active colitis is associated with an impaired health-related quality of life.[4-6] The difference was primarily observed regarding bowel symptoms, although the difference between the groups in the IBDQ change from baseline to 12 months did not meet the calculated minimum clinically important difference. The lack of significant differences in EQ-5D-3L utility and EORTC QLQ-C30 scores between the groups might be due to lower sensitivity and weaker correlation of these measures with disease relapse compared with the total IBDQ score. Given the nature of the EQ-5D-3L questions, patients experiencing relapse are more likely to report worse scores in the dimensions of usual activities, pain or discomfort and anxiety or depression, but not in mobility or self-care.

Limitations of this trial were the absence of a sham-surgery control group to determine the contribution of the placebo effect, which might have biased some of the health-related quality-of-life read outs, and the long duration of the trial, which might compromise the external validity. Nonetheless, this pragmatic trial

was done across 21 international sites, enhancing its external validity. Participation bias might have been introduced, as it is likely that only a subset of patients who were in remission were willing to participate in a randomised surgical trial to undergo an additional appendicectomy. With the publication of beneficial results of appendicectomy trials, patient self-preference patterns might have been influenced. Finally, in this pragmatic trial, not all patients underwent follow-up endoscopy to objectively determine the relapse rate. Since a per-protocol analysis was not prespecified in the statistical analysis plan, these data are not presented here. However, the incidences of relapse were similar between both groups, and a similar difference between the groups was observed (appendix p 17).

In conclusion, appendicectomy is a viable and safe strategy for reducing the relapse rate in patients with ulcerative colitis compared with standard medical therapy at 1 year, offering a potential addition to standard medical therapies.

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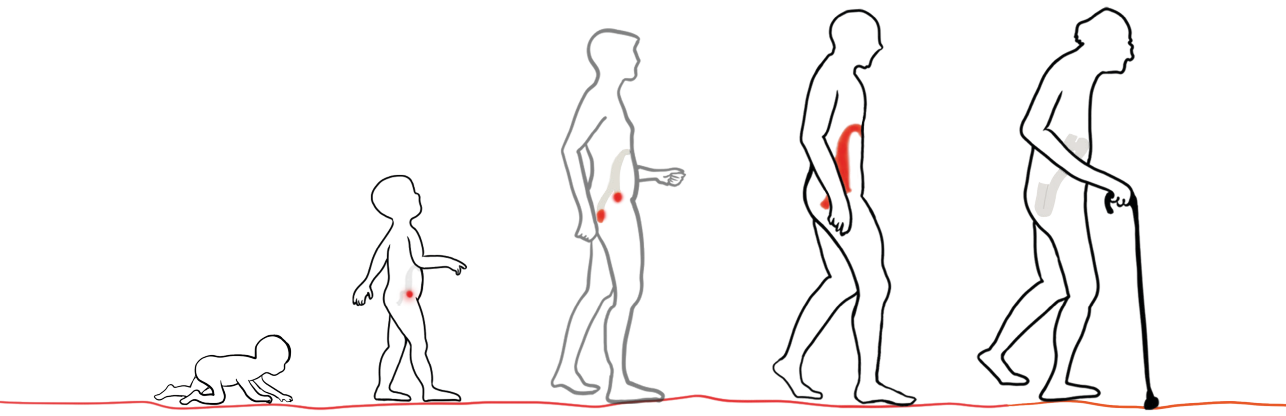
Supplementary materials

5

Chapter 5

Predictors of maintained remission at one year following appendicectomy in ulcerative colitis: post-hoc analysis of the ACCURE trial

Eva Visser, Thomas D Pinkney, Lianne Heuthorst, Geert R D'Haens, Willem A Bemelman, Christianne J Buskens



British Journal of Surgery, 2025

Abstract

Background

The ACCURE trial demonstrated that appendicectomy reduces one-year relapse rates in ulcerative colitis (UC) patients in remission compared to standard medical therapy. This study explored patient-level predictors of maintained disease remission up to one year post-appendicectomy.

Methods

A post-hoc analysis of ACCURE trial data. Time-dependent Cox regression identified baseline characteristics associated with maintained remission at one year. Interaction terms between treatment group and baseline factors were calculated to investigate the effect of appendicectomy on efficacy outcome.

Results

Among 156 patients, 51 of 82 appendicectomy patients (62.2%) maintained remission, compared with 31 of 74 (41.9%) in the non-appendicectomy group (p=0.011). In multivariate analysis across the entire cohort, appendicectomy (HR 0.07, 95% CI 0.01-0.53, p=0.011) and older age (per 10-year increase: HR 0.73, 95% CI 0.54-0.98, p=0.030) were associated with reduced hazard of disease relapse, while former smoking (HR 3.32, 95% CI, 1.63-6.77, p<0.001) and pancolitis (vs proctitis/ left-sided colitis; HR 2.12, 95% CI 1.03 to 4.38, p=0.042) increased it. Interaction analyses showed an enhanced protective effect of appendicectomy in younger patients ($p_{interaction}$=0.005**)** and former smokers ($p_{interaction}$=0.031). Younger patients derived greater benefit from appendicectomy than older patients, whereas in the control group, older age was linked to better remission outcomes. This indicates an inverse relationship between age and remission outcomes across treatment groups.

Conclusion

Younger age and former smoking were significant predictors of maintained remission up to one year following appendicectomy in UC. These findings provide a potential basis for refining patient selection criteria for appendicectomy in UC management.

Dear editor,

Epidemiological studies have suggested that appendicectomy, particularly when performed during childhood, may reduce the risk of developing ulcerative colitis (UC).[1] This observation has led to a growing interest in its potential therapeutic role in modifying the course of UC. The ACCURE trial, the first randomized controlled superiority trial of this intervention, demonstrated that appendicectomy significantly reduces clinical relapses within one year in patients with UC compared to standard medical therapy.[2] As 36% of patients still relapse following appendicectomy, the identification of upfront patient and disease characteristics associated with the optimal benefit might result in a more targeted treatment approach. As such, this analysis aimed to explore patient-level predictors of maintained disease remission up to one year after appendicectomy in the ACCURE trial cohort.

A post-hoc analysis of 156 patients from the ACCURE trial (NTR2883 and ISRCTN60945764; Fig. S1) was undertaken. Remission was defined as the absence of relapse according to predefined study criteria within 12 months, confirmed by an endoscopic Mayo score (subscore 0 or 1). Time-dependent Cox regression was used to identify baseline characteristics associated with maintained remission at one year, and interaction terms between treatment group and baseline factors were calculated to assess the effect of appendicectomy on efficacy outcome (supplementary methods).

Among the 82 appendicectomy patients, 51 (62%) maintained remission at 12 months, compared with 31 (42%) of the 74 patients in the non-appendicectomy group (p=0.011; Table S1, supplementary results). In multivariate analysis (Table S2), the protective effect of appendicectomy on maintaining remission remained significant (appendicectomy versus non-appendicectomy; HR 0.07, 95% CI 0.01 to 0.55 p=0.011). Similarly, older age (continuous; per 10-years increased; HR 0.72, 95% CI 0.53 to 0.97, p=0.030) showed a significant protective effect with a reduced hazard of disease relapse. In contrast, former smoking and pancolitis increased the risk of disease relapse (HR 3.33, 95% CI 1.63 to 6.81, p<0.001 and HR 2.12, 95% CI 1.03 to 4.38, p=0.042 respectively).

Interaction analyses found that younger age significantly enhanced the protective effect of appendicectomy (continuous; age 10-years increase HR 1.97, 95% CI 1.23 to 3.16, $p_{interaction}$=0.005; Figure 1). This resulted in an inverse relationship between age and remission outcomes across treatment groups. Specifically, in the appendicectomy

group, younger age showed a trend towards a reduced risk of disease relapse (per 10-year increase: HR 1.39, 95% CI 0.96 to 1.99, p=0.078). In contrast, in the control group, older age was associated with a reduced risk of disease relapse (per 10-year increase HR 0.72, 95% CI 0.53 to 0.96, p=0.028). Stratification by age (<50 versus ≥50 years) confirmed that younger patients had a reduced likelihood of relapse following appendicectomy (HR 0.20, 95% CI 0.06 to 0.67, $p_{interaction}$=0.009). Similarly, former smokers benefited more from appendicectomy compared to non-smokers or active smokers (HR 0.28, 95% CI 0.09 to 0.89, $p_{interaction}$=0.031).

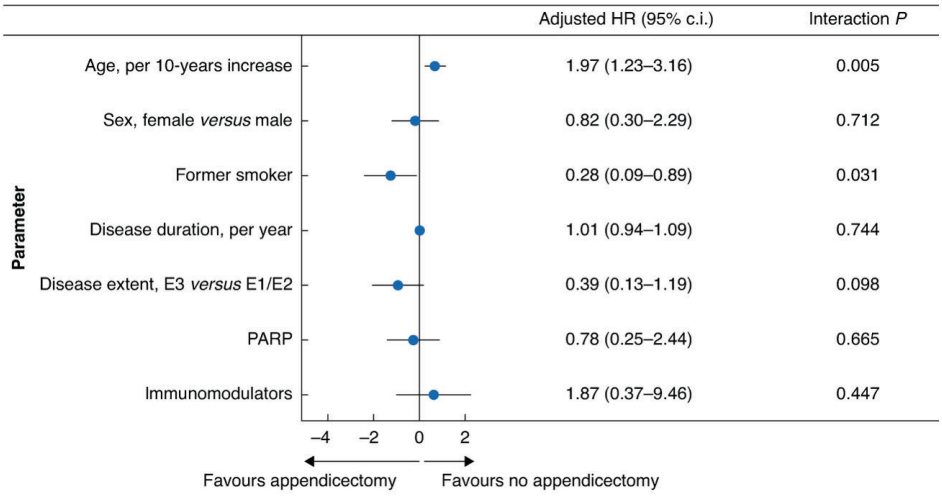


Figure 1. Forest plot of the association of appendicectomy on maintained remission in interaction analyses

PARP, peri-appendiceal red patch history. The forest plot is displayed on a logarithmic scale and represents the interaction effects of appendicectomy on maintained remission for various baseline characteristics. Adjusted hazard ratios and 95% confidence intervals are shown for each variable. The treatment effect of appendicectomy is represented by the vertical dotted line, and the hazard ratio for each variable is represented by the dots. Hazard ratio is estimated for each interaction coefficient using the non-appendicectomy group as reference.

These findings suggest that the protective effect of appendicectomy against disease relapse over 12 months was particularly pronounced in younger patients and former smokers, whereas younger age, former smoking and pancolitis were identified as significant risk factors for disease relapse in the overall cohort.

The present findings align with previous research describing an inverse relationship between appendicectomy and development of UC, particularly when performed earlier in life.[1] The underlying mechanisms remain speculative, but might reflect age-related differences in the immunological role and microbiota composition

of the human appendix.[3] The appendix undergoes structural changes with age, transitioning from lymphoid-rich tissue in the mucosa and Peyer's patches to fibrotic structures as demonstrated in murine models,[4] potentially reducing its immunomodulatory capacity. In younger individuals, the appendix might exhibit more active immune processes, including T cell activation, and greater microbiota variability, potentially enabling appendicectomy to modulate these pathways more effectively.

Former smokers, a group known to have a higher relapse risk in UC,[5] also showed significant benefit from appendicectomy. This may highlight the potential of appendicectomy to mitigate relapse risk, particularly in patients with a higher baseline risk, although no clear biological mechanism has been established. These interpretations remain hypothetical and should be considered exploratory.

The strength of these analyses is the robust data set derived from a well-designed RCT, which allowed for a detailed exploration of predictors and treatment interactions. Furthermore, the availability of the efficacy outcome and time-to-event data for all patients strengthens the reliability of the findings. However, several limitations must be acknowledged. The post-hoc and exploratory nature of the analyses, along with the relatively small sample size, increases the possibility of chance findings. Additionally, mechanistic interpretations are speculative and warrant further investigation.

In conclusion, this analysis identifies younger age and former smoker status, both acknowledged as risk factors for relapse, as predictors of greater benefit from appendicectomy in UC patients in remission without advanced medical therapy. These results provide a potential basis for refining patient selection criteria for appendicectomy in UC management, although further biological research is warranted to clarify underlying mechanisms.

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Supplementary materials

6

Chapter 6

Histopathological findings of appendix specimens in quiescent ulcerative colitis: correlations with clinical outcomes in the ACCURE trial

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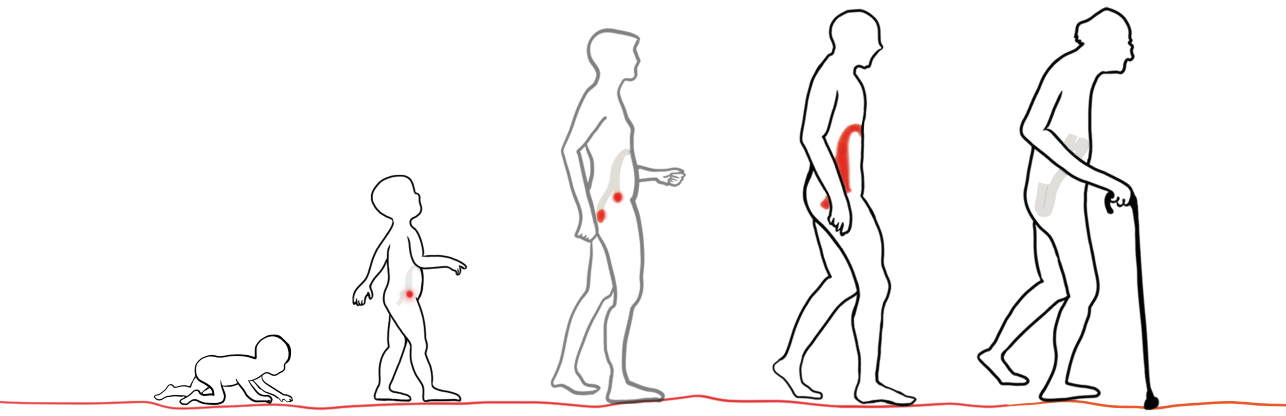


Submitted (under review)

Abstract

Background

The ACCURE trial demonstrated that appendicectomy reduces relapse rates within one year in patients with ulcerative colitis (UC) in remission. We aimed to explore appendiceal histopathology in quiescent UC and assess its association with postoperative relapse.

Methods

Appendix specimens from Dutch participants in the ACCURE trial were reassessed by a blinded gastrointestinal pathologist using the Robarts Histopathology Index (RHI; range 0-33). Active appendiceal inflammation was defined as RHI >3. Baseline clinical data, preoperative endoscopic findings including the presence of a peri-appendiceal red patch (PARP), and clinical outcomes were retrieved and correlated to histopathological findings. Inter-observer agreement between local and central scoring was assessed, along with relapse-free survival in relation to RHI severity.

Results

Of 65 patients, 49 (75.4%) maintained remission and 16 (24.6%) relapsed within one year. Active inflammation was present in 55.4% (36/65). Inter-observer agreement with local scoring was moderate (κ =0.47, 95% CI 0.29-0.64, p<0.001). Active inflammation was seen more frequently in patients with UC diagnosis at younger age (median 28 vs 34 years, p=0.09), and PARP was associated with greater inflammation (RHI 15.5 vs 5.0, p=0.005). Patients with extensive epithelial neutrophil involvement (>5% of crypts) had higher relapse rates compared to those with less extensive infiltration (<5% crypt involvement; 44.4% vs 18.0%, p=0.05). Relapsing patients also had a larger appendiceal diameter compared to those who remained in remission (median 9 mm vs 7 mm, p=0.03).

Conclusion

Active appendiceal inflammation is prevalent in quiescent UC and may be associated with relapse risk. Although based on current results it cannot be concluded that an appendectomy might be beneficial in this patient group as it is unknown what the relapse rate would have been without appendectomy, the finding might be clinically relevant as relapse rates are significantly reduced in the appendectomy group.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterised by histopathological features of both chronic and active inflammation limited to the colonic mucosa.[1] The hallmark of active inflammation is the presence of neutrophils in the mucosa; present in the lamina propria or epithelium (cryptitis, crypt abscess formation). Subsequent epithelial damage may lead to erosions and/or ulcerations. Chronicity is marked by structural changes such as crypt architectural distortion and Paneth cell metaplasia.[2] Although histological healing is increasingly recognised as an important treatment target, achieving complete histological remission remains challenging and is not yet a formal treatment goal.[3] However, combined endoscopic and histological healing – referred to as histologic-endoscopic mucosal improvement (HEMI) or remission (HEMR) – has been associated with improved treatment outcomes and is increasingly used as a clinical trial endpoint.[4]

The role of the appendix in UC pathogenesis remains unclear, but a contribution has been hypothesised with recent trials reporting improved disease outcomes after appendicectomy.[5] The appendix, an evolutionary remnant rich in gut-associated lymphoid tissue (GALT), including abundant immune cells such as B and T lymphocytes and macrophages,[6] is thought to modulate intestinal immune responses relevant to UC.[7,8] Histopathological studies specifically examining the appendix in UC are limited, but existing data indicates active appendiceal inflammation is present in approximately 50% of UC patients, irrespective of endoscopic disease activity or extent in the colon.[6,9,10] Notably, in active UC, active appendiceal inflammation has been associated with treatment response in these studies, further emphasizing the need for a deeper understanding of its potential role.

The ACCURE trial, the first randomised controlled trial evaluating appendicectomy as a therapeutic intervention in patients with quiescent UC, demonstrated a significantly lower relapse rate in those who underwent appendicectomy.[11] However, the primary trial publication focused solely on predefined clinical outcomes and did not report detailed appendiceal histopathology, leaving a gap in understanding its potential involvement in UC. Therefore, this study aims to further investigate the histopathology of the appendix in quiescent UC patients and examine its potential association with the clinical disease course in the ACCURE trial cohort.

Methods

Study design and population

This study was an investigator-initiated histopathological analysis of appendix specimens obtained from participants in the Dutch cohort of the ACCURE trial (NTR2883), a randomised controlled trial evaluating the clinical effectiveness of appendicectomy in maintaining remission in UC patients. Detailed methodology and outcomes of the ACCURE trial have been published previously.[11-13] In short, the trial included UC patients in remission who had been treated for disease relapse within the preceding year but were not receiving advanced medical therapy (e.g., biologics or small molecules). Patients were randomised either to undergo laparoscopic appendicectomy in addition to continued maintenance therapy or to continue maintenance therapy alone.

For the present analysis, appendix specimens were collected from participants assigned to the appendicectomy arm within the Dutch cohort. Patients were excluded if they were diagnosed with Crohn's disease during follow-up or if histopathological data of their resected appendix specimen was unavailable for blinded central assessment.

Data collection and variables

Baseline demographic and clinical characteristics were retrieved from the ACCURE trial database and local pathology reports, including age at operation, age at UC diagnosis, sex (male or female), disease duration (from diagnosis to surgery), disease extent (proctitis [E1], left-sided colitis [E2], or pancolitis[E3]), time from last exacerbation to appendicectomy, patient-reported number of prior exacerbations, and partial Mayo score. Endoscopic parameters were retrieved from the endoscopy reports and included history of peri-appendiceal red patch (PARP; if ever reported, and whether present on baseline endoscopy), and Mayo endoscopic score (MES; from baseline endoscopy). Appendiceal pathology reports from previously conducted evaluations at local participating centres were retrieved and specimen results were categorised into three groups: no inflammation (appendix sana), active inflammation, and fibrosis. Macroscopic appendiceal characteristics, including maximum diameter were also collected from local pathology reports. Clinical follow-up data included occurrence and timing of UC relapse, defined as confirmed relapse by either (1) endoscopy (Mayo subscore $\geq$2) or (2) elevated faecal calprotectin ($>$ 150µg/g) confirmed by centrally blinded review by a critical event committee. Data also included follow-up MES and the date of the 12-month follow-up visit.

Histopathological assessment

All available appendectomy specimens were re-evaluated by an independent expert gastrointestinal pathologist who was blinded to clinical data and outcomes. Tissue samples were formalin-fixed, paraffin-embedded and stained with hematoxylin and eosin for histological assessment. Histological scoring was performed using the RHI, a validated UC-specific histological scoring system for assessing mucosal disease activity. The RHI assessed four characteristics of mucosal activity, each graded from 0 to 3 and multiplied by weighting factors: (1) Inflammatory infiltrate (x1); (2) Neutrophils in the lamina propria (x2); (3) Neutrophils in the epithelium (x3); and (4) Erosion or ulceration (x5). Total scores range from 0 to 33, with higher scores indicating greater inflammatory activity.[14] Active appendiceal inflammation was defined as an RHI >3, and absence of histological appendiceal inflammation was defined as RHI ≤3. For further subgroup analyses, inflammation severity was categorised as remission (RHI≤3), mild inflammation (RHI 4-10), moderate (RHI 11 to 20) and severe (RHI ≥21).

Clinical outcome assessment and correlation analysis

To evaluate its clinical relevance, histopathological features were correlated with baseline disease characteristics, preoperative endoscopic findings, and postoperative clinical outcomes. Comparisons were made between patients who maintained remission and those who experienced a relapse during follow-up. Secondary outcomes included assessment of inter-observer agreement between local pathologists and the central RHI scoring, and analysis of time-to-first-relapse in relation to RHI severity categories.

Statistical methods

Categorical variables were summarised using counts and percentages, and differences between groups were analysed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were reported as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. Inter-observer agreement for histological active inflammation classification (local vs expert pathologist) was evaluated using Cohen's kappa (κ), interpreted as follows: κ <0.00 (poor agreement), 0.00-0.20 (slight), 0.21-0.40 (fair), 0.41-60 (moderate), 0.61-0.80 (substantial), and 0.81-1.00 (almost perfect).[15] Correlations between baseline clinical characteristics and appendix RHI scores were assessed using Spearman's rank correlation (ρ) for continuous, and Mann-Whitney U or Kruskal-Wallis tests for categorical variables. The association between RHI scores and relapse was similarly analysed with Mann-Whitney U test. Kaplan-Meier survival

analysis with log-rank test was performed to compare time-to-relapse across RHI severity groups. Hazard ratios (HR) with 95% confidence intervals (CI), were calculated, considering relapse as the event of interest, while participants without relapse were censored at their last follow-up visit. All tests were two-sided, and a P-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS® version 28.0.1.1 (IBM, Armonk, NY, USA) or Stata version 17.0.0.

Ethics, patients and public involvement

The study was approved by the Medical Ethics Review Committee of the Academic Medical Centre on April, 12 2012 (NL37531.018.11) and adhered to the ethical guidelines and World Medical Association's Declaration of Helsinki. All patients provided written informed consent prior to any study-related procedures.

Results

A total of 65 Dutch ACCURE participants randomly assigned to appendicectomy were included in this histopathology study (Figure 1). Among the included patients, 49 (75.4%) maintained remission, while 16 (24.6%) had experienced a relapse within one year. Of these relapses, 11 were confirmed by endoscopy, and 5 were confirmed by FCP levels exceeding 150 µg/g. Baseline demographic and clinical characteristics are summarised in Table 1. Overall, patients had a median age at appendicectomy of 40 years (IQR, 33 to 49) and a median disease duration of 5.2 years (IQR, 2.4 to 11.9). Disease extent was evenly distributed: proctitis (E1) in 36.9% (24/65), left-sided colitis (E2) in 33.8% (22/65), and pancolitis (E3) in 29.2% (19/65). A history of PARP was previously documented in 16 patients (24.6%), with 4 cases during trial baseline endoscopy.

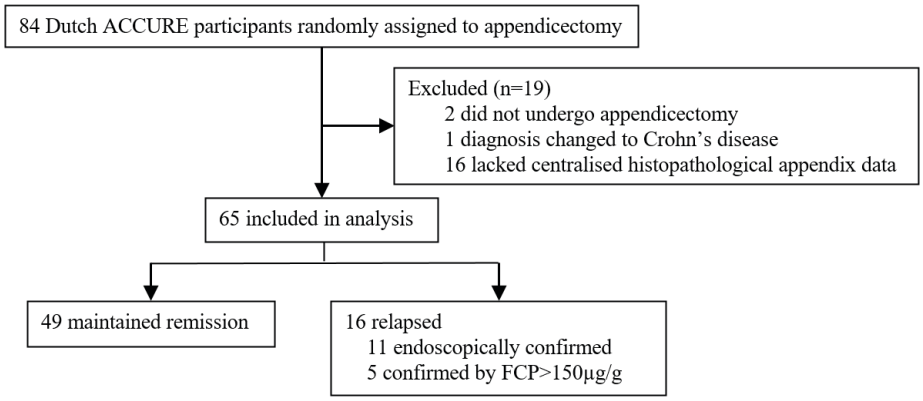


Figure 1. Flow diagram of ACCURE patients included in this analysis

Table 1. Demographic and clinical baseline characteristics of the cohort (n=65)

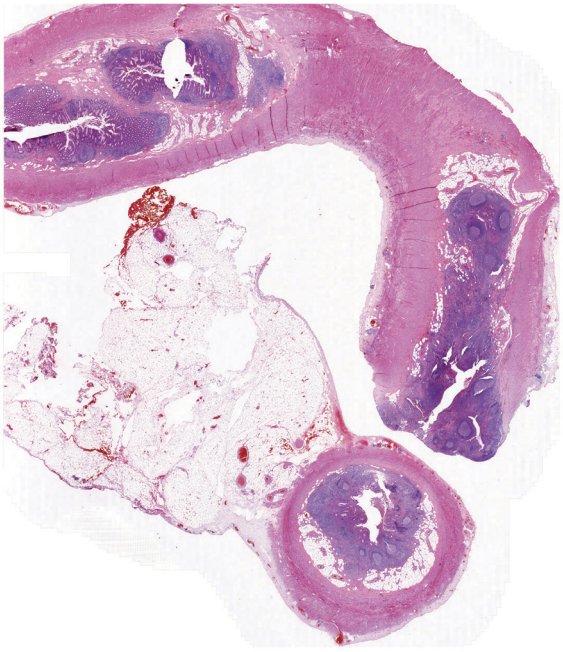
		Active appendiceal inflammation*		
Characteristic	**Cohort (n=65)**	**Yes N=36**	**No n=29**	**p-value**
Age at operation, years	40 (33-49)	39 (32-49)	41 (34-56)	0.26
Age at diagnosis, years	31 (25-39)	28 (24-35)	34 (26-46)	0.09
Sex, female	36 (55.4%)	20 (55.6%)	16 (55.2%)	0.98
Disease duration, years	5.2 (2.4-11.9)	5.2 (1.6-13.0)	5.2 (2.8-11.1)	0.91
Disease extent				0.67
Proctitis (E1)	24 (36.9%)	15 (41.7%)	9 (31.0%)	
Left-sided (E2)	22 (33.8%)	11 (30.6%)	11 (37.9%)	
Pancolitis (E3)	19 (29.2%)	10 (27.8%)	9 (31.0%)	
Time since last exacerbation, months	7.8 (5.1-11.5)	7.1 (4.9-11.6)	8.1 (5.3-11.5)	0.88
Number of prior exacerbations (patient-reported)	5 (3-10)	5 (3-10)	5 (2-7)	0.62
Peri-appendiceal red patch history**	16 (24.6%)	11 (30.6%)	5 (17.2%)	0.09
At baseline endoscopy	4 (6.2%)	4 (23.5%)	0 (-)	0.08
Mayo endoscopic score at baseline				0.98
0	26 (48.1%)	14 (48.3%)	12 (48.0%)	
1	28 (51.9%)	15 (51.7%)	13 (52.0%)	
Partial Mayo score at baseline=0	48 (73.8%)	26 (72.2%)	22 (75.9%)	0.74
Maximum diameter appendix, mm[a]	7 (5-10)	8 (6-10.1)	6 (5-7.8)	**0.02**

Data are median (IQR) or number (%).
**Active appendiceal inflammation was defined as RHI>3.*
Missing data for time since last exacerbation: 2 patients; 9 for number of exacerbations; 11 for endoscopy (confirmed by faecal calprotectin level <150µg/g according to protocol).
[a]16 not reported.

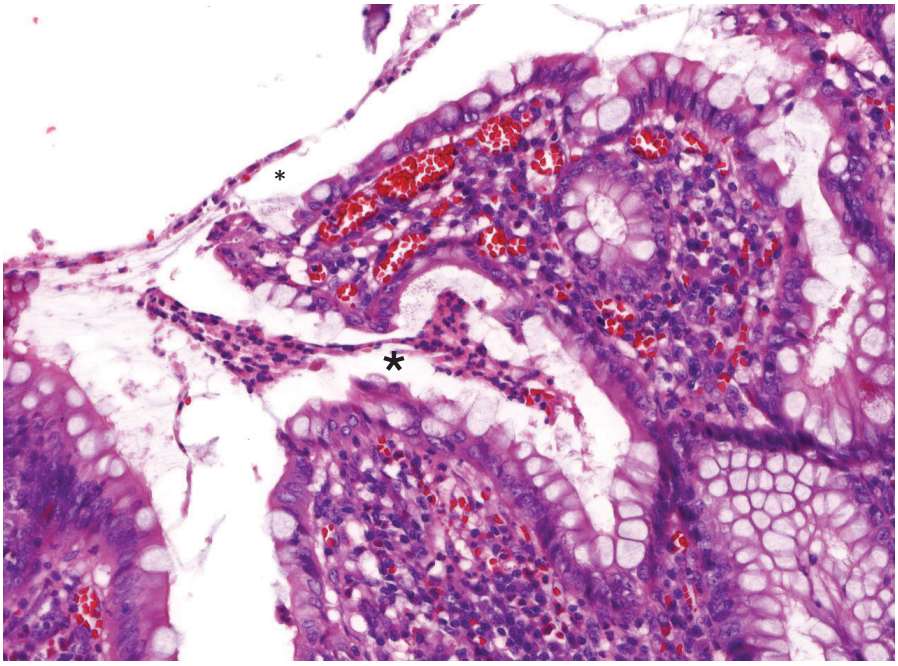
Histopathological findings of the appendix

Central reading showed a median RHI of 6 (IQR, 0 to 13) in the overall cohort. Active inflammation was present in 36 of 65 (55.4%) of the appendices, while 29 (44.6%) had no inflammation. Of these without inflammation, 9 appendices (13.8%) showed complete fibrous obliteration of the appendiceal lumen and therefore no RHI could be scored. Excluding fibrotic appendices, the median RHI was 7 (IQR, 1 to 15). The highest RHI observed was 31 where the appendix showed severe active inflammation (Figure 2). Detailed histological findings (Table 2) of the 56 non-fibrotic appendices indicated that most patients demonstrated a mild (41% [23/56]) or moderate (32% [18/56]) increase in chronic inflammatory infiltrates. Neutrophilic infiltration was also prevalent, with 59% (33/56) showing lamina propria neutrophils and 66% (37/56) showing epithelial neutrophils. Erosions or ulcerations were present in 27% (15/56) of evaluated specimens, although severe erosion or ulceration was uncommon (1.8% [1/56]).

A. Histological section from the proximal appendix and a transverse section toward the distal appendix



B. Higher magnification (transverse section)



C. Higher magnification (transverse section)

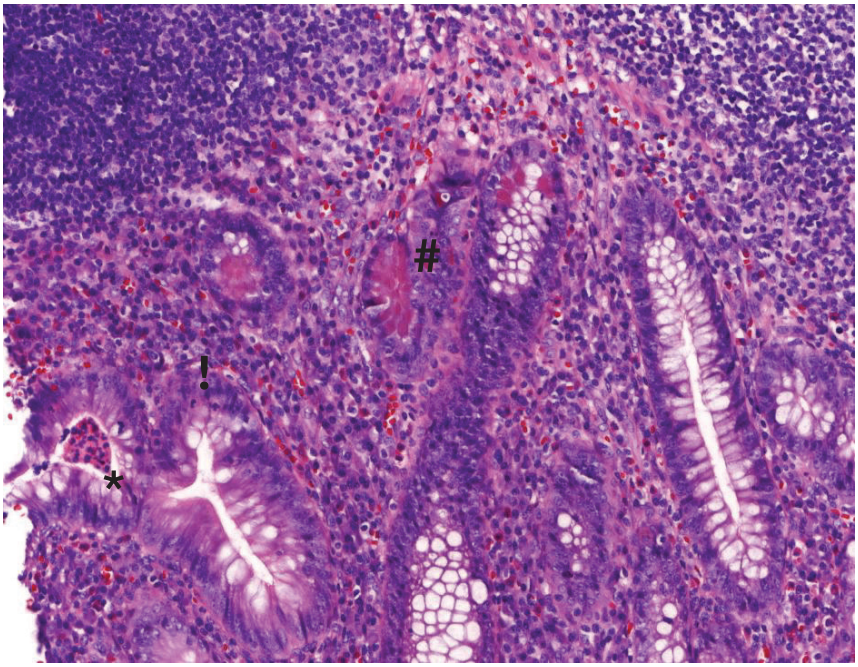


Figure 2. Appendix with severe active inflammation
** Crypt abscess.*
 # Prominent Paneth cells.
! Cryptitis.

Local pathology reports classified 32.3% of specimens as appendix sana, 43.1% as active inflammation, and 24.6% as fibrosis. Inter-observer agreement between local pathologist and centralised RHI scoring by the expert IBD pathologist was moderate (κ =0.467, 95% CI 0.29 to 0.64, $p<0.001$). Most discrepancies were found in scoring of appendix sana by the local pathologist, while upon central reading scored active inflammation (n=10). The RHI in these 10 cases ranged from 4 to 15.

Table 2. Histopathology characteristics of the resected appendix specimen (N=65)

Characteristic	
Total fibrotic obliteration	9 (13.8%)
RHI, median (IQR)*	6 (0-13)
Chronic inflammatory infiltrate (x1)	
(0) No increase	12/56 (21.4%)
(1) Mild increase	23/56 (41.1%)
(2) Moderate increase	18/56 (32.1%)
(3) Marked increase	3/56 (5.4%)
Lamina propria neutrophils (x2)	
(0) *No increase*	23/56 (41.1%)
(1) *Mild but unequivocal increase*	14/56 (25.0%)
(2) *Moderate increase*	19/56 (33.9%)
(3) *Marked increase*	0/56 (-)
Epithelial neutrophils (x3)	
(0) *None*	19/56 (33.9%)
(1) *<5% crypts involved*	19/56 (33.9%)
(2) *<50% crypts involved*	12/56 (21.4%)
(3) *>50% crypts involved*	6/56 9.2%)
Erosion or ulceration (x5)	
(0) *No erosion, ulceration or granulation tissue*	41/56 (73.2%)
(1) *Recovering epithelium + adjacent inflammation*	8/56 (14.3%)
(2) *Unequivocal erosion*	6/56 (10.7%)
(3) *Ulcer or granulation tissue*	1/56 (1.8%)
Active inflammation (RHI>3)**	35 (54.7%)
Reported by local pathologist	
Appendiceal inflammation	
No (appendix sana)	21 (32.3%)
Active inflammation	28 (43.1%)
Fibrosis	16 (24.6%)

** Median RHI without fibrotic appendices: 7 (IQR, 1-15).*
*** 9 patients with TFO are considered as absence of appendiceal inflammation (RHI=0).*

Association between baseline characteristics and active appendiceal inflammation

Baseline demographic and clinical characteristics were compared between patients with (RHI >3) and without (RHI ≤3) active appendiceal inflammation. No significant associations were observed in age at appendicectomy, sex, disease duration, disease extent, time since last exacerbation, number of prior exacerbations, Mayo endoscopic score, or partial Mayo score (Table 1). Patients with active appendiceal inflammation tended to have a younger median age at UC diagnosis compared to those without inflammation (28 years vs 34 years, p=0.09). Similarly, they had a numerically higher prevalence of PARP compared to those without (30.6% vs 17.2%,

p=0.09), with the presence of PARP significantly associated with higher median RHI scores (15.5 [IQR, 12.8 to 22.8] vs 5.0 [IQR, 0.0 to 9.5], p=0.005). Correlation analyses between continuous RHI scores and baseline characteristics yielded similar results.

Association between appendix histopathology and disease course

The relationship between appendiceal histopathology and clinical disease course post-appendicectomy was further explored. The median maximum diameter was significantly greater in patients who relapsed post-surgery compared to those who remained in remission (9 mm [IQR, 7-10.3] vs 7 mm [IQR, 5-8] p=0.03). Additionally, higher RHI scores showed a trend towards correlation with the maximum diameter (ρ = 0.254, p=0.08). Patients who experienced a relapse demonstrated numerically higher RHI scores compared to those maintaining remission (9.5 [IQR, 1.8 to 16.5] vs 3 [IQR, 0.0 to 12.0], p=0.09; Figure 3). Among the 36 patients with active appendiceal inflammation, those who relapsed were younger at time of UC diagnosis (25.0 years [IQR, 21.5 to 29.5] vs 32.0 [IQR, 26.3 to 38.0], p=0.04) and had a longer disease duration (9.0 years [IQR, 5.2 to 30.9] vs 4.6 [IQR, 1.1 to 8.6], p=0.04). Among the 29 patients without appendiceal inflammation, these differences were not observed (p=0.44 and p=0.78, respectively).

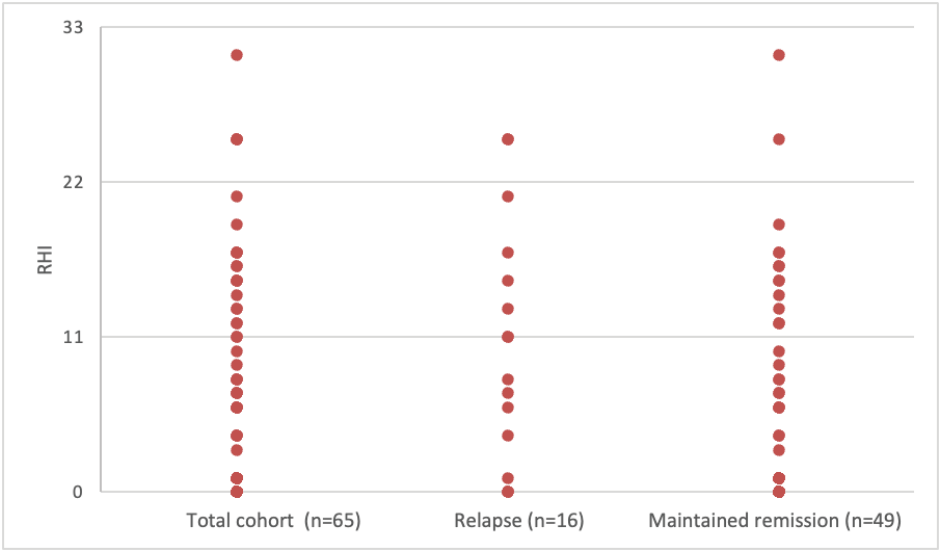


Figure 3. Appendix histopathology and disease course
Abbreviation: RHI: Robarts Histopathology index.

Kaplan-Meier survival analysis demonstrated a clear trend toward shorter time-to-relapse with increasing appendiceal histological severity (Figure 4). At 12 months, relapse-free survival was highest in patients without appendiceal inflammation (82%) and progressively decreased across those with mild (RHI 4-10; 71%), moderate (RHI 11-20; 68%), and severe inflammation (RHI ≥21; 36%). Although not statistically significant, the HR for relapse in patients with active appendiceal inflammation compared to those in histological remission was 2.7 (95% CI 0.76 to 10.13, p=0.12), supporting a potential link between histopathological severity and disease recurrence.

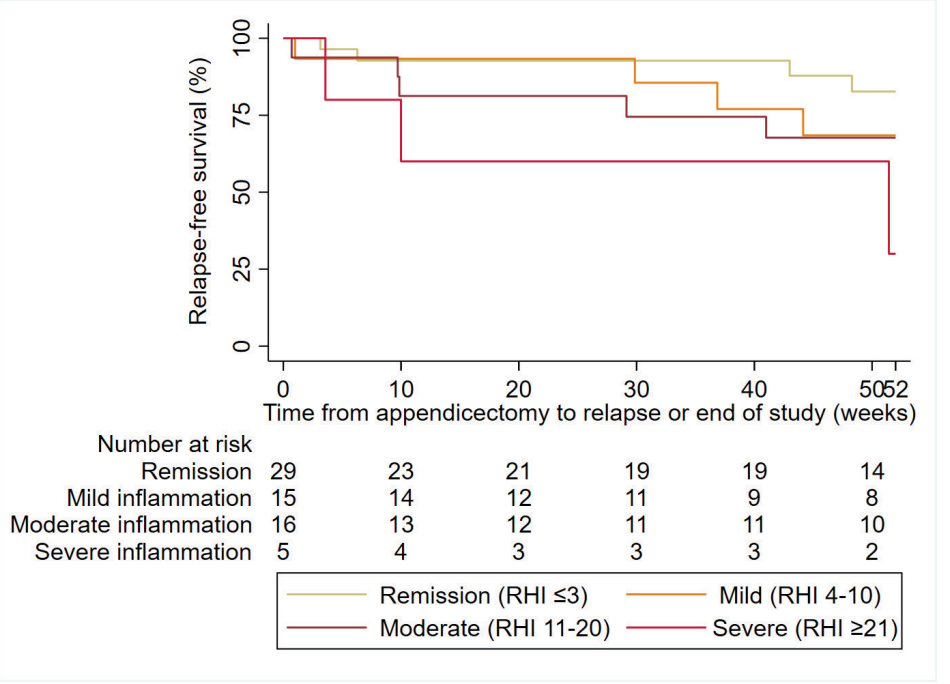


Figure 4. Kaplan-Meier survival subgroups

Discussion

This study provides the first detailed histopathological analyses of appendix specimens in quiescent UC directly linked to clinical outcomes following appendicectomy, conducted within a randomised controlled trial (ACCURE). We demonstrated that active appendiceal inflammation was common in quiescent UC, present in over half of the patients (55%). Notably, a history of PARP was significantly associated with more severe appendiceal inflammation (higher RHI scores). Although not statistically significant, we observed trends toward a younger

age at UC diagnosis (p=0.09) and a greater maximum appendiceal diameter (p=0.08) in patients with active appendiceal inflammation compared to those without. Furthermore, active appendiceal inflammation was numerically associated with a 2.7-fold increased hazard of relapse post-appendicectomy (p=0.12) Together, these findings support a potential link between appendiceal histopathology and the clinical course of UC.

Our results align with previous observational studies reporting a high prevalence of active appendiceal inflammation in UC patients, regardless of disease activity or extent.[6,9,10] Neutrophilic infiltration, notably both in the lamina propria and epithelium of the appendix, was frequent (59% and 66%, respectively). Importantly, moderate neutrophilic infiltration in the lamina propria of the appendix emerged as a potential histopathological marker associated with relapse, consistent with prior research identifying neutrophilic activity as an indicator of colonic mucosal inflammation and predictor of relapse.[14,16] Extensive epithelial neutrophil involvement (> 5% crypts involved) significantly correlated with higher relapse rates, reinforcing the clinical relevance of neutrophilic infiltration patterns as a prognostic marker. These findings in quiescent UC support the theory that the appendix may serve as a persistent immune-priming site in UC, potentially contributing to ongoing subclinical inflammation and relapse despite apparent mucosal healing in the colon.[7,17-19] Among patients with inflamed appendices, those who relapsed had a longer disease duration compared to those who maintained remission. Given the overall reduction in relapse rates post-appendicectomy, this observation that non-relapsing patients with inflammation had a shorter disease duration supports the hypothesis that appendicectomy might be more effective when performed earlier in the disease course.

Appendiceal fibrosis, by contrast, was associated with a numerically lower relapse rate compared to non-fibrotic appendices (13% vs 28%), suggesting it may represent a post-chronic active inflammatory state that has transitioned to an immunologically inactive phase. However, these possibilities cannot be differentiated with histology assessment at a single time point, and fibrosis may also reflect physiological, age-related changes unrelated to disease activity.

The association between PARP and higher RHI scores (PARP+: RHI 15.5 vs PARP – : RHI 5.0, p=0.005) aligns with previous suggestions that peri-appendiceal inflammatory changes may indicate active local immune processes influencing the clinical course of UC.[6,8] Although PARP has been correlated with a more aggressive disease course,[20]

its utility as a clinical indicator for underlying active appendiceal inflammation appears limited. Only a minority of patients (31%) with a histologically confirmed active appendiceal inflammation exhibit a visible PARP during colonoscopy. As such, PARP may primarily identify a small subset of patients with pronounced local inflammation, and additional diagnostic approaches modalities may be needed to reliably detect appendiceal involvement.

Macroscopic appendiceal characteristics observed in this study further support this need. Patients who relapsed had a significantly larger maximum appendiceal diameter compared to those who remained in remission (9 mm vs 7 mm, p=0.03). This suggests that the appendiceal diameter might serve as a clinically accessible, preoperative predictor of relapse risk. This finding is consistent with prior studies in the general population, where an increased appendiceal diameter measured by ultrasound is an established diagnostic criterion for acute appendicitis.[21] Non-invasive modalities such as intestinal ultrasound could therefore offer valuable support in patient stratification, warranting further research in the context of UC.

The strength of this study includes its prospective design within a rigorous randomised trial setting and blinded centralised histological assessment. A key limitation of this study is the inability to directly assess the therapeutic impact of appendicectomy, as appendix specimens from the control (non-appendicectomised) group were unavailable. This prohibits any conclusions on causality, and limits the interpretation of the clinical relevance of the effect of appendectomy on recurrence in patients with active appendiceal inflammation. Consequently, the identification of preoperative indicators – such as PARP or increased appendiceal diameters – becomes critical for inferring treatment effect in future research. Early findings from the ACCURE trial suggest that these markers may help identify patients most likely to benefit from appendicectomy. Hypothetically, if the procedure reduces relapse risk by 20% and this benefit is concentrated in patients with PARP or larger appendiceal diameter, such markers would enable targeted patient selection. Another limitation is that the study was not powered to detect differences in histopathological subgroups, limiting statistical significance.

In conclusion, our findings demonstrate that active appendiceal inflammation is frequently present in patients with quiescent UC and may be associated with an increased risk of relapse, supporting a potential pathogenic role of the appendix in UC. Whether this is the group most benefitting from appendectomy remains to be determined. Future larger-scale studies are warranted to further investigate

the prognostic value of active appendiceal inflammation and evaluate surrogate markers – such as PARP and intestinal ultrasound – as non-invasive indicators of appendiceal involvement.

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Part III

Appendectomy for inducing remission in ulcerative colitis

7

Chapter 7

Efficacy of appendicectomy versus Janus kinase inhibitor in inducing remission in biologic-failed patients with active ulcerative colitis: one-year results of a multicentre prospective cohort study (COSTA)

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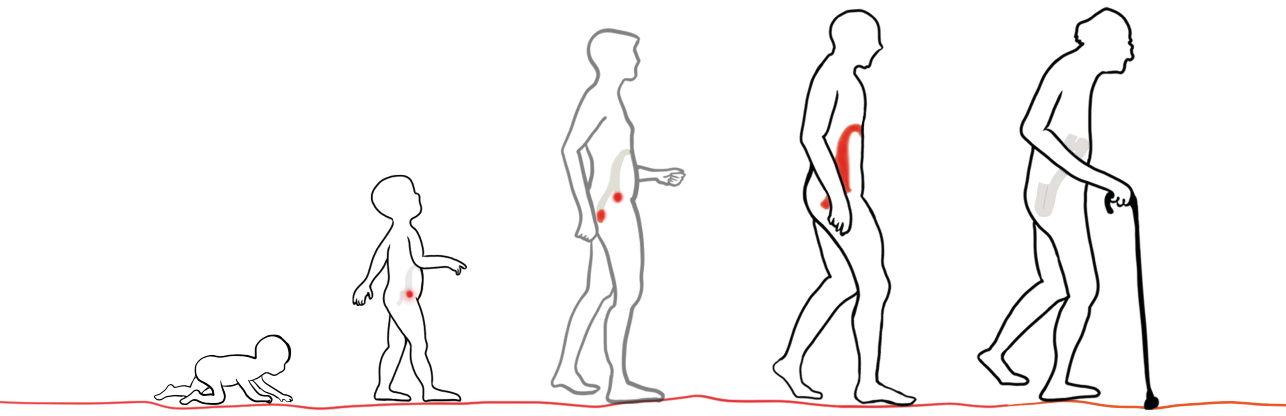

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Abstract

Background

We evaluated the efficacy of laparoscopic appendicectomy in inducing remission, compared with Janus Kinase (JAK) inhibitor therapy, in patients with active ulcerative colitis who failed biologic therapy.

Methods

In this multicentre, patient-preference, interventional cohort trial, patients with a total Mayo score (TMS) of 5-12 with endoscopic subscore ≥2, despite biologic therapy were offered one of three treatments: laparoscopic appendicectomy (intervention); switching medical treatment to a JAK-inhibitor (control); (procto)colectomy (registry). The primary outcome was clinical remission (TMS ≤2, no subscore >1) at 12 months without therapy failure (defined as [re]start of oral corticosteroids; switch to other advanced therapies; initiation experimental treatment in a clinical trial; (procto)colectomy). Secondary outcomes included corticosteroid-free clinical remission without therapy failure, time-to-first symptomatic remission, clinical response, endoscopic outcomes, therapy failure, colectomy rates, and safety.

Results

116 patients were included in the modified intention-to-treat-analysis (appendicectomy: 67; JAK-inhibitor: 49). A higher proportion of patients were in clinical remission at 12 months in the appendicectomy group compared to the JAK-inhibitor group (32.8% vs 12.2%; difference, 20.6 percentage points; 95% CI, 6.1-35.1; p=0.01). Corticosteroid-free clinical remission was attained in 32.8% vs 12.2% (difference, 20.6 percentage points; 95% CI, 6.1-35.1; p=0.01), clinical response in 73.1% vs 53.1% (difference, 20.1 percentage points; 95% CI, 2.5-37.6; p=0.03), and endoscopic response in 48.4% vs 25.6% (difference, 22.9 percentage points; 95% CI, 5.0-40.7; p=0.02). Time-to-symptomatic remission (HR 1.06; 95%CI 0.62-1.82; p=0.82), therapy failure (58.2% (39/67) vs 57.1% (28/49); difference, 1.1 percentage points; 95% CI, −17.1-19.3; p=0.91) and colectomy rates (9.0% vs 8.2% difference, 0.8 percentage points; 95% CI, −9.5-11.1; p=1.0) were similar. Appendicectomy-related complications occurred in 4% of patients and were all minor.

Conclusion

Appendicectomy as an adjunct to advanced therapy in biologic-exposed patients with active ulcerative colitis was more effective than switching to a JAK-inhibitor in achieving clinical remission at 12 months, and can be performed safely in this patient group.

Funding

ZonMW; Clinicaltrials.gov number NCT03912714.

Research in context

Evidence before this study

We conducted a comprehensive literature search in PubMed from inception to Dec18, 2024, using the terms: ("appendectomy"[MeSH Terms] OR "append*"[Title/Abstract]) AND ("colitis, ulcerative"[MeSH Terms] OR "ulcerative colitis"[Title/Abstract] OR "ulcerative proctocolitis"[Title/Abstract]) AND ("induction, remission"[MeSH Terms] OR "colitis, ulcerative / surgery*"). This search identified several retrospective cohort studies and a limited number of prospective observational studies suggesting potential benefit of appendicectomy in therapy-refractory ulcerative colitis, particularly proctitis. However, these studies were limited by retrospective design, small sample sizes, and heterogeneous endpoints. Importantly, no prospective studies had directly compared appendicectomy with advanced pharmacologic therapies, nor had any focused on biologic-exposed patients. Additionally, one recently published randomised controlled trial (ACCURE) examined appendicectomy for preventing relapse in patients with ulcerative colitis in remission and demonstrated a reduction in relapse rates.

Added value of this study

The COSTA study is the first prospective comparative study evaluating appendicectomy against a guideline-recommended advanced therapy (Janus kinase [JAK] inhibitors) in patients with moderately to severely active ulcerative colitis who failed biologic therapy. In a pragmatic, multicentre design using patient-preference assignment, we found significantly higher rates of clinical and corticosteroid-free remission at 12 months without therapy failure in the appendicectomy group compared to JAK-inhibitor group. This benefit extended to endoscopic outcomes, with no significant differences in serious adverse events or colectomy rates. These findings demonstrate that appendicectomy can be a safe and effective therapeutic strategy in biologic-exposed patients.

Implications of all the available evidence

When combined with prior observational data and the findings from the ACCURE trial, our study suggests that appendicectomy may alter the disease course of ulcerative colitis and offers a feasible, low-risk therapeutic option for patients failing biologic therapy. It supports reconsideration of appendicectomy not only as an experimental option but as a potential adjunct to medical therapy in selected patients. These findings may contribute to clinical decision-making and to future guideline recommendations for the management of biologic-refractory ulcerative colitis.

Introduction

Ulcerative colitis is a chronic inflammatory condition affecting the rectum and colon, presenting with symptoms such as increased stool frequency, rectal bleeding and urgency.[1] Disease management is guided by extent and severity, with treatment options ranging from mesalamine, corticosteroids, and immunosuppressants to more advanced therapies such as biologic agents (e.g., anti-cytokines and anti-integrins) and small molecules (e.g. Janus kinase [JAK] inhibitors and Sphingosine-1-phosphate receptor modulators).[1-3] These therapies aim to control symptoms and achieve mucosal healing.[2,4,5] Despite therapeutic advances, 10-30% of patients remain refractory to medical therapy and ultimately require proctocolectomy.[6] Furthermore, long-term usage of medical therapies carries risks, including increased incidence of infections, cardiovascular events and malignancy.[7]

It has been postulated that appendicectomy could modify the disease course of ulcerative colitis. In a case series of patients with ulcerative proctitis,[8] 40% achieved complete remission following appendicectomy. A pilot study further demonstrated clinical response in approximately one-third of patients with therapy-refractory colitis who were initially referred for colectomy.[9] with 24% of patients showing endoscopic improvement after a median follow-up of eight years.[10] Given that laparoscopic appendicectomy is a minimally invasive procedure with a favourable safety profile, its potential as a disease-modifying intervention warrants further investigation.

Despite promising observational data, no prospective clinical trial has directly compared appendicectomy with medical therapy in active ulcerative colitis. Additionally, data on its effectiveness in biologic-exposed patients remain limited. This underscores the need for well-designed comparative studies to determine its potential therapeutic role. Therefore, we aimed to evaluate the efficacy of laparoscopic appendicectomy in inducing remission at 12 months, compared with JAK-inhibitor therapy, in patients with moderately to severely active ulcerative colitis despite optimised biologic therapy.

Methods

Study design and oversight

This investigator-initiated, multicentre, patient-preference, controlled interventional cohort trial was conducted at five centres in the Netherlands. Ethical approval was

obtained on August 21, 2018. The protocol was approved by the central ethics committee and institutional review board at each participating hospital, and written informed consent was obtained from all patients. The trial was prospectively registered at ClinicalTrials.gov (NCT03912714) prior to any study-related intervention. The study protocol evolved during the trial, including refinements to outcome definitions and the evolution of the comparator arm. All amendments were approved by the central ethics committee. These changes were made prior to any formal unblinded data analysis, and no outcome data influenced the decision to make these changes. A detailed overview of protocol changes, including justifications, timelines and affected patients, is provided in the Supplementary (pp 3-4 and p 11). The amendments were made to enhance clarity, ensure alignment with emerging clinical standards, and improve the scientific rigour of the study.

The trial was funded by ZonMw (DoelmatigheidsOnderzoek program; Project Number 852002005). The funder had no role in the design of the study, data collection, data analysis, interpretation of the results, or the decision to submit the manuscript for publication.

Patients

Patients were eligible if they were 16 years or older and had moderately to severely active ulcerative colitis, which was defined as a total Mayo score of 5 to 12 including an endoscopic subscore of 2 or 3, despite treatment with optimised biologics (biologic-exposed) at the time of screening. The Mayo score is a 4-point scale consisting of four subscores: rectal bleeding, stool frequency, physician's global assessment and endoscopic findings.[11] Each subscore ranges from 0 to 3, with the total Mayo score calculated as the sum of these components (range 0 to 12). Eligible patients were being considered for JAK-inhibitor or restorative proctocolectomy following a multidisciplinary team meeting. Patients previously exposed to JAK-inhibitors were eligible for appendicectomy if they had not been previously counselled on this treatment option during physician interactions. Patients were excluded from the trial if they had prior appendicectomy; suspected Crohn's disease; toxic megacolon or severe acute colitis requiring hospitalisation; or history or suspicion of colonic dysplasia or malignancy. Patients requiring more than 20 mg of oral prednisone daily or those with surgical contraindications were deemed ineligible for appendicectomy to ensure patient safety.

Trial procedures

At screening, the Mayo score was assessed in all patients, and an endoscopy was performed to confirm active disease (Mayo 2 or 3). Eligible patients were counselled using a patient preference model during an outpatient visit and were offered three treatment options: 1) laparoscopic appendicectomy (intervention group); 2) initiation of a JAK-inhibitor (control group); 3) (procto)colectomy, with or without ileo-anal pouch anastomosis (registration arm).

Patients in the appendicectomy group were allowed to continue their biologic therapy at stable dose but were not switched to a different advanced therapy. Those in the JAK-inhibitor group stopped biologics and started JAK-inhibitor at registered doses (e.g., tofacitinib, filgotinib or upadacitinib), while those in the proctocolectomy group underwent standard surgical management with subsequent withdrawal of all medication.

A postoperative outpatient visit was scheduled within 9 weeks to monitor for surgical complications. Efficacy assessments were conducted at predefined time points at 3, 6, and 12 months post-treatment, including partial Mayo score assessment, medication usage, adverse events monitoring, and therapy failure evaluation. Follow-up endoscopic evaluations in the appendicectomy group were performed at 6 and at 12 months postoperatively for assessment of the full Mayo score. In the JAK-inhibitor group, endoscopy was performed within 12 months according to clinical guidelines. Endoscopy was conducted earlier if deemed indicated for ongoing exacerbation or consideration of treatment modification. Follow-up endoscopies were centrally and blindly reviewed by three IBD-experts (ML, RG and GD). Follow-up assessments were conducted via scheduled outpatient clinic visits, telephonic consultations or electronically through the MyIBDcoach application or as hard copies.[12,13] The study design is presented in the Supplemental Material Figure S1.

Efficacy and safety assessments

The primary outcome was the proportion of patients in clinical remission at 12 months without therapy failure. Clinical remission was defined as a total Mayo score of 2 or lower, with no individual subscore exceeding 1 point. Therapy failure was defined as the occurrence of any of the following within 12-months post-treatment: (re)start of oral corticosteroids; switch to a different biologic or small molecule

therapy; start of experimental treatment for active ulcerative colitis in a clinical trial; (procto)colectomy.

Key secondary outcomes were: corticosteroid-free clinical remission at 12 months without therapy failure (i.e., oral corticosteroids had to be withdrawn for at least 12 weeks before week 52); time to symptomatic remission (i.e., partial Mayo score≤2 with no individual subscore>1); clinical response (i.e., ≥2 point TMS reduction and ≥30% decrease from baseline) at 12 months; endoscopic improvement (i.e., endoscopic subscore ≤1) at 6 and 12 months; endoscopic response (i.e., decrease in endoscopic subscore ≥1 point from baseline) at 6 and 12 months; therapy failure within 12 months, and proportion of patients undergoing (procto)colectomy within 12 months. The partial Mayo score excludes the endoscopic subscore and ranges from 0 to 9.[14] Surgery-related complications were reported using the Clavien-Dindo classification, with minor complications defined as grade ≤II and major as grade ≥IIIa.[15] Adverse events were reported and graded according to the Common Terminology Criteria for Adverse Events, version 5.0, 2017).

Statistical analyses

Sample size calculations were based on expected clinical remission rates at 12 months of 40% of the patients in the appendicectomy group and 17% in the JAK-inhibitor group. The 17% estimate was based on remission rates reported in the OCTAVE clinical trials.[16] Assuming an initial 1:1 enrolment ratio between the two groups, a sample size of 60 patients per group was required to achieve 80% power with a two-sided alpha of 0.05.

Baseline demographic and clinical characteristics of the patients were summarised using descriptive statistics. The primary and secondary efficacy outcome analyses followed a modified intention-to-treat approach, including all patients who underwent appendicectomy or received at least one dose of the JAK-inhibitor in the corresponding treatment group. Binary efficacy outcomes were compared between the appendicectomy and JAK-inhibitor groups using Fisher's exact test and Pearson chi-square test, as appropriate, reported with absolute risk difference (ARD) and 95% confidence intervals (CI). An additional logistic regression analysis on the primary outcome was used to adjust for baseline confounders. Prespecified confounders included sex (male vs female), age (continuous), disease extent (E1 vs E2 vs E3), severe endoscopic mayo score (Mayo 3), concomitant oral corticosteroid

usage (yes vs no), and the number of prior advanced medical therapies (continuous). Logistic regression analyses were performed for 6-month endoscopic outcomes (i.e., endoscopic improvement and endoscopic response) adjusting for endoscopy indication (follow-up or exacerbation suspicion), and results were reported as adjusted odds ratios with 95% CIs. Time to first symptomatic remission was analysed using Kaplan-Meier survival analysis, with group differences assessed using the log-rank test. A Cox proportional hazards model was used to obtain the hazard ratio and 95% CI.

Patients with missing data for the primary outcome were considered non-responders (failures). Missing data were not imputed for endoscopic outcomes at 6 months, as these assessments were not routinely scheduled for patients in the JAK-inhibitor group. Missing data for these outcomes were therefore not due to random loss to follow-up, but are instead a direct result of the follow up of the study design. Missing 12-month follow-up endoscopies were considered failures for endoscopy outcomes at 12 months. Other missing secondary outcome data were not imputed. Sensitivity analysis with a per-protocol approach was also performed, including only patients from the modified intention-to-treat population who had no major protocol deviations, specifically those who initiated JAK-inhibitor treatment while awaiting appendicectomy and those without an available baseline endoscopy. The safety population for adverse events included all patients who underwent appendicectomy or received at least one dose of the JAK-inhibitor. All statistical analyses were conducted using SPSS Version 28.0.1.1 or Stata version 17.0, with two sided p-values <0.05 considered statistically significant.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was provided from all patients.

Role of the funding source

The funding had no involvement in the design of the study, the collection or analysis of data, the interpretation of the results, or the preparation of the manuscript.

Results

Between August 24, 2018 and December 15, 2023, a total of 211 patients were screened for eligibility, of whom 125 (59%) patients were enrolled in the study (Figure 1). Among these, 69 patients opted for appendicectomy, 51 for a JAK-inhibitor, and five for proctocolectomy. Three patients (two in the appendicectomy group and one in the JAK-inhibitor group) were excluded from the analysis due to a change of diagnosis to Crohn's disease; one JAK-inhibitor (tofacitinib) patient withdrew consent post-inclusion. This resulted in a total of 116 evaluable patients in the modified intention-to-treat analysis. Baseline demographic and clinical characteristics were generally balanced across the treatment groups (Table 1). The median total Mayo score and number of prior advanced medical therapies were similar in the appendicectomy and JAK-inhibitor groups (TMS: 9.0 [IQR, 7.0 to 10.0] vs 9.0 [IQR, 8.0 to 10.0], p=0.37; prior advanced therapies: 2.0 [IQR, 1.0 to 3.0] vs 2.0 [IQR, 1.0 to 2.5], p=0.90, respectively). However, significant differences included a lower proportion of patients in the appendicectomy group were receiving concomitant oral corticosteroids compared to the JAK-inhibitor group (26.9% [18/67] vs 44.9% [22/49], p=0.04). Additionally, at screening, the majority of patients in the appendicectomy group were on anti-TNF therapy (47.8% [32/67]), whereas most in the JAK-inhibitor group were on integrin receptor antagonists (36.7% [18/49]; p=0.002). Other differences were numerical and not statistically significant, including a lower proportion of male patients in the appendicectomy group compared to the JAK-inhibitor group (37.3% [25/67] vs 53.1% [26/49], p=0.09), a shorter median disease duration (6.6 years [IQR 2.8 to 13.5] vs 7.8 years [IQR, 3.1 to 15.2], p=0.54), and lower prevalence of pancolitis (43.3% [29/67] vs 59.2% [29/49], p=0.18). Furthermore, the median time since start advanced therapy at screening was 10.4 months (IQR, 6.0 to 17.3) in the appendicectomy group and 8.6 months (IQR, 3.5-17.0) in the JAK-inhibitor group (p=0.11). Notably, five patients (7.5%) in the appendicectomy group initiated small molecule therapy (two tofacitinib, two filgotinib, one ozanimod) while awaiting appendicectomy.

Only five patients (4%, [5/121]) directly opted for proctocolectomy after counselling. These patients had distinct baseline characteristics compared to the other treatment groups (Table S1). They had a longer disease duration (median 8.9 years [IQR 6.5 to 14.1]) and a higher burden of prior exacerbations (median 5.0 [IQR, 3.5 to 18.0]). The majority (80% [4/5]) had pancolitis, a higher median total Mayo score (10.0 [IQR 9.0 to N/A]), and a notably higher proportion (80% [4/5]) were on concomitant oral corticosteroids at baseline.

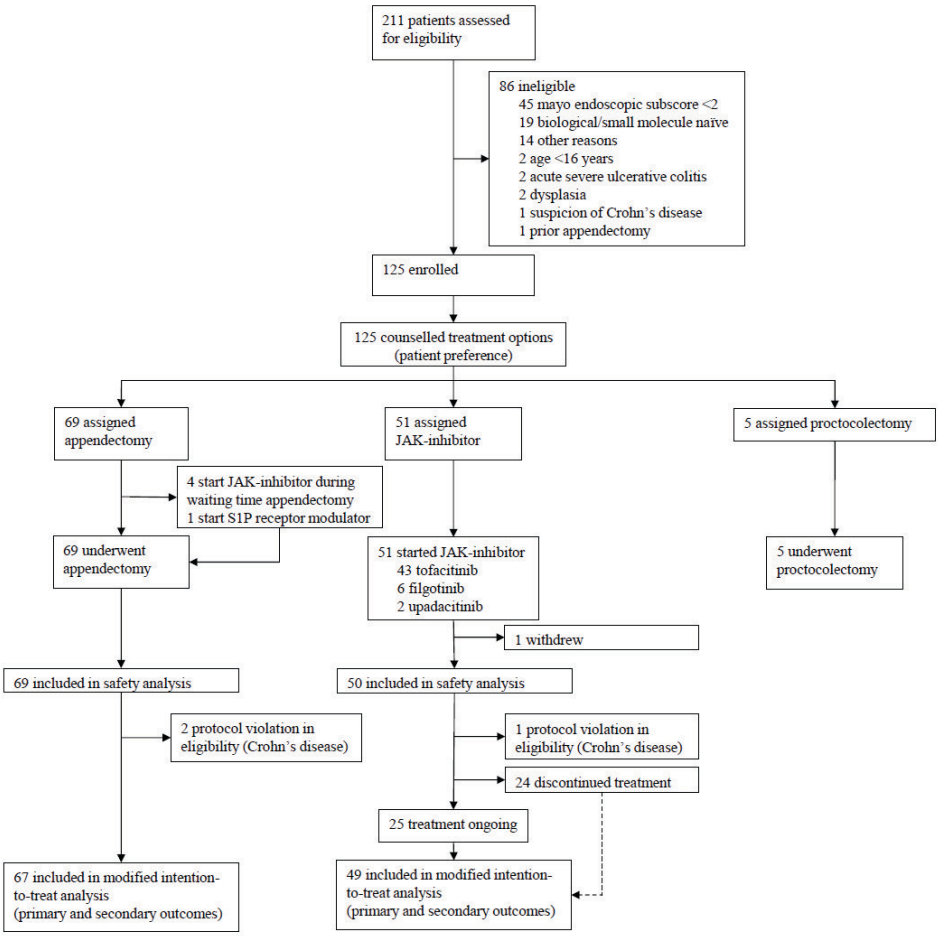


Figure 1. Trial profile

Clinical remission at 12 months

At 12 months, a higher proportion of patients achieved clinical remission without therapy failure in the appendicectomy group compared to the JAK-inhibitor group (32.8% vs 12.2%; difference, 20.6 percentage points; 95% CI, 6.1 to 35.1; p=0.01) (Figure 2). These results remained consistent after adjusting for prespecified confounders (p=0.02; Table S2) and in the sensitivity analysis (p=0.03; Table S3). One patient (1%) in the appendicectomy group and three (6%) in the JAK-inhibitor group were classified as treatment failures due to missing follow-up endoscopy (Table S4). The appendicectomy patient had discontinued biologic therapy for ulcerative colitis after achieving clinical remission but later required anti-TNF therapy for pyoderma gangrenosum. Among the three JAK-inhibitor patients classified as failures due to

missing endoscopy, two remained on tofacitinib and with faecal calprotectin levels below 50 µg/g, while one had an elevated faecal calprotectin level (737 µg/g).

Table 1. Baseline patient- and disease characteristics of the patients included in the modified intention-to-treat analysis

Characteristic	Appendicectomy N=67	JAK-inhibitor (control) N=49	P-value
Gender, male — no. (%)	25 (37.3)	26 (53.1)	0.09
Age - yr	39 (27.0-47.0)	42.0 (33.0-55.0)	0.10
Body-mass index* — kg/m^2	24.3 (22.1-27.6)	24.7 (22.0-27.3)	0.82
Smoking, former — no. (%)	27 (40.3)	20 (40.8)	0.96
Disease duration — yr	6.6 (2.8-13.5)	7.8 (3.1-15.2)	0.54
Prior exacerbations — no.	5.0 (3.0-7.0)	4.0 (3.0-7.0)	0.49
Duration since start current exacerbation — mo.	8.4 (5.6-12.5)	5.4 (1.5-16.0)	**0.05**
Disease extent			0.18
Proctitis (E1) — no. (%)	9 (13.4)	3 (6.1)	
Left-sided (E2) — no. (%)	29 (43.3)	17 (34.7)	
Pancolitis (E3) — no. (%)	29 (43.3)	29 (59.2)	
Endoscopic Mayo score			0.15
Mayo 2 — no. (%)	35 (52.2)	18 (36.7)	
Mayo 3 — no. (%)	29 (43.3)	24 (49.0)	
Not performed (confirmed by calprotectin >150µg/g) — no. (%)	3 (4.5)	6 (12.2)	
Partial Mayo score†	6.0 (4.0-7.0)	6.0 (5.0-7.0)	0.41
Total Mayo score‡	9.0 (7.0-10.0)	9.0 (8.0-10.0)	0.37
Oral corticosteroids as current concomitant medical therapy — no. (%)	18 (26.9)	22 (44.9)	**0.04**
Advanced medical therapy at screening			
TNFα antagonists — no. (%)	32 (47.8)	13 (26.5)	**0.02**
Integrin receptor antagonist — no. (%)	17 (25.4)	18 (36.7)	0.19
IL-12 and/or IL-23 antagonist — no. (%)	12 (17.9)	7 (14.2)	0.60
JAK inhibitors — no. (%)	4 (6.0)	0 (-)	0.14
S1P receptor modulator — no. (%)	0 (-)	0 (-)	
Time since start – mo.	10.4 (6.0-17.3)	8.6 (3.5-17.0)	0.11
Prior advanced medical therapy			
Prior advanced medical therapies — no.	2.0 (1.0-3.0)	2.0 (1.0-2.5)	0.90
TNFα antagonists — no. (%)	36 (53.7)	31 (63.3)	0.30
Integrin receptor antagonist — no. (%)	15 (22.4)	9 (18.4)	0.60
IL-12 and/or IL-23 antagonist — no. (%)	3 (4.5)	3 (6.1)	0.70
JAK inhibitors — no. (%)	0 (-)	2 (4.1)	0.18
S1P receptor modulator — no. (%)	0 (-)	0 (-)	

Data are n (%) or median (IQR).
** Body-mass index is the weight in kilograms divided by the square of the height in meters.*
† The partial Mayo Score is a non-invasive 9-point score which comprises three components of the total Mayo Score (stool frequency, rectal bleeding and Physician's global assessment).
‡The total Mayo score is a 12-point score of four categories (stool frequency, rectal bleeding, physician global assessment and endoscopic appearance).
Data were missing for 0 patients in the appendicectomy group, and 3 in the JAK-inhibitors group for body mass index; 0, and 4, respectively, for smoking; 7, and 2 for prior number of exacerbations; 0, and 1 for duration since start current exacerbation; 3, and 6 for endoscopy; 3, and 6 for total Mayo score; 4 and 11 for time since start advanced medical therapy till intervention (appendicectomy or JAK-inhibitor).

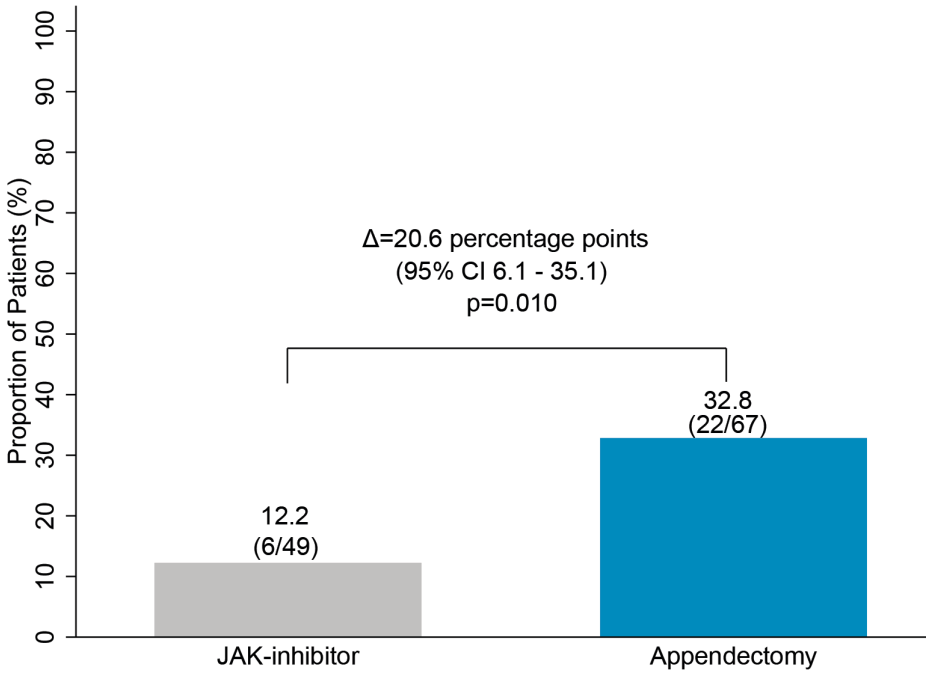


Figure 2. Primary Outcome Clinical Remission at 12 months After Treatment Without Therapy Failure.*

Clinical remission was defined as a total Mayo score of 2 or lower, with no individual subscore exceeding 1 point. Therapy failure was defined as the occurrence of any of the following post-treatment within the 12-month follow-up period: (re)start of oral corticosteroids, switch to a different biologic or small molecule therapy, start of trial therapy for active ulcerative colitis, or (procto)colectomy.

Treatment modification during follow-up and therapy failure

Details of advanced medical therapy usage during follow-up are shown in Figure S2. Among the 22 appendicectomy responders (i.e., achieved clinical remission), background maintenance therapies included infliximab (n=7), adalimumab (n=5), vedolizumab (n=2), ustekinumab (n=4), tofacitinib (n=3) or filgotinib (n=1). Four patients discontinued all ulcerative colitis medications (two infliximab, one adalimumab, one tofacitinib), and one remained on immunomodulators alone. Among the 45 appendicectomy patients who failed to achieve clinical remission, 73.3% (33/45) transitioned to another advanced therapy, of whom six subsequently underwent proctocolectomy and 13.3% (6/45) started oral steroids, while the remaining 6 (13.3%) had persistent active disease without therapy escalation.

Among the six JAK-inhibitor responders, all remained on standard tofacitinib therapy. Among the 43 JAK-inhibitor failures, 41.9% (18/43) initiated another advanced medical therapy, of whom one subsequently underwent proctocolectomy and 9.3% (4/43) started oral steroids, while the remaining 15 (34.9%) had persistent active disease without further treatment modification at 12 months.

Secondary efficacy outcomes

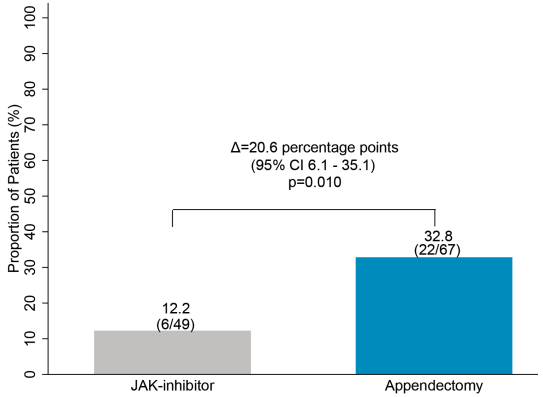
Corticosteroid-free clinical remission at 12 months without therapy failure was achieved more frequently in the appendicectomy group than the JAK-inhibitor group (32.8% [22/67] vs 12.2% [6/49]; difference, 20.6 percentage points; 95% CI, 6.1 to 35.1; p=0.01). Time to first symptomatic remission was similar between groups (26 weeks [IQR, 14 to 52] vs 25 weeks [IQR, 14 to 52]; HR 1.06; 95% CI 0.62 to 1.82; p=0.82).

A higher percentage of patients with clinical response at 12 months was observed in the appendicectomy group compared to the JAK-inhibitor group (73.1% (49/67) vs 53.1% (26/49); difference: 20.1 percentage points; 95% CI, 2.5 to 37.6; p=0.03).

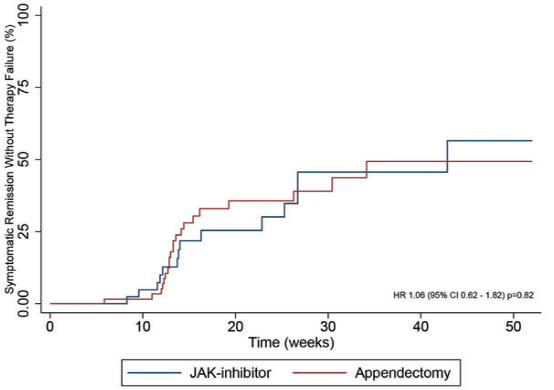
At 6 months, 43.5% (24/62) of the patients in the appendicectomy group undergoing endoscopy showed endoscopic improvement and 45.0% (27/60) endoscopic response, which were higher than JAK-inhibitors in which 6-month endoscopy was performed (endoscopic improvement: 17.1% [6/35]; OR, 3.45, 95% CI, 1.12 to 10.47; p=0.03; endoscopic response: 21.2% [7/33]; OR 2.66, 95% CI 0.89 to 7.98; p=0.08) (Table S2).

At 12 months, endoscopic improvement rates were higher in the appendicectomy group compared to the JAK-inhibitor group (55.2% [37/67] vs 32.7% [16/49], difference 22.6 percentage points, 95% CI, 4.8 to 40.3; p=0.02), as well as endoscopic response rates (48.4% [31/64] vs 25.6% [11/43], difference 22.9 percentage points; 95% CI, 5.0 to 40.7; p=0.02). The therapy failure rate was comparable between groups (58.2% (39/67) vs 57.1% (28/49); difference 1.1 percentage points, 95% CI, −17.1 to 19.3; p=0.91). Colectomy percentages within 12 months between the two groups were also similar (appendicectomy 9.0% (6/67) vs JAK-inhibitor 8.2% (4/49), difference 0.8 percentage points, 95% CI, −9.5 to 11.1; p=1.0).

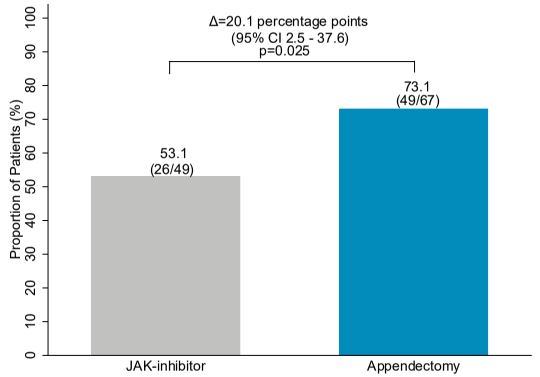
A. Corticosteroid-free remission at 12 months without therapy failure*



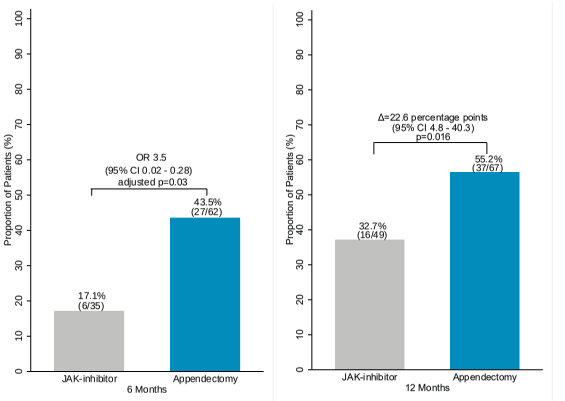
B. Time to first symptomatic response without therapy failure**



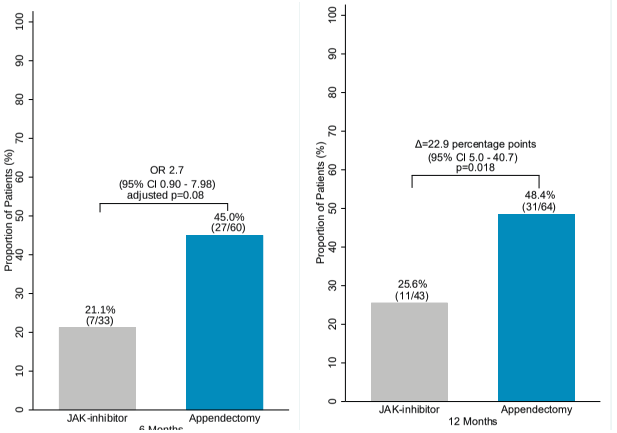
C. Clinical response at 12 months***



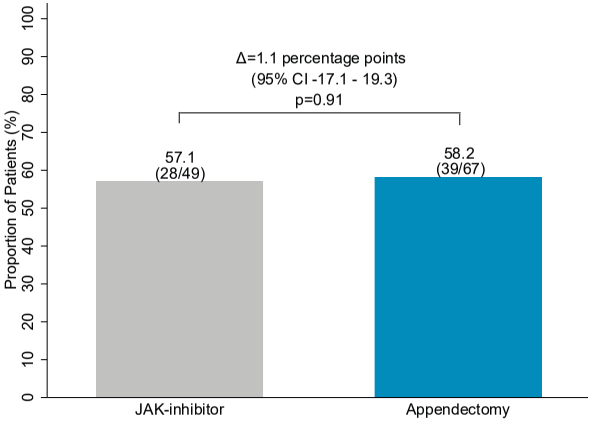
D. Endoscopic improvement at 6 and 12 months months****



E. Endoscopic response at 6 and 12 months*****



F. Therapy failure within 12 months post-treatment******



G. (procto)colectomy within 12 months

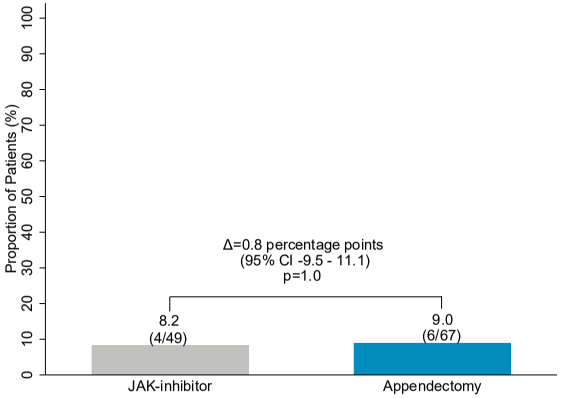


Figure 3. Key secondary outcomes

* *Defined as no corticosteroid-usage ⩾12 weeks prior to 12 month follow-up visit*

** *Symptomatic remission was defined as a partial Mayo score⩽2 with no individual subscore exceeding 1 point. Time was from the start of treatment to first follow-up visit data where symptomatic remission was achieved without therapy failure. Patients who did not achieve symptomatic remission without therapy failure during the 12-month follow-up period were censored at their last recorded follow-up contact date.*

*** *Clinical response was defined as ⩾2 point TMS reduction and ⩾30% decrease from baseline.*

**** *Endoscopic improvement was defined as a endoscopic subscore ⩽1.*

***** *Endoscopic response was defined as decrease in endoscopic subscore ⩾1 point from baseline.*

****** *Therapy failure was defined as the occurrence of any of the following post-treatment within the 12-month follow-up period: (re)start of oral corticosteroids, switch to a different biologic or small molecule therapy, start of trial therapy for active ulcerative colitis, or (procto)colectomy.*

Safety

Postoperative complications occurred in 3 of 69 (4.3%) appendicectomy patients, all classified as minor (Figure 4A). These included one case of postoperative urinary retention, one suspected early abscess formation managed with oral antibiotics, and one superficial wound infection treated with antibiotics. Among these patients, one (33%) achieved clinical remission at 12 months. Additionally, two patients (2.9%) were incidentally diagnosed with a grade I neuroendocrine tumour of the appendix, requiring no further treatment post-appendicectomy.

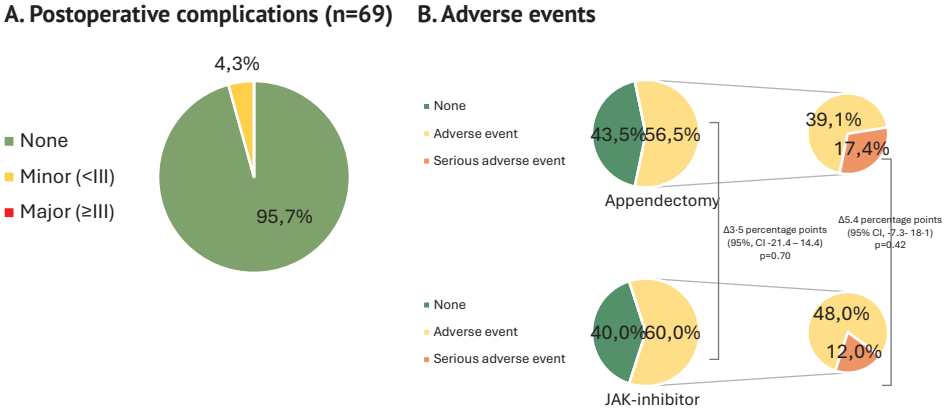


Figure 4. Safety

Adverse events were reported in 56.5% (39/69) appendicectomy patients and 60.0% (30/50) of JAK-patients (difference 3.5 percentage points, 95%, CI -21.4 to 14.4; p=0.70) (Figure 4B and Table S5). The most frequently reported adverse events (>5%) were: gastro-intestinal disorders related to IBD (14.5% vs 8.0%), infections (7.2% vs 10.0%), gastrointestinal disorders unrelated to IBD (4.3% vs 10.0%), musculoskeletal disorders (7.2% vs 4.0%), nervous system disorders (2.9% vs 10.0%), skin disorders (5.8% vs 6.0%) and surgical procedure-related events (5.8% vs 6.0%).

Serious adverse events (SAEs) occurred at similar rates between the groups, with 17.4% (12/69) of appendicectomy patients and 12.0% (6/50) of JAK-inhibitor patients (difference 5.4 percentage points, 95% CI, -7.3 to 18.1; p=0.42). The most common serious adverse events were hospitalisations due to ulcerative colitis, accounting for eight out of 12 SAEs in the appendicectomy group and four of six SAEs in the JAK-inhibitor group. Other reported serious adverse events in the appendicectomy

group included postoperative urinary retention, transient ischemic attack occurring post-caesarean section, severe esophagitis following initiation of tofacitinib, and hematemesis due to Mallory-Weiss syndrome. In the JAK-inhibitor group, additional serious adverse events included acute appendicitis and hospital admission for spontaneous rectal prolapse.

Discussion

The COSTA study demonstrated that appendicectomy as adjunct to biologic therapy effectively induced remission in 33% of patients with moderately to severely active ulcerative colitis refractory to biologic therapy, achieving significantly higher remission rates than JAK-inhibitors at 12 months. Rates of corticosteroid-free remission, clinical response, endoscopic response and endoscopic improvement were consistently ~20% higher in the appendicectomy group. Time to symptomatic remission and therapy failure rates, including corticosteroid usage, escalation to a different advanced medical therapy, trial therapy or proctocolectomy were comparable between groups. Appendicectomy was well-tolerated, with a low postoperative complication rate (4%), reinforcing its potential as a promising adjunctive or alternative intervention for biologic-refractory patients.

This is the first prospective comparative trial directly evaluating appendicectomy with medical therapy in a biologic-exposed population, demonstrating superior remission rates with a comparable safety profile. These findings align with prior observational studies and another randomised trial, showing effectiveness of appendicectomy in inducing and maintaining remission.[8,9,17] Remission rates (33% for appendicectomy, 12% for JAK-inhibitors) were slightly lower than in other reported studies, possibly due to differences in patient population. Unlike Bolin et al., who focused on ulcerative proctitis, our cohort more closely resembled the pilot trial by Stellingwerf et al.,[18] which reported 18% endoscopic remission at 12 months. In a subsequent follow-up by Reijntjes et al., endoscopic improvement was observed in 24% of patients, further supporting the long-term benefit of appendicectomy.[10] Additionally, our population was more treatment-refractory than that in the tofacitinib trial by Sandborn et al.[16], as all patients had failed prior biologic therapy before enrolment. Furthermore, their 12 months follow-up cohort included only patients who had achieved clinical response to induction therapy, which had a significant effect on 12-months outcomes. Although our cohort more closely resembled the pilot trial,[9] remission rates in our study exceed those

observed, possibly because the pilot cohort included colectomy-referred patients only who were hence even more refractory. This suggests the potential beneficial effectiveness of appendicectomy in a biologic-exposed population not specifically selected for proctocolectomy.

The lack of difference in time to symptomatic remission was unexpected, given the 8-week induction period for tofacitinib and the median 13-week response time in the pilot appendicectomy trial. The first follow-up visit at 3 months may have missed earlier symptomatic remission, while the more treatment-refractory cohort may have required longer before reaching symptomatic remission.

All secondary clinical and endoscopic efficacy outcomes also favoured appendicectomy by approximately 20%, reinforcing its potential not only to achieve clinical remission but also to induce endoscopic healing. Specifically, 81.8% (18/22) of patients in the appendicectomy group achieved clinical remission with endoscopic healing (Mayo 0) compared to 67% (4/6) in the JAK-inhibitor group.

Despite the higher remission rates in the appendicectomy group, therapy failure rates were comparable between groups, which may be attributed to the lack of standardization of medical therapy escalation in our study. Moreover, we did not observe a reduction in colectomy rates at 12 months. This may be explained by the small sample size and low number of colectomies (n=10; six in appendicectomy, four in JAK-inhibitor group), limiting the interpretability of this outcome. Longer follow-up is needed to assess whether appendicectomy could delay or prevent proctocolectomy over time. Notably, our 8.6% colectomy rate was lower than the 17% reported by Barnes et al.[19] within 12 months following a second advanced therapy switch. Larger studies are required to clarify the long-term impact of appendicectomy on colectomy risk. The low colectomy rates in both the intervention and control group also indirectly suggest that patients were satisfied with their chosen treatment. All patients had been counselled for the option of colectomy and were fully aware of the advantages and disadvantages. Notably, only a small minority (4% [5/121]), directly opted for colectomy, indicating that colectomy is generally considered a last-resort option.

The mechanisms underlying the effect of appendicectomy in ulcerative colitis remain unresolved, but are speculated to involve gut immune modulation and microbiota shifts. The appendix has been proposed to play a role in mucosal immune regulation, serving as a reservoir for inflammatory lymphoid cells and microbiota.[20-22]

Given long-term safety concerns with JAK-inhibitors, including risks of thromboembolism, infections, and potential malignancy, appendicectomy offers an attractive option for patients seeking non-pharmacologic treatment alternatives. However, patient selection remains crucial, as not all patients respond. The impact of appendicectomy on cancer risk remains uncertain.[23-25] In mouse models, appendicectomy has been shown to reduce colitis severity, but this was accompanied by impaired T-cell mediated immunosurveillance and increased colitis-associated carcinogenesis, likely due to altered mucosal immune responses.[26] In clinical practice, however, patients with ongoing inflammation face an increased risk of developing of colorectal cancer irrespective of appendicectomy, necessitating continued surveillance.[27]

The rapid evolution of advanced therapy complicates treatment decisions. At the start of this trial, JAK-inhibitors were reserved for patients with multiple biologic failures, but treatment paradigms have since shifted.[7] This shift makes it difficult to determine the optimal timing of appendicectomy within the treatment algorithm. Future studies should evaluate for which patients and when appendicectomy may be most beneficial. In combination with the results of our recently published ACCURE trial,[17] however, it appears attractive to consider appendicectomy rather early in the disease course.

Strengths of this study include its patient-preference comparative trial design, which limits patient-preference bias that would be more pronounced in a randomised trial comparing surgical and medical therapy. Besides, centralised and blinded endoscopic assessments ensured objective and standardised outcome evaluation. This study also has limitations. First, medical therapy escalation lacked standardization, which may have influenced therapy failure outcomes and made it challenging to isolate the effect of appendicectomy. Second, the imbalance in enrolment ratio (favouring appendicectomy) may indicate a form of selection bias, as some patients were specifically referred for appendicectomy since this treatment was only available within this trial. However, particularly in the early phase of the study, JAK inhibitors were also not yet part of standard clinical practice, and most patients were referred to a tertiary IBD centre for second opinion regarding biologic-refractory disease. Third, the final modified intention-to-treat cohort included 116 patients instead of the initially planned 120, due to exclusion of four patients post-enrolment. While this slightly reduced the final sample size, the study maintained adequate power to detect meaningful differences between treatment groups. Lastly, the study was not

designed to assess within-treatment modifications post-intervention (e.g., changes in medication dose or frequency, or the addition of background therapies), limiting conclusions about subsequent therapy adjustments.

In conclusion, appendicectomy as an adjunct to advanced therapy in biologic-failing patients with moderately to severely active ulcerative colitis was more effective than switching to JAK-inhibitors to achieve clinical remission and endoscopic improvement at 12 months, with a low complication rate and a comparable safety profile. These findings suggest that appendicectomy may be an attractive therapeutic option for this patient population. Further studies are needed to identify the optimal patient population, predictive markers of response, long-term outcomes, and the underlying mechanisms of appendicectomy in ulcerative colitis.

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Supplementary materials

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8

Chapter 8

Intestinal ultrasound predicts response to appendectomy in active ulcerative colitis

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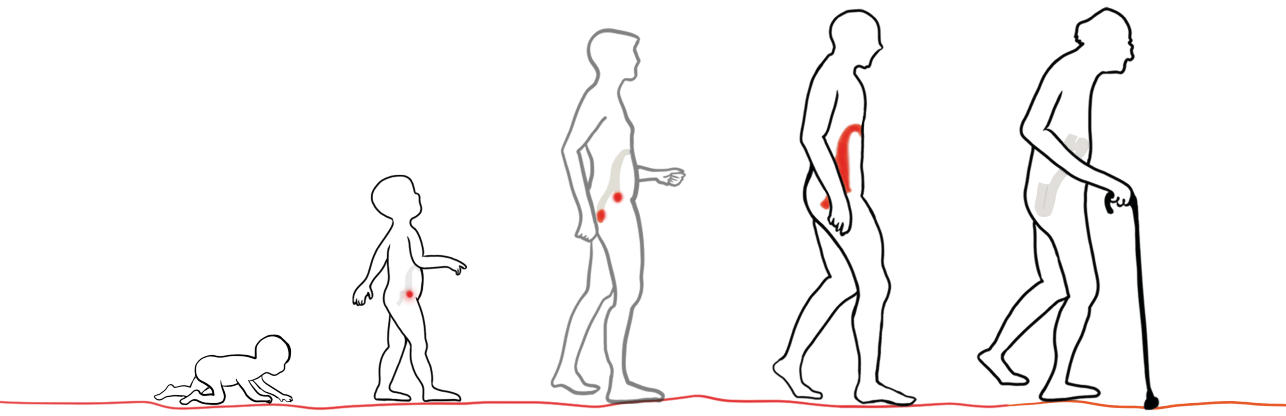

Final draft manuscript

Appendectomy has emerged as a potential therapeutic option for active ulcerative colitis (UC).[1,2] The recent COSTA trial reported a 33% clinical remission rate in therapy-refractory UC patients who underwent appendectomy, which was significantly higher than the control group receiving Janus kinase inhibitors (12%).[3] Still, only a subset of patients benefit from appendectomy. Therefore, there is an unmet need for a reliable preoperative tool to predict response. The only current predictive marker for appendiceal inflammation is a peri-appendiceal red patch (PARP). However, endoscopy is invasive and PARP is present in only 10-20% of UC patients, whereas microscopic inflammation in the appendix is found in 50% of UC patients (both in remission and active disease).[4] Previously, we have demonstrated that response to appendectomy was more frequently seen in patients with histological appendiceal inflammation.[1] Intestinal ultrasound (IUS) is a non-invasive diagnostic modality used for diagnosing appendiceal inflammation in patients suspected for acute appendicitis.[5] In this study, we investigated whether appendiceal IUS predicts response to appendectomy in active UC.

Participants from the Amsterdam UMC site of the COSTA trial were included in this sub-study. UC patients with clinically and endoscopically confirmed active disease refractory to at least one advanced therapy underwent preoperative IUS of the appendix. The following parameters were assessed: transverse appendiceal diameter (TAD), bowel wall thickness (BWT), layer specific thickness of the mucosa, submucosa and muscularis propria, presence of Color Doppler signal (CDS), loss of wall stratification, and relative submucosal echogenicity (RSE), which has been postulated as a measure for chronicity (see Supplementary Table 1 for definitions). Clinical response to appendectomy was defined as a $\geq$2 point reduction in the total mayo score (TMS) and a $\geq$30% decrease from baseline without therapy failure at 12 months postoperatively.

Of the 55 participants, the appendix was visualized in 45 cases (82%). Baseline characteristics are presented in Supplementary Table 2, and IUS parameters in Supplementary Table 3. None of the appendices exhibited a loss of wall layer stratification. CDS assessment was not feasible in 24 patients (53% [24/45]) due to deep pelvic localization, and this parameter was therefore excluded from further analysis.

Clinical response was achieved in 18 of 45 patients (40%) with a visualized appendix. Clinical responders had a numerically higher TAD than non-responders

(median 4.9 [IQR, 3.4-6.3] vs 4.4 [IQR, 3.7-5.1] mm, p=0.524), while RSE (94.6 [SD, 28.5] vs 115.5 [SD 41.0] grayscale values, p=0.05) and submucosal thickness (0.6 [SD 0.3] vs 0.8 [SD 0.3] p=0.104) were lower in responders compared to non-responders. Receiver operating characteristic curve analyses determined TAD ≥6 mm as the optimal cut-off for predicting clinical response with 38.9% sensitivity, 92.6% specificity, 77.8% positive predictive value (PPV), 69.4% negative predictive value (NPV) and 68.9% accuracy. For non-response, submucosal thickness >0.75 mm had 50% sensitivity, 82.4% specificity, 82.4% PPV, 50% NPV and 62.2% accuracy. Similarly, RSE >111 grayscale values predicted non-response with 50.0% sensitivity, 70.6% specificity, 73.7% PPV, 46.2% NPV and 57.8% accuracy. Multivariate logistic regression (Supplementary Table 3) identified significant predictive parameters for clinical response: TAD ≥6 mm was associated with higher odds of response (odds ratio [OR] 19.6, 95% CI 1.69-227.5, p=0.017), whereas RSE >111 grayscale value was associated with lower odds of response (OR 0.09, 95% CI 0.01-0.78, p=0.028).

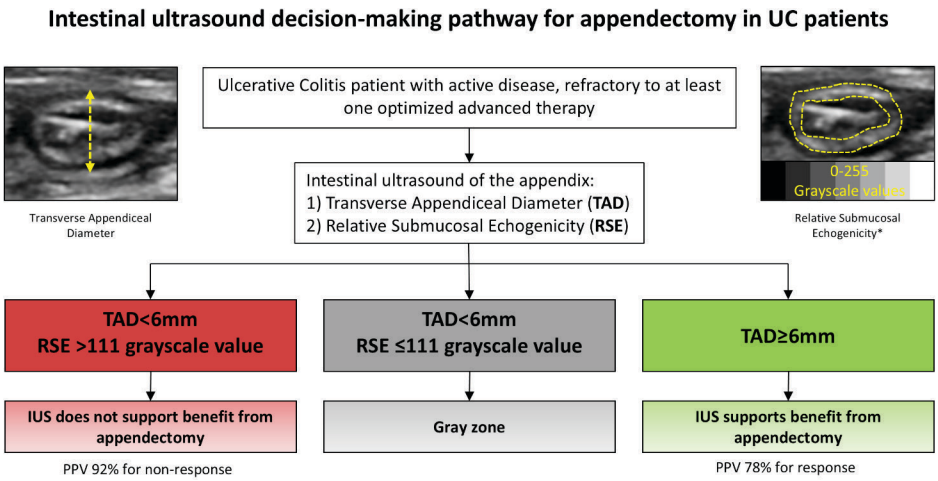

Figure 1. Intestinal ultrasound decision-making pathway for appendectomy in therapy-refractory UC patients

Abbreviations: UC: ulcerative colitis. RSE is the difference in areal grayscale values (0-255) between the submucosa and muscularis propria.

Based on these findings, we developed a flowchart (**Figure 1**) illustrating a potential decision-making pathway for appendectomy in therapy-refractory UC patients. The flowchart categorizes patients based on TAD and RSE cut-offs, guiding patient

selection by stratification of response to appendectomy. Of the 9 patients (20% [9/45]) with positive TAD (≥6 mm), 7 (78% [7/9]) responded to appendectomy and are classified as likely to benefit (green: IUS supports benefit from appendectomy). In contrast, among the 36 patients (77% [36/45]) with a negative TAD (<6 mm), response to appendectomy was less likely, with 11 patients (31% [11/36]) who responded. Within this group, RSE served as a secondary stratification marker. Positive RSE (>111 grayscale values) was observed in 12 patients (33% [12/36]), of whom 11 (92% [11/12]) were non-responders, indicating a high likelihood of non-response (red: IUS does not support benefit from appendectomy). Negative RSE (≤111 grayscale values) was found in 24 patients, with a less reliably predictable response to appendectomy (10 responders and 14 non-responders; gray zone: appendectomy benefit uncertain).

Our findings indicate that IUS can predict clinical response to appendectomy in UC patients. Specifically, TAD ≥6 mm is associated with response, while RSE >111 grayscale values predict non-response.

A TAD ≥6 mm on IUS has been used as a marker of acute appendicitis in the general population and is routinely used by radiologists in clinical practice for diagnosing acute appendicitis[5]. In a previous study, TAD ≥6 mm occurred in >40% of active UC patients (without clinical or biochemical suspicion of an acute appendicitis) suggesting appendiceal involvement in a significant amount of UC patients.[6] Several hypotheses on immunological changes or microbiome composition exist on how appendiceal inflammation drives colonic inflammation.[7] In the current cohort we hypothesize that a TAD ≥6 mm suggests active inflammation that could be treated with an appendectomy. On the other hand, RSE >111 predicted non-response to appendectomy. Submucosal hyper-echogenicity has been associated with chronicity and chronic damage of the bowel wall in UC and the window of opportunity for an appendectomy has perhaps past by for this group of patients.[8]

In conclusion, we demonstrated that IUS can predict clinical response to appendectomy in active, therapy-refractory UC patients. Specifically, TAD ≥6 mm was associated with a favorable response, while an RSE >111 grayscale values predicted non-response. Based on these findings, we propose a decision-making pathway. Our findings suggest that IUS may serve as a novel, cost-effective, and non-invasive point-of-care tool for guiding appendectomy decisions in UC but

needs further validation. It may assist in clinical decision-making regarding the choice between pursuing appendectomy or initiating new anti-inflammatory treatment.

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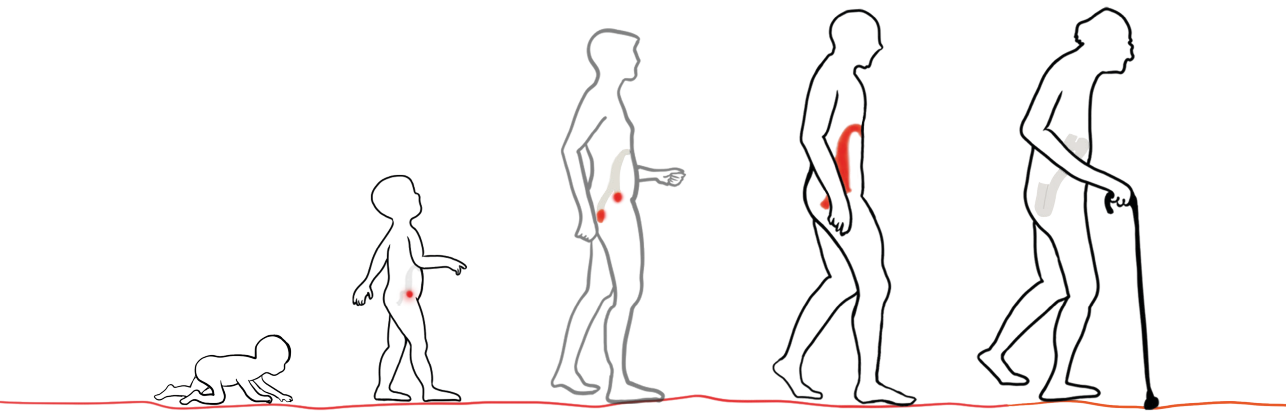
Supplementary materials

9

Chapter 9

Response to appendectomy in active ulcerative colitis depends on appendiceal phenotypic subtype and immunological activity

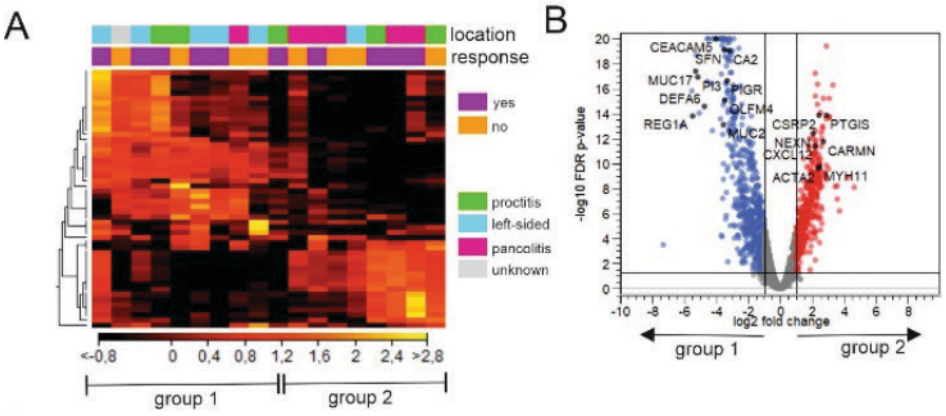
Marte A J Becker, **Eva Visser**, Lianne Heuthorst, Jarmila D W van der Bilt, Christianne J Buskens, Manon E Wildenberg



Submitted (under review)

The appendix has been linked to the pathophysiology of ulcerative colitis (UC) for decades as epidemiological studies have consistently demonstrated an inverse relationship between appendectomy and the development of UC. A case-control study showed that UC patients had significantly fewer appendectomies in their history than controls (0.6% vs 25%) and individuals who underwent appendectomy before the age of 20 were at significantly lower risk of developing UC later in life (standardized incidence ratio 0.45).[1,2] Beyond its protective implications, recent studies have shown the potential of appendectomy in altering the disease course in patients already diagnosed with UC. The ACCURE trial demonstrated that UC patients in remission who underwent an elective appendectomy had a 35% reduced risk of relapse during the following year, indicating an effect on remission maintenance.[3] Even more intriguing, the COSTA trial indicated a potential for remission induction. In this study, 33% of patients with moderate to severe active UC achieved clinical remission after appendectomy, compared to only 12% on JAK-inhibitors.[4]

Despite these promising results, appendectomy was beneficial to only a subset of patients, similar to currently used medical interventions. As the mechanism through which appendectomy modifies disease course remains unclear, predicting therapy responses is challenging. To understand the mechanism of action and improve patient selection, we performed extensive molecular profiling on appendiceal biopsies from the aforementioned trials. The discovery cohort contained UC patients with moderately-to-severely active disease (n=18). Although unsupervised hierarchical clustering of samples identified two distinct clusters of samples (Fig 1a, denoted as Group 1 and Group 2), these clusters did not correlate with response to appendectomy or the extent of colitis. Instead, comparison of the two separate clusters suggested a phenotypical dichotomy (Fig 1b), with one subtype (Group 1; n=10) displaying higher expression of epithelial-related markers (e.g. *MUC2, PIGR, OLFM4, DEF6A*), while the other (Group 2; n=8) was characterized by increased expression of stromal-related genes (e.g. *PTGIS, CXCL12, ACTA2, MYH11*). Cellular deconvolution indeed confirmed these findings, revealing a significantly greater proportion of enterocytes in Group 1 and more enrichment of stromal cells in Group 2 (Fig S1a). This phenotypic dichotomy was further validated by immunohistochemistry, which demonstrated a clear increase in the pancytokeratin (epithelium) to collagen (stroma) ratio (Fig 1c) in Group 1. Notably, specimens in Group 2 largely maintained clear epithelial morphology, indicating that the appendices did not undergo complete fibrotic transformation.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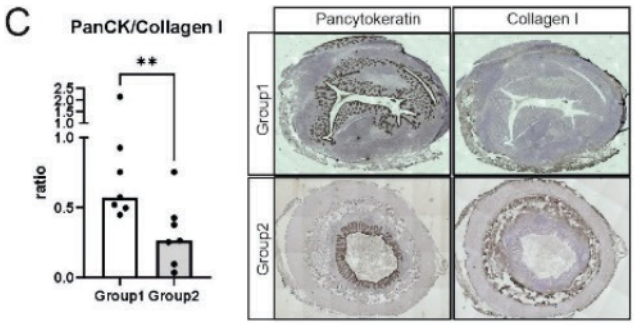
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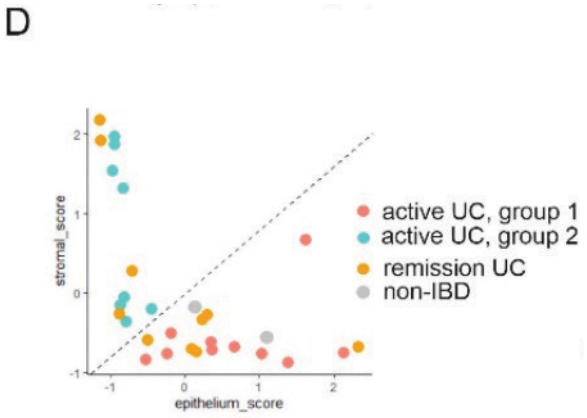
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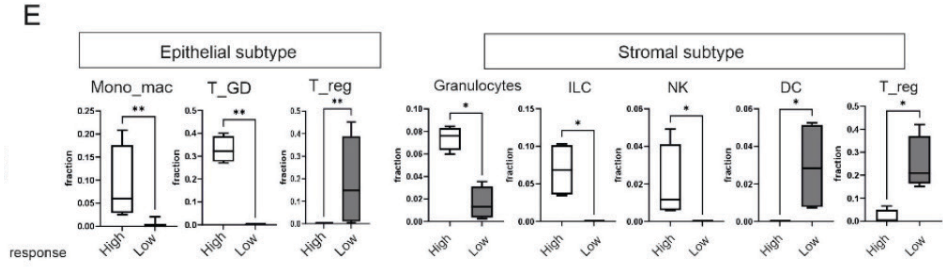
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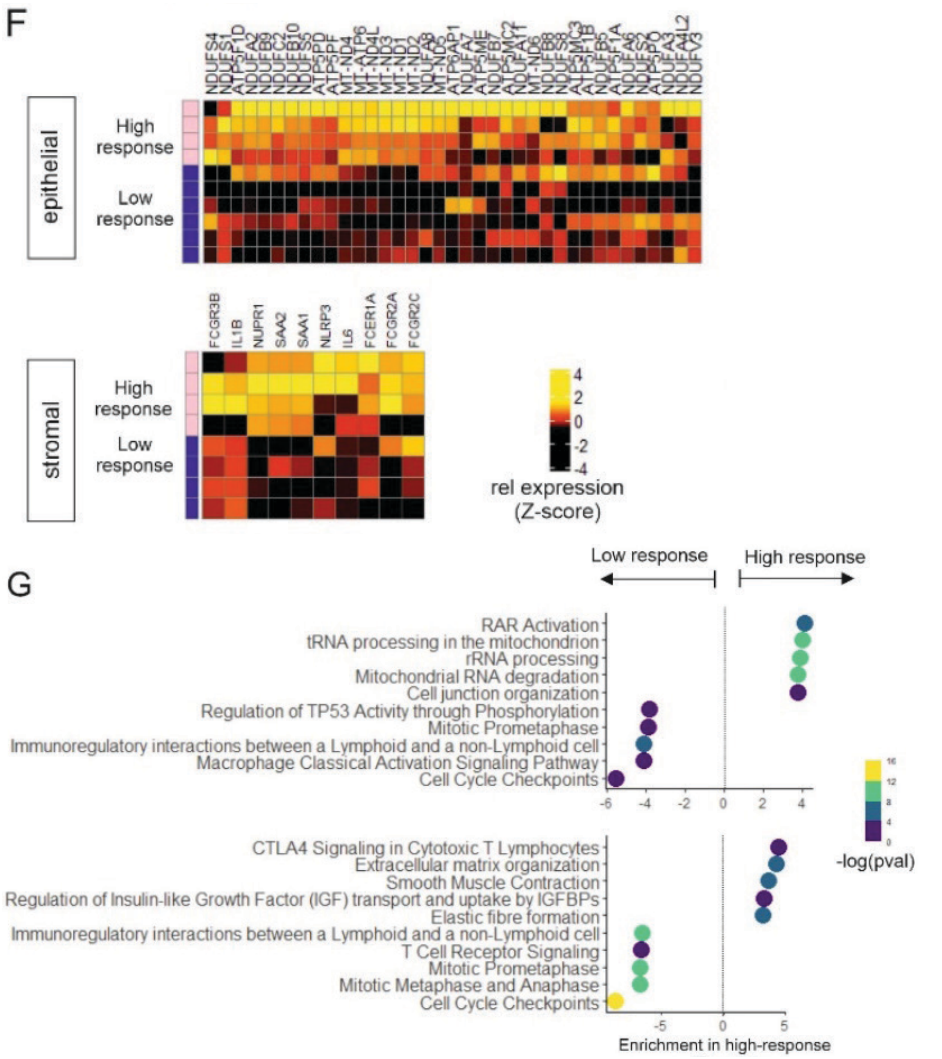

Figure 1.

*Identification of two distinct phenotypes in the appendix of UC patients. (A) RNASeq analysis was performed on appendiceal specimens in 18 patients with moderate to severe UC, and samples were clustered unsupervised, revealing 2 subtypes not related to disease location or response to appendectomy. (B) Volcano plot depicting DEG between group1 and group2 identified in the clustering. (C) Immunohistochemistry on sections obtained from the same appendices included in RNASeq for epithelial marker Pancytokeratin and stromal marker Collagen I (n=13). Expression was quantified digitally, bars represent median, dots represent individual specimens. **p<0.01, MannWhitney U-test. Right panel shows representative stainings of one sample in group1 (top images) and one sample in group 2 (bottom images). (D, left) Geneset scores were calculated based on the top100 differentially expressed genes differentiating the epithelial and stromal phenotypes for the 18 active UC patients (red/blue), as well as for an additional 10 patients in remission (orange) and two non-IBD controls (grey (E) Deconvolution of RNASeq data indicates differential composition of the immune associated with high response rate depending on the underlying phenotypic subtype. (F) Heatmaps depicting expression of genes associated with mitochondrial activity (top) and acute phase responses (bottom) in the individual phenotypic subtypes. (G) Pathway analysis (Ingenuity pathway analysis) comparing the high response cluster to the low response cluster in the separate subtypes.*

The occurrence of two phenotypic subsets of appendices was validated in a second cohort, consisting of UC patients in remission (ACCURE trial, n=10) and non-IBD controls (n=2). Based on the expression pattern of the first cohort (active UC), scores were calculated for expression of both epithelial and stromal genesets. Indeed the second cohort similarly showed two distinct phenotypical subtypes (Fig 1d, orange, epithelial n=6, stromal n=4).

As mentioned, clinical response to appendectomy was not directly associated with the primary phenotypic subtype of the appendix, as both subtypes included responders as well as non-responders. However, *within* each subtype clustering of responders and non-responders was more apparent (Fig S1b). In the stromal subtype, two clusters were apparent, one with a high response rate (3/4 patients) and one with a lower response rate (1/4 patients). The high-response cluster was associated with an innate immune response with increased abundance of granulocytes and innate lymphoid cells (ILC, NK cells) and lower proportions of regulatory T cells. Pathway analysis also showed increased activity of acute phase immune responses (e.g. SAA1, SAA2, NLRP3, IL6) and stromal activation (fig 1f, top). Within the epithelial subtype, clustering based on response was less evident, although relatively high- and low-response clusters were observed (high response 3/4 and low 3/6 respectively). In this case, the relative high-response cluster was associated with increased immune activation as shown by higher abundance of monocytes/macrophages and gamma-delta T cells and reduced regulatory T cells (Fig 1e). Pathway analysis identified mitochondrial activity (e.g. expression of mitochondrial genes) and increased oxidative phosphorylation in the high response cluster (Fig 1f, bottom). Together, these data suggest that in any case, a certain level of immune activity in the appendix is necessary for a response to appendectomy, but the specific type of response required differs depending on the overall phenotype/ state of the appendix.

The different signals associated with response within the two phenotypic subtypes have practical implications. Studies focusing on prediction and patient selection should stratify data for the phenotypic subtypes prior to downstream analysis. Failure to do so not only leads to dilution of signal, but may even result in detection of signals not relevant for a subset of patients. As large scale RNASeq analysis is not a feasible tool for clinical purposes, we performed a proof-of-principle analysis using polymerase chain reaction (pcr) to discriminate the two subtypes. Using a limited subset of four genes (*PIGR, CEACAM5, IGFBP5, DES*) we were able to recapitulate the separation observed in the RNASeq study (Fig S1c). Additionally, expression

patterns associated with response in the epithelial subtype did not differ evidently in the stromal subtype and vice versa (Fig S1c), although it should be noted the numbers in each group were too small to perform meaningful statistical analyses.

Our study is limited through several factors. Due to the unexpected dichotomy in subtypes, the numbers in this study are too small to provide statistically sound data regarding predictive markers. Further studies on larger groups, taking into account the phenotypical subtypes, will be required to generate definitive epithelial and stromal response signatures. Additionally, response to appendectomy was evaluated specifically in patients with moderate to severe UC. Whether similar biological processes apply to remission maintenance rather than remission induction after appendectomy requires further evaluation.

In summary, our data identify two distinct phenotypic subtypes (stromal versus epithelial) of the appendix in UC patients present irrespective of disease activity. These subtypes have both clinical and scientific relevance, as they exhibit divergent biological pathways associated with response to appendectomy. Recognizing this distinction will be crucial for refining patient selection criteria and further exploring the underlying mechanisms of action in further studies.

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Supplementary materials

Part IV

Colorectal cancer in ulcerative colitis patients undergoing colectomy

10

Chapter 10

The impact of advanced medical therapies on time to resection and colorectal cancer outcomes in ulcerative colitis patients undergoing colectomy

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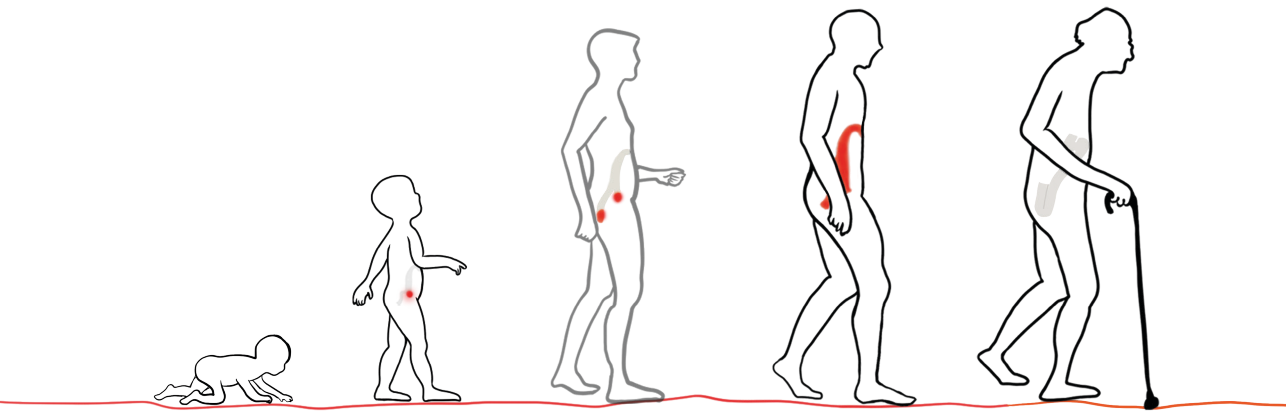
*Shared senior authorship



Journal of Crohn's and Colitis, 2025

Abstract

Background

We aimed to evaluate the impact of advanced medical therapies (biologicals and small molecules) on time to colectomy and oncological outcomes in ulcerative colitis (UC).

Methods

This cohort study included UC patients who underwent colectomy between 2003 and 2022 at 2 referral centers in Belgium and the Netherlands. Exposure was the use of advanced medical therapies. Primary outcomes were time to colectomy and colorectal cancer (CRC) rate, compared between 4 periods: P1 (2003-2007), P2 (2008-2012), P3 (2013-2017), and P4 (2018-2022). Secondary outcomes were oncological outcomes, including incidental cancers found unexpectedly in resection specimens or during endoscopic follow-up for medication switch.

Results

Among 716 patients, the usage of advanced therapies increased from 36.8% in P1 to 89.7% in P4 ($P < .0001$). Median time to colectomy remained comparable (P1: 7.1 years [interquartile ranges (IQR), 2.8-12.9] vs P4: 7.2 years [IQR, 2.7-14.6]; P = not significant). Colectomy and colorectal cancer was diagnosed in 72 (10.1%) patients, with no significant change over time ($P = .44$). Proportion of CRC was lower in patients treated with advanced therapies (4.7% vs 23.6%, $P < .0001$) and related to a shorter follow-up (median 6.1 vs 10.3 years, $P < .0001$). Advanced therapy patients had higher incidental cancer rates (37.5% vs 8.3%, $P = .002$), which was associated with reduced CRC-related survival (HR for CRC-related death: 3.3, 95% CI 1.17-9.4; $P = .02$).

Conclusion

Despite increased usage of advanced medical therapies, time to resection and CRC rates have remained unchanged in UC patients undergoing colectomy over the past 2 decades. Advanced therapy patients had higher incidental cancers rates, associated with decreased CRC survival. Awareness of timely colectomy is crucial for this group.

Introduction

Patients with ulcerative colitis (UC) face an elevated risk of developing colorectal cancer (CRC) due to chronic inflammation that leads to neoplastic progression.[1-7] Risk factors for CRC in UC patients include male sex, family history of CRC, concomitant primary sclerosing cholangitis (PSC), and longstanding, extensive, and severe colitis. Therefore, the European Crohn's and Colitis Organisation (ECCO) recommends performing surveillance colonoscopy in patients with at least distal colitis 8 years after symptom onset to detect neoplasia early.[8]

Since the introduction of the first tumor necrosis factor-α inhibitor (anti-TNF-α) in 1998, the medical landscape has evolved, with now more than 5 distinct mechanisms of action available by 2022, including anti-TNFs (infliximab, adalimumab, and golimumab), the integrin receptor antagonist vedolizumab, interleukin 12/23 inhibitors (ustekinumab, mirikizumab), Janus kinase (JAK) inhibitors (tofacitinib, filgotinib, and upadacitinib), and S1P receptor modulators (ozanimod and etrasimod).[9] This expanding armamentarium has contributed to an improved control of inflammation although a therapeutic ceiling of 30% remission rates persists.[10,11] However, simultaneously, postponed colectomy with an accumulative inflammatory burden might lead to an increased risk of CRC.[12-14]

While population-based cohort studies have reported a decline in overall CRC incidence among UC patients,[3,6,15] recent nationwide pathology studies have shown a contrasting trend with an increased IBD-/UC-related CRC incidence over the past 3 decades.[13,16,17] This discrepancy may result from a shift in surgical indication, moving from primarily therapy-refractory UC to managing colorectal neoplasia (CRN), and potentially reflects the beneficial impact of advanced medical therapies on improved disease control. However, previous studies have been unable to link descriptive trends of IBD-/UC-related CRC with clinical data on therapy usage and disease characteristics.

Therefore, we aimed to evaluate the impact of advanced medical therapies, including biologicals and small molecules, on time to colectomy and proportion of CRC in UC patients who underwent colectomy at 2 large tertiary referral centers in the Netherlands and Belgium. In addition, we sought to evaluate the association between usage of advanced medical therapies and oncological outcomes.

Methods

Study design and setting

This cohort study was conducted at the Academic Medical Centre (AMC) in Amsterdam, the Netherlands, and the University Hospitals Leuven (UZ Leuven) in Belgium. This study was reviewed by the Medical Ethics Review Committee of the Academic Medical Centre, which confirmed on February 14, 2019, that the Medical Research Involving Human Subjects Act (WMO) did not apply. The study adhered to ethical guidelines and the Declaration of Helsinki.

Consecutive patients ≥18 years with established UC who underwent colectomy between January 1, 2003 and December 31, 2019 at AMC or between January 1, 2003 and October 19, 2022, at University Hospital Leuven were included. Eligible patients were identified using a defined set of search terms in the hospitals' electronic medical records, detailed in Table S1 in the Appendix. The data were extracted between January and July 2023.

Patients without IBD-related colectomy indications were excluded. Exclusion criteria were: (1) surgery indication was sporadic colorectal neoplasia (s-CRN), (2) absence of active inflammation or IBD-associated dysplastic lesions in the pathology report of the resected colon, and (3) absence of active inflammation or IBD-associated dysplastic lesions on preoperative endoscopy, as the s-CRC pathophysiology differs intrinsically from that of IBD/UC-CRN.[5,7] CRN cases were independently verified by three reviewers (EV, GB, and CB) based on endoscopy and pathology reports. Further details are listed in Table S2 in the Appendix.

Data collection

Data were collected on baseline characteristics (sex, age, smoking status, PSC presence, family history of CRC), disease characteristics (diagnosis date, endoscopy, and pathology reports, medical therapy), surgery and pathology specimens characteristics (surgery date, setting, indication, tumor stage and localization), and oncological outcomes (cancer recurrence, overall- and cancer-related death). Dates of colectomy were categorized into 4 5-year periods: P1 (2003-2007), P2 (2008-2012), P3 (2013-2017), and P4 (2018-2022) corresponding with the phases of advanced medical therapies availability. Disease extent and severity were coded according to the ECCO guidelines (proctitis, left-sided colitis, extensive colitis) and the Mayo endoscopic score, respectively.[8,18,19]

Advanced medical therapy

Conventional medical therapy was defined as the usage of 5-aminosalicylates (5-ASA), corticosteroids, and/or immunomodulators (thiopurines, methotrexate). Advanced medical therapy was defined as usage of one or more biologics (i.e. anti-TNF agents [infliximab, adalimumab, golimumab], integrin receptor antagonists [vedolizumab], or interleukin inhibitor [ustekinumab]) and/or small molecules (i.e. JAK-inhibitor [tofacitinib, filgotinib, upadacitinib], or S1P receptor modulator [ozanimod]). Time duration from the initiation of advanced medical therapy to colectomy was calculated as the time between the start date of the first advanced medical therapy and the date of resection.

Surgical and pathological assessment

Surgery settings were categorized into elective (planned) and (semi-)acute (< 72 h or during hospitalization) surgeries. Surgical indications were categorized as colitis-associated or cancer (risk)-associated. Colitis-associated indications included therapy refractory disease or complicated disease, such as colonic stricture, colonic perforation, hemorrhage, and toxic megacolon. Cancer (risk)-associated indication included endoscopically confirmed CRN, such as dysplasia and CRC, as well as increased cancer risk due to longstanding IBD or inadequate surveillance. Colorectal neoplasia was further categorized by type: indefinite, low-grade, or high-grade dysplasia, CRC, neuroendocrine tumor (NET), or other malignancies. An incidental cancer was defined as cancer unexpectedly found in the pathology of the resected specimen, or during endoscopy scheduled for recently switched medication (within the last year) evaluating therapy effect in refractory UC patients. Colectomy and colorectal cancer was staged according to the pathological tumor-node-metastasis and American Joint Committee on Cancer 8th edition.[20]

Outcomes

Primary outcomes were time from UC diagnosis to colectomy and CRC rate in colectomy specimens, compared between the 4 distinct time periods. The secondary outcome was to verify whether the usage of advanced medical therapy was associated with an increased risk of CRC or worse oncological outcomes in CRC patients.

Statistical methods

Categorical variables were summarized by numbers, frequencies, and percentages, while continuous variables were reported as medians and interquartile ranges (IQRs). The χ^2 test and Kruskal–Wallis test were used for categorical variables and continuous variables, respectively. Cox proportional hazard (PH) regression analyses were performed to evaluate differences in time-to-resection variables and to calculate adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Time-to-resection variables were: (1) time from initiation of advanced medical therapy to colectomy, and (2) time from UC diagnosis to colectomy, with colectomy considered as an event for both analyses. To account for potential confounding factors, these models were adjusted for: age at colectomy, sex, and disease severity (Mayo 3 vs Mayo 0-2). PH assumption was tested using Schoenfeld residuals, and time-dependent covariates were included in the model to account for violations of the PH assumption. Logistic regression analysis was used to study the associations between known risk factors and CRC in the study cohort, including sex, age, former smoking, PSC, family history of CRC, extensive disease, and time since initiation of advanced therapy with results presented as odds ratios (OR) and 95% CIs. Multivariate logistic regression models were adjusted for disease severity (Mayo 3 vs Mayo 0-2) and disease duration. Unadjusted Kaplan–Meier survival analyses were used to estimate survival outcomes and visually compare time-to-event outcomes between groups. Differences in survival curves were assessed with log-rank test. Cox PH regression models were used to estimate HRs and 95% CIs for survival outcomes, from colectomy date to last clinical follow-up date or death. Patients who were alive at the end of follow-up were censored. These survival analyses were adjusted for disease severity (Mayo 3 vs Mayo 0-2). All tests were two-sided and *P* values less than .05 were considered statistically significant. Statistical analyses were performed using SPSS version 28.0.1.1 (IBM, Armonk, NY, USA) and STATA version 17.0.

Results

Study population and UC characteristics

A total of 724 UC patients underwent colectomy between 2003 and October 2022. Eight patients underwent resection for s-CRC and were, therefore, excluded. In total, 716 patients were included, comprising 275 patients from AMC and 441 from UZ Leuven. The cohort included 425 males (59.4%), with a median age at resection of 43 years (IQR, 32-54). The majority (70.8%) were treated with advanced medical therapy

prior to surgery, with a significantly increasing proportion over time (P1: 36.8% vs P2: 71.8% vs P3: 81.3% vs P4: 89.7%; $P < .0001$), and increasing time between initiation of advanced medical therapy and resection (P1: 0.5 years [IQR, 0.7-4.2] vs P2: 1.7 years [IQR, 0.7-2.8] vs P3: 1.9 years [IQR, 0.8-4.6] vs P4: 3.0 years [IQR, 1.2-6.2]; $P < .0001$) (Figure S1 and Model 1 in Table S5 in Supplementary Appendix.). The PH assumption was not violated (global test of PH assumption, $P = 0.64$; Table S4 in Supplementary Appendix).

The indication for colectomy did not change significantly over time and was primarily colitis-related in 77.1% (P1: 79.1% vs P2: 73.0% vs P3: 75.7% vs P4: 81.2%, $P = 0.10$). Among 80 patients undergoing surgery for preoperatively diagnosed dysplasia, 16 (20.0%) had no dysplasia/CRC in the resected specimen, while 16 were diagnosed with CRC. Additional baseline characteristics are summarized in Table 1 and comparisons over time are available in Table S3 in Supplementary Appendix). There were no significant differences between the 2 centers in disease duration, CRC rates, or incidental cancer rates (Table S6 in Supplementary Appendix).

Table 1. Baseline characteristics of the study cohort ($n = 716$)

Characteristic	All patients (N = 716)	No advanced medical therapy (N = 209a, 29.2%)	Advanced medical therapy (N = 507, 70.8%)
Male sex	425 (59.4%)	134 (64.1%)	291 (57.4%)
Age at UC diagnosis	30 years (22-43)	33 years (25-46)	29 years (22-42)
Age at colectomy	43 years (32-54)	48 years (38-60)	40 years (29-51)
Smoking status			
Former	178/673 (26.4%)	42/184 (22.8%)	136/489 (27.8%)
Current	50/673 (7.4%)	19 (19.1%)	31 (6.1%)
PSC	58/715 (8.3%)	29/208 (13.9%)	30/507 (5.9%)
Family history of CRC	32/227 (14.1%)	13/77 (16.9%)	19/150 (12.7%)
Extent UC before colectomy			
Proctitis	16 (2.2%)	6 (2.9%)	10 (2.0%)
Left sided	215 (30.0%)	54 (25.8%)	161 (31.8%)
Extensive	219 (30.6%)	77 (36.8%)	142 (28.0%)
Not defined/unknown	266 (37.2%)	72 (34.4%)	194 (38.3%)
Endoscopic severity UC before colectomy			
Mayo 0	54 (7.5%)	36 (17.2%)	18 (3.6%)
Mayo 1	46 (6.4%)	28 (13.4%)	18 (3.6%)
Mayo 2	157 (21.9%)	54 (25.8%)	103 (20.3%)
Mayo 3	375 (52.4%)	50 (23.9%)	325 (64.1%)
Unknown	84 (11.7%)	41 (19.6%)	43 (8.5%)
Medical therapy in history			

Table 1. Continued

Characteristic	All patients (N = 716)	No advanced medical therapy (N = 209a, 29.2%)	Advanced medical therapy (N = 507, 70.8%)
Conventional	699/706 (99.0%)	193/200 (96.5%)	506/506 (100%)
5-ASA	672 (95.2%)	178/201 (88.6%)	13/507 (2.6%)
Corticosteroids	657 (93.1%)	157/202 (77.7%)	500/506 (98.8%)
Immunomodulators	527 (74.6%)	98/201 (48.8%)	417/505 (82.6%)
Advanced therapy	507/710 (71.4%)		
Infliximab	464 (63.5%)		
Adalimumab	167 (23.5%)		
Golimumab	31 (4.4%)		
Vedolizumab	197 (27.7%)		
Ustekinumab	29 (4.1%)		
Tofacitinib	63 (8.9%)		
Filgotinib	9 (1.3%)		
Upadacitinib	5 (0.7%)		
Other[b], such as:	95 (13.3%)		
Anti-Madcam	18 (2.5%)		
Visilizumab	15 (2.1%)		
Ertrolizumab	12 (1.7%)		
RhuMab Beta 7	12 (1.7%)		
Risankizumab	6 (0.8%)		
Time from initiation advanced therapy to resection	1.8 years (0.7-4.2)		
Surgery			
Setting			
Elective	554 (77.4%)	176 (84.2%)	378 (74.6%)
(semi-)acute	162 (22.6%)	33 (15.8%)	129 (25.4%)
Indication			
Treatment refractory	552 (77.1%)	101 (48.3%)	451 (89.0%)
Dysplasia or cancer (risk) associated	164 (22.9%)	108 (51.7%)	56 (11.0%)

Data are median (IQR), n (%), or n/N (%), except where indicated otherwise. Abbreviations: UC, ulcerative colitis; PSC, primary sclerosing cholangitis; CRC, colorectal cancer; 5-ASA, 5-aminosalicylates.
[a]*Medication data were missing for 6 patients; denominators represent available data.*
[b]*Includes but is not limited to the given examples.*

Time to colectomy

The median time from UC diagnosis to colectomy was 7.2 years (IQR, 2.8-14.1) and did not increase over time despite the increased use of advanced medical therapy (P1: 7.1 years [IQR, 2.8-12.9] vs P2: 6.1 years [IQR, 2.3-14.8] vs P3: 7.5 years [IQR, 3.0-14.5] vs P4: 7.2 years [IQR, 2.7-14.6], *P* = not significant [ns]; Table 2, Model 2 in Table S5 and Figure S2 in Appendix). The PH assumption was violated (global test

of PH assumption, $P = .01$; Table S4) and time-dependent covariates were included in the model.

Table 2. Time to colectomy and colorectal neoplasia of the cohort ($n = 716$) and CRC subgroup characteristics ($n = 72$) compared over time.

Characteristic	Total cohort 2003-2022 (N = 716)	P1: 2003-2007 (N = 163)	P2: 2008-2012 (N = 174)	P3: 2013-2017 (N = 214)	P4: 2018-2022 (N = 165)	Adjusted P-value[a]
Time from UC diagnosis to colectomy (disease duration), years	7.2 (2.8-14.1)	7.1 (2.8-12.9)	6.1 (2.3-14.8)	7.5 (3.0-14.5)	7.2 (2.7-14.6)	ns[c]
Colorectal neoplasia[b]	151 (21.1%)	35 (21.5%)	41 (23.6%)	44 (20.6%)	31 (18.8%)	ns[d]
CRC	72 (10.1%)	16 (9.8%)	21 (12.1%)	21 (9.8%)	14 (8.5%)	ns[d]
Dysplasia	84 (11.7%)	19 (11.7%)	23 (13.2%)	22 (10.3%)	20 (12.1%)	ns[d]
NET	2 (0.3%)	–	1 (0.6%)	1 (0.5%)	–	
Other (B-cell Lymphoma)	1 (0.1%)	–	–	1 (0.5%)	–	
	CRC subgroup 2003-2022 (N = 72)	**CRC subgroup P1 (N = 16)**	**CRC subgroup P2 (N = 21)**	**CRC subgroup P3 (N = 21)**	**CRC subgroup P4 (N = 14)**	**P value**
Time from UC diagnosis to colectomy (disease duration), years	18.2 (10.4-24.7)	16.4 (8.1-26.0)	18.5 (13.5-24.3)	19.8 (14.0-25.3)	17.0 (7.3-22.3)	ns[c]
Advanced therapy	24 (33.3%)	2 (12.5%)	4 (19%)	10 (47.6%)	8 (57.1%)	**0.01**[e]
Time from initiation advanced therapy to resection, years	4.0 (0.9-10.3)	0.2 (0.2-0.2)	5.3 (0.9-10.3)	2.8 (0.9-5.6)	8.8 (2.6-15.1)	**<0.0001**[c]

Data are n (%) or median (IQR).
Abbreviations: CRC, colorectal cancer; UC, ulcerative colitis; ns, not significant ($P \geq .05$); NET, neuroendocrine tumor.
[a]*Adjusted for age at colectomy, sex, and disease severity (Mayo 3 vs Mayo 0-2).*
[b]*The total count of CRN cases (151) does not equal the sum of individual neoplasia types as some patients were diagnosed with more than 1 type of neoplasia, leading to overlapping counts in the reported categories.*
[c]*Cox regression analysis with P3 used as the reference group.*
[d]*Logistic regression.*
[e]χ^2 *test.*

CRN rates in colectomy specimens

Colectomy and colorectal cancer was diagnosed in 72 colectomy specimens (10.1%), and this proportion was not significantly different over time (P1: 9.8% vs P2: 12.1% vs. P3: 9.8% vs P4: 8.5%; $P = .44$). Incidental cancers accounted for 18.1% (13/72),

and these patients had more often severe preoperative endoscopic disease activity compared to non-incidentals (70.0% vs 6.5%, $P < .0001$).

Dysplasia was found in 84 resected specimens (11.7%), and this proportion remained unchanged (P1: 11.7% vs P2: 13.2% vs P3: 10.3% vs P4: 12.1%; $P = .70$). In 64 of the 148 dysplasia/CRC patients (43.2%), neoplasia was found at multiple sites (P1: 42.9% vs P2: 45.0% vs P3: 38.1% vs P4: 48.4%; P = ns). Other malignancies were two NETs and one B-cell lymphoma.

CRC cohort

Among the 72 CRC patients, the majority were male (84.7%) with a median age at resection of 49 years (IQR, 42.3-58.8). The median time from UC diagnosis to colectomy in cancer patients was 18.2 years (IQR 10.4-24.7) and did not increase over time ($P = .68$; Table 2). Twenty-four patients (33.3%) were treated with advanced therapy prior to surgery, with a significantly increasing proportion from 12.5% in P1 to 57.1% in P4 ($P = .01$) and time from first initiation from 0.2 years (IQR 0.2-0.2) in P1 to 8.8 years (IQR 2.6-15.1) in P4 ($P < .0001$). In univariate logistic regression analysis, risk factors for the development of UC-CRC were male gender (OR 4.3, 95% CI 2.2-8.3), years of UC duration (OR 1.09, 95% CI 1.06-1.11), and PSC (OR 3.3, 95% CI 1.70-6.65) (Table 3). Advanced medical therapy was associated with a lower risk of CRC (HR 0.38, 95% CI 0.230-0.63, $P < .0001$), but this group also had significantly shorter duration of follow-up (median 6.1 years vs 10.3 years, $P < .0001$). After adjustment for disease severity and disease duration in multivariate analysis, male sex (adjusted OR 4.3, 95 CI 1.90-9.78), disease duration (adjusted OR 1.07, 95% CI 1.04-1.10), and advanced therapy (adjusted OR 0.36, 95% CI 0.19-0.69) remained significant predictors.

At diagnosis, lymph nodal metastases and distant metastases were present in 25 patients (34.7%) and in 9 patients (12.5%), respectively. Although not significantly different, these percentages were higher in the advanced medical therapy group (11/24 45.8% vs 14/47 29.8%, $P = .18$ and 4/24 = 16.7% vs 5/48 = 10.4%, $P = .45$). In patients treated with advanced medical therapy, a significantly higher proportion of an incidental cancer was found (9/24 = 37.5% vs 4/48 = 8.3%, $P = .002$, Table 4).

Table 3. Logistic regression analysis for CRC

		Univariate risk for CRC		Multivariate risk for CRC	
Characteristic	**CRC cohort (N = 72)**	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**Adjusted P value[a]**
Male sex	61 (84.7%)	4.3 (2.2-8.3)	**<.0001**	4.3 (1.90-9.78)	**<.0001**
Age at UC diagnosis, years	29.0 (21-43.0)	0.99 (0.98-1.01)	ns	1.01 (0.98-1.03)	ns
Disease duration, years[b]	18 (10.0-24.0)	1.09 (1.06-1.11)	**<.0001**	1.07 (1.04-1.10)	**<.0001**
Smoker	6/69 (8.7%)	1.2 (0.5-3.0)	ns	0.66 (0.19-2.36)	ns
PSC	15 (20.8%)	3.3 (1.70-6.65)	**<.0001**	2.11 (0.99-4.49)	ns
Family history of CRC	7/36 (19.4%)	1.60 (0.64-4.05)	ns	0.95 (0.30-3.03)	ns
Extent before colectomy					
Proctitis/left sided	18 (24%)	Extensive: 1.81 (0.97-3.36)	ns	Extensive: 1.59 (0.80-3.16)	ns
Extensive	29 (40.3%)				
Not defined/unknown	25 (34.7%)				
Advanced therapy	24 (34.3%)	0.16 (0.10-0.27)	**<.0001**	0.36 (0.19-0.69)	**.002**
Time from initiation of advanced therapy to resection, years	4.0 (0.9-10.3)				

Data are n (%), n/N (%), or median (IQR).
Abbreviations: CRC, colorectal cancer; UC, ulcerative colitis; PSC, primary sclerosing cholangitis; ns, not significant (P ≥ .05).
[a]*Adjusted for disease severity (mayo 3 vs 0-2) and disease duration.*
[b]*Disease duration is the time from UC diagnosis to colectomy.*

Table 4. Patients with CRC and advanced medical therapy use (*n* = 72)*

	No advanced medical therapy (N = 48)	**Advanced medical therapy (N = 24)**	**P value[a]**
pT, T3-4	28/47 (59.6%)	15/24 (62.5%)	.81
pN+	14/47 (29.8%)	11/24 (45.8%)	.18
M1	5/48 (10.4%)	4/24 (16.7%)	.45
AJCC stage > II	29/47 (61.7%)	17/24 (70.8%)	.45
Incidental cancer	4 (8.3%)	9 (37.5%)	**.002**

Data are n (%) or n/N (%).
Abbreviations: CRC, colorectal cancer; N+, lymph nodal involvement; M1, distant metastasis; AJCC, American Joint Committee on Cancer.
[a]χ^2 *test.*

Mortality and survival in CRC

After a median follow-up of 65.5 months (IQR, 24.5-117.8), the overall mortality rate was 37.5% (27/72), of which there were 15 CRC-related deaths (20.8%), 3 deaths from other GI-malignancies (2 gallbladder cancers and 1 cholangiocarcinoma in PSC patients), 7 deaths were unrelated and 2 unknown.

The 5-year and 10-year overall survival rates were 79.3% and 59.0%. The overall survival and CRC-related death in patients with advanced medical therapy was not significantly different when compared to patients without advanced medical therapy (HR for death 0.08, 95% CI 0.006-1.021, *P* = .05, and HR for CRC-related death 0.433, 95% CI 0.05-3.55, *P* = .44; Models 3 and 4 in Table S5). However, all deaths in the advanced medical therapy were CRC-related, whereas this was only 45.5% (10/22) in patients without advanced medical therapy. The PH assumptions were not violated (global test of PH assumption, *P* = .60 and *P* = .21; Table S4).

Patients with incidental cancer had significantly lower CRC-related survival when compared to non-incidentals (HR for CRC-related death 3.3, 95% CI 1.17-9.4, *P* = .02, Model 5 in Table S5). Furthermore, the mortality was all CRC-related, in contrast to patients without an incidental cancer (CRC-related mortality of 42.9% (9/21)). The PH assumption was not violated (global test of PH assumption, *P* = .25; Table S4).

Discussion

We aimed to study the impact of the expanding armamentarium of advanced medical therapies on the time to colectomy and the CRC rate in UC patients. Contrary to our hypothesis, we did not observe an increase in time to colectomy, nor a decrease in cancer proportion over the last 2 decades, despite the significantly increased usage of advanced therapies at 2 large tertiary referral centers. More worrisome, however, was the high proportion of N+ cancers (45.8%), M + cancers (16.7%), and incidental cancers (37.5%) in patients treated with advanced medical therapies.

The CRC rate of 10.1% in our cohort is higher than the 4.8% reported CRC rate in colectomy patients in the Swiss IBD cohort study and the 4.9% (381/7734) in Scandinavian colectomy patients undergoing colectomy for CRC.[3,21] These differences can be attributed to referral bias and variations in study populations—ours being a selection from 2 tertiary referral centers, focusing on UC patients undergoing colectomy who were referred for endoscopic diagnosed UC-CRC. However, we observed a lower CRC rate compared to the 16.9% in a Dutch nationwide

PALGA study and in contrast to those findings, no increasing trend over time was seen.[13] Interestingly, at first sight, this study seems to confirm previous findings of a decreased malignancy risk related to increased use of advanced medical therapies. Indeed, the proportion of CRC in patients on advanced therapies was lower (4.7% vs 22.8%), but one should realize that the follow-up in the advanced medical therapy group was also significantly lower (median 6 years versus 10 years in patients without advanced therapies), which introduces a bias as the median time to develop CRC in UC patients is over 10 years. The high rate of advanced cancers (64.8%) with no decrease over time, despite improved surveillance protocols, is worrisome. These data align with the findings of the previously mentioned pathology study,[13] underscoring the danger of uncontrolled inflammation and the importance of timely referral to surgery in these patients. This might be even more important for the patient group being treated with advanced medical therapy, as all deaths in this group were CRC-related.

Our findings also reveal a disconcerting trend where patients treated with advanced therapies showed a higher rate of incidental cancer, which has a worse CRC-related survival. As expected, the finding of an incidental cancer was related to underlying severe UC activity, since endoscopic identification of a malignancy is difficult in patients with inflammation-induced changes in the colonic mucosa, but the small sample size of this subgroup (*n* = 10 CRC patients with endoscopic Mayo 3) limited the ability to perform more detailed stratified analysis. It is difficult to speculate why the survival in this incidental cancer patient group is so poor as numbers were small, precluding any additional meaningful analysis. First, it might be suggested that an undetected cancer is more likely to be an advanced cancer, and although a high rate of advanced cancer was indeed found in this group, it was not significantly higher when compared to patients without advanced medical therapy. Second, this patient group may have an immune-compromised status, which accelerates tumor progression. This highlights a potentially complex interplay between advanced medical therapy and surgical timing, suggesting that while advanced therapies reduce inflammation, and therefore would reduce the risk for UC-CRC development, they may not mitigate the risk of neoplasia in a subset of patients, particularly those who are refractory to multiple lines of therapies. Finally, undetected cancer might lead to surgical techniques not performed according to oncological principles. This includes inadequate preoperative staging and failure of initiating appropriate multimodal therapies (e.g. neoadjuvant therapy in advanced colon- and rectal cancer).[22] Adequate surveillance in patients with active disease is challenging,

as it complicates the detection of flat lesions. This, combined with an expanding arsenal of medical therapies that reduce the need for colectomy,[14] might lead to a postponed surgical intervention, thereby potentially increasing CRC risk with poor survival.

To the best of our knowledge, this is the first study to analyze the risk and survival of CRC in UC patients on advanced therapy undergoing colectomy. One of the major strengths of this study is its large sample size and the comprehensive data collection over two decades, providing a robust dataset for analyzing trends over time. However, this study also has several limitations. First, the design was of a retrospective nature, which has its inherent limitations related to missing data, although all data on primary outcomes parameters could be reliably retrieved. In addition, the effect of different types of advanced medical therapies could not be analyzed as numbers were too small to perform subgroup analyses. Finally, the study's generalizability may be limited by its focus on 2 large tertiary referral centers with a complex patient population consisting of patients referred for surgery, and findings cannot be directly extrapolated to UC patients who did not undergo colectomy.

In conclusion, this study demonstrated that in the last 2 decades, the increased usage of advanced medical therapies did not result in an increased time to resection, and CRC rate has remained unchanged in UC patients undergoing colectomy. A significantly higher rate of incidental cancers was seen in colectomy patients being treated with advanced medical therapies. Especially patients with an incidental cancer were demonstrated to have poor survival with significantly decreased CRC-related survival, which might be a result of endoscopic undetectable cancers due to ongoing inflammation. This information should be incorporated in clinical decisions when counseling patients on advanced therapies who are treatment-refractory for either cycling to yet another therapy line or instead opting for colectomy.

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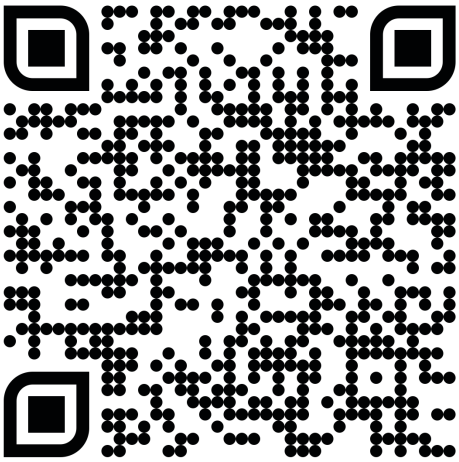
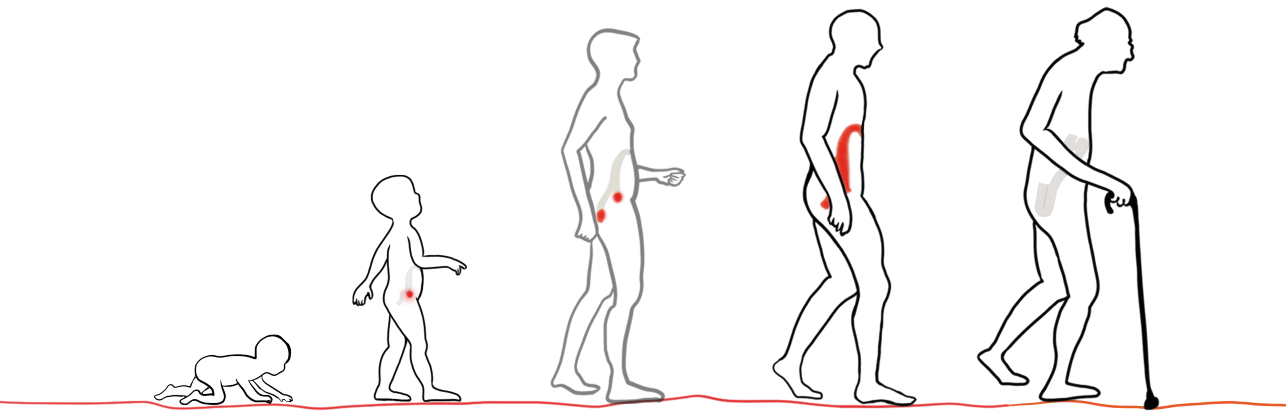
Supplementary materials



11

Chapter 11

Summary



This thesis, titled "New insights into the management of ulcerative colitis", investigates the evolving role of surgical interventions, particularly appendectomy, in the management of UC, juxtaposing these findings against the efficacy of current medical therapies and assessing the impact of advanced therapies on CRC outcomes in UC patients undergoing colectomy. The work is structured into four parts, each addressing different aspects of UC management, with a primary emphasis on the clinical utility of appendectomy in both maintenance and induction of remission.

Part I establishes a reference framework by synthesising the absolute efficacy of approved advanced medical therapies in UC. This systematic review and meta-analysis (**Chapter 2)** demonstrated that approved biologic agents and small molecules provided significant absolute benefits in inducing and maintaining remission in patients with moderate to severe UC compared with placebo or active comparators. The pooled risk differences (Δ) for clinical remission were +13.1% for induction (based on 11,414 patients) and +21.1% for maintenance (based on 6,600 patients), providing a benchmark for evaluating non-pharmacological interventions such as appendectomy.

Part II focuses on the ACCURE trial, the first RCT to assess laparoscopic appendectomy in addition to medical therapy for maintenance of remission in UC patients not receiving biologics. **Chapter 3** outlines the statistical analysis plan, detailing the trial design, primary outcomes and predefined analyses. **Chapter 4** presents the main results of the ACCURE trial, which showed that appendectomy was a safe and well-tolerated procedure in a cohort of 197 patients, and significantly reduced one-year relapse rates compared to standard medical therapy alone (36% vs 56%, p=0.005). A relative risk reduction of 35% indicates the potential of appendectomy as an adjunct to medical therapy in maintaining remission in UC. **Chapter 5** investigates clinical and patient demographic predictors of maintained remission post-appendectomy and demonstrated that younger age (age 10-years increase hazard ratio [HR] 1.97, 95% CI 1.23 to 3.16, $p_{interaction}$=0.005) and a history of smoking (HR 0.28, 95% CI 0.09 to 0.89, $p_{interaction}$=0.031) were associated with a stronger benefit from appendectomy. These findings may inform patient selection and support a more targeted approach to surgical intervention. **Chapter 6** explores histopathology findings in appendiceal specimens and their correlation with relapses. Appendiceal inflammation was prevalent in over half (55.4%) of patients with quiescent UC, potentially predicting relapse risk, particularly among patients with extensive epithelial neutrophil infiltration (44.4% vs 18.0%, p=0.05).

Part III evaluates the efficacy of therapeutic appendectomy as an adjunct to advanced medical therapy in remission induction in biologic-failed patients with moderately to severely active UC. The COSTA trial (**Chapter 7**) found, in a cohort of 116 patients, appendectomy to be superior to JAK inhibitors in achieving clinical remission without therapy failure at 12 months (32.8% vs 12.2%, p=0.01) and could be performed safely in this patient population, with only 4% experiencing minor complications. These results suggest that appendectomy may represent a potential therapeutic intervention in biologic-failed patients. **Chapter 8** explores the predictive value of IUS in identifying responders to appendectomy. A transverse appendiceal diameter (TAD) of ≥6 mm was associated with favourable treatment response, while increased relative submucosal echogenicity (RSE >113) predicted non-response. A clinical decision-making pathway based on these imaging features was proposed. **Chapter 9** investigates the biological activity in the appendix of responders and non-responders to appendectomy and identified two distinct phenotypic subtypes (stromal and epithelial) and found that these subtypes exhibit divergent biological pathways associated with response to appendectomy. This understanding is crucial for future patient selection strategies.

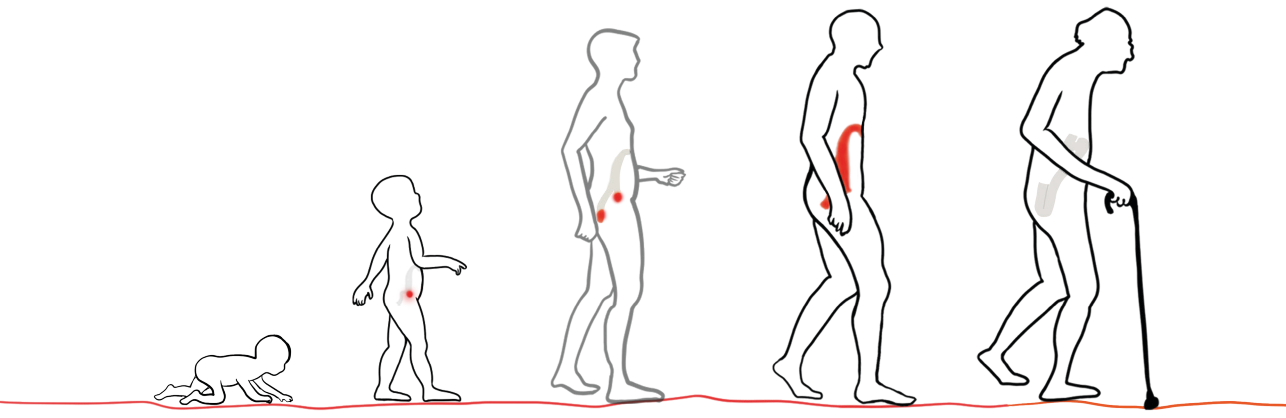
Part IV transitions to the implications of advanced medical therapies on colectomy and oncological outcomes in UC patients who underwent colectomy. **Chapter 10** shows that, despite the increasing use of biologics and small molecules over the past two decades, the time to colectomy (median 7.2 years, IQR 2.8 to 14.1) and overall CRC rates (10.1% [72/716]) remained unchanged. Notably, incidental cancers were more frequent in patients previously treated with advanced therapies (37.5% vs 8.3%, p=0.002) and were associated with poorer CRC-related survival (HR 3.3, 95% CI 1.17 to 9.4; p=0.02). This section raises important considerations regarding the timing of surgical intervention in this high-risk patient group.

Overall, this thesis demonstrates that appendectomy, both as an adjunct to maintenance and induction therapy, offers clinically meaningful benefits in selected UC populations. It also identifies predictive markers that may guide surgical decision-making and provided new insights into the biological activity of the appendix. While the increasing use of advanced medical therapies did not alter the time to resection, it was associated with a higher prevalence of incidental CRC in patients undergoing colectomy.

12

Chapter 12

General discussion and future perspectives



The findings of this thesis challenge traditional treatment paradigms in UC, positioning surgical appendectomy as a promising adjunct to medical therapy, and potentially as a first-line treatment in selected cases. Through the pragmatic ACCURE and COSTA trials, representing the first controlled studies evaluating the role of appendectomy in remission maintenance (ACCURE) and induction (COSTA), this work reframes the appendix from a vestigial structure into a potentially clinically relevant therapeutic target.

Therapeutic ceiling of advanced medical therapies

The therapeutic landscape for UC continues to evolve. Our systematic review and meta-analysis in **Chapter 2** established an absolute benefit of 13% in clinical remission rates during induction therapy, compared to placebo or an active comparator. This therapeutic range was reaffirmed by a network meta-analysis published in 2024, reporting relative efficacy estimates across treatment agents. Based on its supplementary data, we calculated a comparable pooled absolute remission rate (Δ) of 13%.[1] Recent Phase 2b RCTs of duvakitug and obefazimod (ABX464) show promising but similar remission rates, mirroring earlier outcomes.[2,3] These consistent yet plateauing results indicate that, despite ongoing innovation, the therapeutic ceiling of 10-20% in UC has not yet been broken.[4]

Removal of the appendix for maintenance of remission

Chapter 4 provides the first RCT (ACCURE) evaluating appendectomy as an adjunctive strategy for remission maintenance in UC. To date, no other RCTs have directly assessed appendectomy in this context, positioning ACCURE as a landmark study. Its statistically significant 20% absolute benefit over standard medical therapy alone sets a new benchmark for surgical adjuncts in UC management. The most recent meta-analysis, published in 2020, reported a comparable risk reduction of 0.68 in patients treated with 5-ASA.[5] The trial's prolonged recruitment period (spanning ten years) likely reflects the inherent challenges of the study design, which required patients to be both in remission and willing to undergo surgery and randomisation. Additionally, due to logistical constraints during the COVID-19 pandemic, the primary outcome was amended to include clinical relapses without mandatory endoscopic confirmation. While a masked critical event committee was implemented to mitigate potential bias and preserve external validity, the possibility of performance bias cannot be fully excluded. Future trials should incorporate blinded, centralised endoscopic assessment, as well as blinded data

entry and analysis. Modern trial designs—such as platform trials, multi-arm multi-stage trials, and trials within cohorts (TwiCs)—should be considered, with particular attention to patient-preference biases, in order to minimise placebo effects and enhance both generalisability and methodological rigour.

Removal of the appendix for induction of remission

The COSTA trial (**Chapter 7**) was the first controlled trial directly comparing appendectomy with a medical therapy in moderately to severely active UC. At 12 months, clinical remission without treatment failure was achieved significantly more often in the appendectomy group (33%) than in the JAK inhibitor group (12%). To date, no similar head-to-head comparisons have been published. However, the ongoing ADVANCED-UC trial (NCT05931458), which randomises patients to receive infliximab with or without adjunctive appendectomy, may provide further insights into the therapeutic role of the appendix in active UC.[6] Future research should consider the use of standardised medical regimens across study arms to enable a clearer evaluation of the isolated effectiveness of appendectomy.

Towards personalised surgical strategies

This thesis identified clinical, imaging, and histopathological predictors of appendectomy response in two distinct UC populations: patients in remission (quiescent UC; **Chapters 5-6)** and those with moderately to severely active, biological-refractory disease (**Chapters 7-9)**. While these groups differ in disease activity, treatment history, and clinical context, integrating predictive markers across both groups provides a more comprehensive foundation for personalised surgical decision-making. In quiescent UC, younger age and smoking history emerged as relevant predictors to response, whereas in active disease, ultrasound markers (TAD ≥6 mm and increased submucosal echogenicity), and transcriptomic phenotypes (stromal versus epithelial) offer a new dimension for preoperative stratification. These findings are complementary rather than interchangeable. Future research should examine whether predictors identified at one stage of disease retain their prognostic value at other stages, and whether a unified model for patient selection can be developed to guide appendectomy decisions across the full spectrum of UC activity.

Although directly comparable datasets are currently lacking for the aforementioned predictors, the observed age-related associations align with previous findings.[7,8]

These associations should be re-evaluated in larger, post-therapeutic appendectomy cohorts to confirm their validity and assess whether similar patterns exists across the broader appendectomy population. In parallel, the biological rationale behind age-dependent effects warrants further mechanistic exploration.

This thesis (**Chapter 6)** also builds on recent pathology-focused research, such as Agrawal et al.,[9] which emphasised the immunological role of the appendix in UC, and previous work from our group (Heuthorst et al.[10]), which found that ulcerative appendicitis is common and independent of disease severity and extent. However, both studies lacked direct clinical correlation. Our findings help bridge this gap by demonstrating a potential link between histological appendiceal inflammation and relapse risk in patients with quiescent UC. If this association is confirmed, this would support the hypothesis that the appendix may act as a priming site in UC pathogenesis, an idea that warrants further investigation. Future research should also explore whether appendiceal inflammation is associated with better disease outcomes post-appendectomy, particularly when identified preoperatively. The presence of a peri-appendiceal red patch (PARP) during colonoscopy, defined as a localised area of erythema surrounding the appendiceal orifice, has been associated with appendiceal inflammation.[11] However, PARPs are observed in only 18% of UC patients in our series,[11] whereas histological inflammation is present in over 50%, indicating limited sensitivity. This highlights the need for alternative modalities, such as ultrasound, to non-invasively detect appendiceal inflammation and assess its correlation with treatment response. Ultimately, such tools could support the identification of patients most likely to respond to appendectomy and allow future comparison between those who benefit from appendectomy and those who do not, stratified by the presence of absence of appendiceal inflammation.

This thesis also introduces a novel biological framework for understanding treatment response to appendectomy in UC. Transcriptomic profiling revealed two distinct responder phenotypes, one characterised by stromal-associated gene expression and the other by epithelial and B-cell related signatures, each with differing immune regulatory features. While responders were found in both groups, the underlying molecular mechanisms appear to diverge suggesting that appendectomy may act through multiple biological pathways. These insights underscore the need for future trials to incorporate biological components aimed at identifying predictive biomarkers of response.

Balancing medical therapy and surgical timing in high-risk UC patients

We also explored the impact of advanced medical therapies on surgical and oncological outcomes in 716 UC patients who ultimately underwent colectomy at two tertiary referral centres (**Chapter 10**). These findings raise important clinical questions about whether surgical decision-making should be redefined or stratified based on prior exposure to advanced therapies, overall disease trajectory, or individual risk profile.[12] This chapter underscores the need to identify both patient- and surgery-related factors that may contribute to poorer prognosis in incidental CRCs, including prolonged disease duration, time since last exacerbation, and limitations in endoscopic surveillance due to active inflammation. Given the dismal oncological outcomes in this subgroup, an oncological resection, such as total mesorectal excision (TME), might be justified in patients with active disease where adequate surveillance is not feasible. The choice of surgical approach, particularly close rectal dissection versus oncological resection (TME), may significantly influence long-term outcomes in incidental CRCs. These findings also prompt critical reflection on whether current surveillance guidelines are sufficiently robust, especially considering that active inflammation often precludes effective neoplasia detection. It is noteworthy that the current ECCO guidelines on IBD and malignancies[13] do not involve surgical expertise, raising concerns about the completeness of the recommendations, given that optimal oncological outcomes rely not only on effective surveillance but also on technically appropriate surgical intervention.

It is important to note that our study focused exclusively on UC patients who ultimately underwent colectomy at tertiary centres and, therefore, does not provide information on the overall incidence of CRC in the broader UC population. Nonetheless, our findings should be interpreted within the context of evolving colectomy trends. A 2023 meta-analysis reported declining colectomy rates in UC over the past three decades.[14] Concurrently, a national pathology study from the Netherlands documented an increasing proportion of CRC diagnoses among colectomised UC patients, raising concerns about an emerging shift in colectomy indication.[15]

As medical therapies are effective at inducing remission and used for longer durations, surgery may be deferred until neoplastic progression, such as dysplasia or cancer, rather than performed for inflammatory disease control. This shift raises concerns about delayed surgical referral, missed therapeutic windows,

and greater inflammatory burden at the time of surgery, potentially contributing to higher rates of incidental or advanced-stage CRC. These trends underscore the importance of timely surgical consideration in patients with longstanding, treatment-refractory inflammation, particularly when endoscopic surveillance is limited or unfeasible. Overall, the findings support the need for early surgical consultation and a more proactive, risk-stratified approach to surgical decision-making in high-risk UC populations, aiming to optimise survival and minimise the risk of undetected malignancy. In patients being considered for a second advanced therapy, timely referral for surgical evaluation should be strongly considered. Early surgical consultation facilitates shared decision-making and may prevent delays in intervention that could negatively impact long-term outcomes, particularly in those with ongoing inflammation and limited endoscopic surveillance options. Balancing the benefits of advanced medical therapy with timely surgical intervention remains a critical challenge in the long-term management of UC.

Implications, methodological considerations, and future perspectives

This thesis challenges the traditional pharmacological paradigm of UC management, positioning the appendix as an active immunological organ involved in disease pathogenesis. Through the ACCURE and COSTA trials, the first controlled studies to investigate appendectomy as a therapeutic strategy for both remission maintenance and induction, appendectomy emerges as a promising adjunct, or even a first line alternative, to medical therapy. These findings support a more integrated and biologically informed treatment framework that combines surgical and pharmacological strategies tailored to individual patient profiles. The demonstrated safety and efficacy of appendectomy in selected populations, particularly those with therapy-refractory or biologic-exposed disease, highlight its potential as a disease-modifying intervention beyond its traditional use as a surgical last resort (colectomy).

The feasibility of conducting rigorous surgical trials in UC is also affirmed, although several methodological limitations warrant attention. First, comparing surgical and pharmacological interventions introduces inherent design challenges, particularly related to patient preference, blinding, and placebo effects. Second, certain analysis, such as those involving imaging and histopathology, were conducted in relatively small, single-centre cohorts, limiting generalisability of the findings in the broader UC population. Third, the follow-up duration in both ACCURE and COSTA trials was limited to 12 months, restricting conclusions about long-term outcomes, including

the durability of remission, sustained medication de-escalation, colectomy-free survival, and long-term safety. However, longer-term observational data from the PASSION cohort study[16] offer early insights: among 25 patients with therapy-refractory UC who were initially referred for colectomy and instead underwent appendectomy, 24% achieved sustained endoscopic improvement and only 36% ultimately required colectomy after a median follow-up of eight years, suggesting a potential durable benefit that warrants further controlled evaluation. To address these limitations, future trials should adopt innovative and pragmatic designs, such as TwiCs, which can mitigate self-selection bias and confounding in preference-sensitive interventions. A pragmatic design incorporating real-world populations, standardised treatment regimens across study arms, centralised endoscopic assessment, and strategies to minimise placebo effects will be essential to ensure both internal validity and external applicability.

Several key research priorities emerge. There remains a critical knowledge gap regarding the role of appendectomy in biologic-exposed patients in clinical remission. Rather than initiating separate trials for each subgroup, future research should focus on integrated, pragmatic study designs, such as platform trials or TwiCs, to evaluate effectiveness across varying patient profiles more efficiently. Mechanistic and translational research should further investigate how appendectomy may influence intestinal immunity, the gut microbiome, and epithelial barrier function, helping to clarify its therapeutic mechanism and potentially explain observed placebo responses. Long-term follow-up studies are also required to determine the durability of treatment effects, assess medication use and colectomy-free survival, and compare outcomes with the only currently available long-term data: the eight-year, non-controlled findings reported by Reijntjes et al.[16] These investigations should be accompanied by cost-effectiveness analyses, particularly in the context of the substantial financial burden posed by chronic biologic therapies. This is especially relevant in low- and middle-income countries, where appendectomy may represent an accessible, cost-effective alternative to long-term pharmacological management. Moreover, differences in disease phenotypes and care pathways, such as more extensive disease or delayed diagnosis at presentation, may influence treatment outcomes in these settings, warranting context-specific evaluation.[17]

Another key direction is the refinement of patient-selection strategies for appendectomy. This thesis identifies a range of promising clinical, imaging, and molecular markers that may help predict treatment response, including clinical characteristics (e.g. age, smoking history), imaging findings (e.g. ultrasound features),

and molecular markers. These indicators should be validated in larger, independent cohorts, and incorporated into predictive models to guide personalised surgical decision-making and maximise therapeutic benefit.

In the context of CRC, findings from this thesis highlight the need to better understand how the timing of colectomy, duration of disease, and surgical technique impact oncological outcomes in UC patients undergoing colectomy. Particular attention should be paid to those who have exhausted medical therapy or in whom adequate surveillance is not feasible due to ongoing inflammation. The increased incidence of incidental cancer in patients previously treated with advanced therapies, underscores the importance of early surgical consultation in selected high-risk individuals. Where endoscopic surveillance becomes unreliable, particularly in patients with ongoing, refractory inflammation, future strategies must either focus on improving alternative diagnostic tools, such as molecular imaging or biomarker-driven risk stratification, or consider earlier surgical intervention as a default strategy in selected cases. Further research should assess how factors such as disease duration, surgical technique, and the timing of colectomy influence oncological outcomes. Comparative studies evaluating oncological resection versus conservative approaches like close rectal dissection will be particularly relevant in this patient population.

Finally, the findings support several practical and policy-relevant recommendations. Based on the evidence presented in this thesis, appendectomy can now be considered a treatment option for selected UC patients, provided it is accompanied by structured postoperative follow-up with outcome monitoring and endoscopic surveillance, in accordance with current guidelines.[18,19] Preoperative evaluation should include diagnostic tools such as ultrasound and targeted biopsies around the appendiceal orifice (caecal patch) to improve response prediction. For patients with therapy-refractory disease, early surgical consultation is especially important for those with a high inflammatory burden or those in whom surveillance is not possible. In light of the accumulating evidence and favourable safety profile, future clinical guidelines should consider formally including appendectomy as a treatment alternative, and its inclusion in national health systems should be explored, particularly for patients who have failed conventional therapies.

In the introduction to this thesis, the appendix was described as a potentially immunologically active organ with an undefined role in UC. The controlled clinical evidence presented here supports that hypothesis, reframing the appendix as a

relevant and modifiable factor in UC pathogenesis. These findings challenge the traditional pharmacological paradigm and call for a shift toward a more integrated and personalised treatment approach that combines surgical and medical strategies based on individual disease biology.

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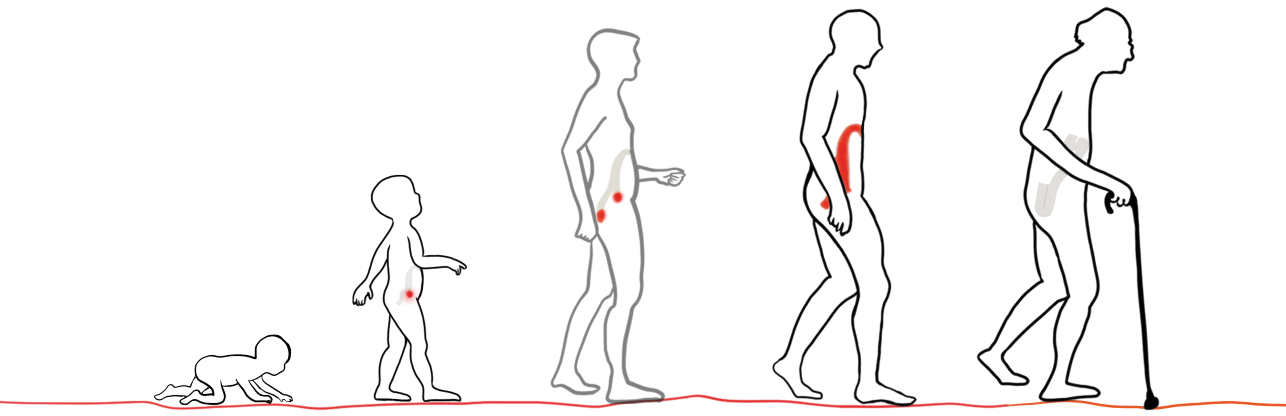
Appendices



Dutch summary – Nederlandse samenvatting

Dit proefschrift onderzoekt nieuwe inzichten en de veranderende rol van de chirurgische interventies, in het bijzonder appendectomie, bij de behandeling van colitis ulcerosa (CU). De bevindingen worden afgezet tegen de effectiviteit van medicamenteuze therapieën, en daarnaast wordt de impact van biologische middelen ("biologicals") en small molecules op colorectale kanker (CRC) bij CU-patiënten die een colectomie ondergingen geëvalueerd. De thesis is opgebouwd uit vier delen, elk gericht op een ander aspect van CU-behandeling, met een nadruk op de klinische waarde van appendectomie bij zowel het behouden als induceren van remissie.

Deel I biedt een referentiekader door de absolute effectiviteit van goedgekeurde geavanceerde medicamenteuze therapieën voor CU samen te vatten. Deze systematische review en meta-analyse (**Hoofdstuk 2**) toonden aan dat biologicals en small molecules significante voordelen bieden bij het induceren en behouden van remissie bij matig tot ernstig actieve CU. De gepoolde absolute risicoverschillen (Δ) voor remissie waren +13.1% voor inductie (gebaseerd op 11,414 patiënten) en +21.1% voor onderhoud (gebaseerd op 6,600 patiënten), wat een maatstaf vormt voor de beoordeling van niet-farmacologische interventies zoals appendectomie.

Deel II richt zich op de ACCURE-studie, de eerste gerandomiseerde gecontroleerde trial (RCT) die laparoscopische appendectomie als aanvullende behandeling onderzocht bij CU-patiënten in remissie die geen biologicals gebruikten. **Hoofdstuk 3** beschrijft het statistisch analyseplan. In **Hoofdstuk 4** wordt aangetoond in een cohort van 197 patiënten dat appendectomie een veilige, goed verdraagbare ingreep is die het percentage opvlammingen op één jaar significant verlaagt vergeleken met standaard medicamenteuze therapie (36% versus 56%, p=0.005). De relatieve risicoreductie van 35% onderstreept het potentieel van appendectomie als aanvullende onderhoudsbehandeling. **Hoofdstuk 5** onderzocht klinische en demografische voorspellers voor remissiebehoud post-appendectomie, waarbij jongere leeftijd (Leeftijd per 10-jaars toename hazard ratio [HR] 1.97, 95% BI 1.23 tot 3.16, $p_{interactie}$=0.005) en een rookverleden (HR 0.28, 95% BI 0.09 tot 0.89, $p_{interactie}$=0.031) geassocieerd waren met meer baat bij appendectomie. Deze bevindingen kunnen mogelijk patiënt selectie bevorderen en dragen bij aan een gerichtere benadering voor chirurgische interventie. **Hoofstuk 6** bespreekt de histopathologische bevindingen in de resectiepreparaten van appendices en hun correlatie met opvlammingen. Bij meer dan de helft (55.4%) van de patiënten met inactieve CU werd inflammatie in de appendix waargenomen, wat mogelijk een

risicofactor is voor opvlamming, met name in patiënten met uitgebreide epitheliale neutrofiele infiltratie.

Deel III beoordeelt de effectiviteit van therapeutische appendectomie als toevoeging aan geavanceerde medicamenteuze behandeling bij patiënten met matig tot ernstig actieve CU die onvoldoende hebben gereageerd op biologicals. De COSTA-studie (**Hoofdstuk 7**) toonde bij 116 patiënten aan dat appendectomie superieur was aan Janus kinase (JAK-)remmers voor het bereiken van remissie zonder therapie falen na 12 maanden (32.8% versus 12.2%, p=0.01) en veilig kon worden uitgevoerd. Deze resultaten suggereren dat appendectomie een potentiële therapeutische interventie kan zijn in deze patiëntengroep. **Hoofdstuk 8** evalueerde de voorspellende waarde van intestinale echografie bij het identificeren van responders. Een transversale appendixdiameter ≥6 mm voorspelde een gunstige respons, terwijl bij patiënten zonder verdikte appendix, een verhoogde submucosale echogeniciteit (RSE >113) een non-respons voorspelde. Op basis hiervan werd een klinisch beslisalgoritme voorgesteld. **Hoofdstuk 9** bestudeerde de biologische activiteit van de appendix bij responders en non-responders en identificeerde twee biologische fenotypes (stromaal en epitheliaal) van de appendix. Ook bleek dat deze fenotypes andere biologische pathways belichten potentieel geassocieerd met behandelrespons. Deze inzichten zijn belangrijk voor toekomstige patiëntselectie.

Deel IV gaat in op de gevolgen van geavanceerde therapieën voor de tijd-tot-chirurgie en oncologische uitkomsten bij CU-patiënten die een colectomie hebben ondergaan. **Hoofdstuk 10** laat zien dat ondanks toegenomen gebruik van biologicals en small molecules, de tijd tot colectomie (mediaan 7.2 jaar, IQR 2.8 tot 14.1) en de totale incidentie van CRC (10.1%) onveranderd bleef. Wel werden meer incidentele carcinomen vastgesteld bij patiënten die eerder met geavanceerde therapieën waren behandeld (37.5% versus 8.3%; p=0.02), met slechtere CRC-gerelateerde overleving (HR 3.3, 95% BI 1.17 tot 9.4; p=0.02). Dit benadrukt het belang van tijdige chirurgische interventie bij hoog risicopatiënten en vraagt aandacht voor potentiële oncologische risico's geassocieerd met biologicals/small molecules.

Samenvattend toont deze thesis dat appendectomie, zowel als toevoeging als onderhouds- als inductietherapie, klinisch relevante voordelen biedt voor een selecte groep CU-patiënten. Er werden voorspellende markers geïdentificeerd die chirurgische besluitvorming kunnen ondersteunen, en nieuwe inzichten verkregen in de biologische activiteit van de appendix. Hoewel geavanceerde therapieën de tijd tot colectomie niet beïnvloedden bij colectomie patiënten, gingen ze gepaard met een hogere prevalentie van incidentele CRC bij geopereerde patiënten.

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Eva Visser, Isabelle D van Dijk, George L Burchell, Willem A Bemelman, Geert R D'Haens, Christianne J Buskens. Efficacy of advanced medical therapies in patients with moderately to severely active ulcerative colitis: a systematic review and meta-analysis. *Submitted (under review)*.

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**Shared senior authorship*

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PhD portfolio

PhD student:	Eva Visser
PhD period:	01-06-2022 – 31-03-2025
Promotores	Prof. dr. Willem A Bemelman & prof. dr. Geert R A M D'Haens
Copromotores	Dr. Christianne J Buskens & dr. Roel Hompes

1. PhD training

	Year	ECTS
General courses		
Basic Course Legalisation and Organization (BROK)	2022	1.5
PubMed	2022	0.1
EndNote	2022	0.1
Project Management	2022	0.7
Practical Biostatistics	2023	1.4
Scientific Writing in English	2023	1.5
Presenting with confidence (in English)	2023	1.0
Advanced topics in Biostatistics	2024	1.5
Computing in R	2024	0.7
Searching for a Systematic Review	2024	0.1
Clinical epidemiology – systematic reviews	2024	0.7
Seminars, workshops and master classes		
Weekly Surgical Department seminars	2022-2025	3.0
IBD Journal Club (biweekly)	2022-2025	1.5
IBD Lunch & Learn (biweekly)	2022-2025	1.5
Surgical Journal Club	2022-2025	3.0
T-Pensant Symposium, OOR regio Leiden	2024	0.2
ICCS Post S-ECCO Wrap-Up	2024	0.2
IBD Research Day	2022-2025	0.2
Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Annual Retreat	2024	1.0
Oral presentations		
Digestive Disease Days (DDD), Nederlandse Vereniging voor Gastro-enterologie (NVGE), Veldhoven	2023	0.5
United European Gastroenterology Week (UEGW), Copenhagen	2023	0.5
IBD Nordic Conference, Malmö	2023	0.5
Today & Tomorrow, Amsterdam	2023	0.5
AGEM Annual Retreat, Garderen 2024	2024	0.5
T-Pensant Symposium, OOR regio Leiden, Den Haag 2024	2024	0.5
Surgical ECCO Wrap-Up, Woerden	2024	0.5
Chirurgendagen (3x), Veldhoven	2024	1.5
IBD Research Day, Zandvoort	2024	0.5
American Society of Colon & Rectal Surgeons (ASCRS), Baltimore	2024	0.5
European Society of Coloproctology (ESCP; 3x), Thessaloniki	2024	1.5
Wetenschapsdag Chirurgie (2x), Amsterdam	2023	1.0
IBD Research Day, Amsterdam	2024	0.5
IBD Research Report, Amsterdam	2025	0.5
European Crohn's and Colitis Organisation (ECCO), Berlin	2025	0.5
Surgical ECCO (S-ECCO), Berlin	2025	0.5
Chirurgendagen, Nieuwegein	2025	0.5
UEGW, Berlin	2025	0.5

Poster presentations		
ECCO, Copenhagen	2023	0.2
IBD Nordic conference, Malmö	2023	0.2
ECCO (2x), Stockholm	2024	0.4
ECCO, Berlin	2025	0.2
(Inter)national conferences		
ESCP	2022-2025	1.0
ECCO	2023-2025	1.0
IBD Today & Tomorrow	2023	1.0
UEGW	2023, 2025	2.0
IBD Nordic Conference	2023	1.0
ASCRS	2024	1.0
DDD	2023-2025	2.0
Chirurgendagen	2023-2025	3.0
IBD Research Day (biyearly)	2023-2024	2.0
Wetenschapsdag Chirurgie Amsterdam	2022-2024	1.0
ICC-day	2022	0.5

2. Teaching

	Year	ECTS
Lecturing		
T-Pansant OOR Regio Leiden	2024	0.5
Supervising		
Bachelor student	2024	1.0
Master student	2025	1.0

3. Parameters of Esteem

	Year
Awards and Prizes	
Best abstract – Chirurgendagen 2024, Veldhoven	2024
Best paper – ASCRS 2024, Baltimore	2024
Six Best – ESCP 2024, Thessaloniki	2024
Best abstract - Wetenschapsdag Chirurgie, Amsterdam	2024
Best Digital Oral Presentation – ECCO 2025, Berlin	2025

4. Publications

	Year
Peer reviewed	2025
Techniques in Coloproctology (2x)	

5. Committees

	Year
Selected member – ECCO Surgical UC Treatment Guideline Committee	2024-2025

Dankwoord

De laatste pagina's van dit proefschrift wil ik benutten om iedereen te bedanken die de afgelopen jaren heeft bijgedragen aan mijn promotietraject. Het waren bijzondere en waardevolle jaren, die ik niet had kunnen doormaken zonder de steun, betrokkenheid en inzet van velen om mij heen.

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About the author

Eva Visser was born on March 18, 1996, in Rotterdam, where she grew up with her sister and their mother, while her father and 'bonus father' remained involved in her life. From an early age, she was a lively mix of energy and curiosity – with a love for music (she played the accordion), being surrounded by friends, and an endless appetite for sports. In her final year of primary school, she gave a class presentation on surgery, a moment that sparked her lifelong ambition to become a surgeon.

She attended the Erasmiaans Gymnasium in Rotterdam and began her medical studies at Erasmus University in 2014. Before starting clinical internships, she set off on a solo backpacking trip through Indonesia, Cambodia, Vietnam, and Australia, reflecting her adventurous spirit and love for meeting new people.

After completing her medical degree, Eva worked as a resident not in training (ANIOS) in the Department of Surgery at Maasstad Hospital in Rotterdam, where her passion for surgery deepened. In 2022, she began a PhD in colorectal surgery at Amsterdam UMC, focusing on IBD surgery under the supervision of prof. dr. W.A. Bemelman, dr. C.J. Buskens, prof. dr. G.R.A.M. D'Haens and dr. R. Hompes. Her research centered on the role of the appendix in UC, surgical outcomes, and CRC risk in colectomised UC patients. She has contributed to multiple national and international studies and coordinated multicentre clinicals trial. She is currently working as a resident not in training in the Department of Surgery at Amphia Hospital in Breda.

Eva is known for her enthusiasm, sociability and team spirit. She thrives in collaboration, whether in the hospital, at research sessions, or during evenings with friends. She draws energy from the people around her and believes that the best ideas are made together. Her enthusiasm is a key trait that define her both personally and professionally. Outside of work, Eva is a dedicated athlete. Running is her greatest passion, complimented by cycling and a love for trying new sports. True to form, she is always chasing the next challenge—whether in science, the clinic or sport.