Research in surgical treatment of Inflammatory Bowel Disease

Rethinking dogmas

Wasmann, K.A.T.G.M.

Publication date
2021

Document Version
Final published version

License
Other

RESEARCH IN SURGICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE

RETHINKING DOGMAS

KARIN WASMANN

Research in surgical treatment of Inflammatory Bowel Disease

Rethinking Dogmas

Karin Wasmann

Cover design: Guusje Dijkmans | Picturale.nl
Karin Sels | Artlook.be
Layout: Renate Siebes | Proefschrift.nu
Printed by: ProefschriftMaken, De Bilt
ISBN: 978-94-6423-106-9

Research in surgical treatment of Inflammatory Bowel Disease

Rethinking Dogmas

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 29 januari 2021, te 14.00 uur

door

Karin Antoinette Theodora Guusje Maria Wasmann

geboren te West Maas en Waal

Promotiecommissie

Promotores:	Prof. dr. W.A. Bemelman	AMC-UvA
	Prof. dr. G.R.A.M. D'Haens	AMC-UvA
Copromotor:	Dr. C.J. Buskens	AMC-UvA
Overige leden:	Prof. dr. M.A. Boermeester	AMC-UvA
	Prof. dr. C.Y. Ponsioen	AMC-UvA
	Prof. dr. J. Stoker	AMC-UvA
	Prof. dr. L.P.S. Stassen	Universiteit Maastricht
	Dr. K.B. Gecse	AMC-UvA
	Dr. M.W. Mundt	Flevoziekenhuis

Faculteit der Geneeskunde

Table of content

Part 2: Ulcerative colitis – Innovative surgical strategies for pouch surgery


RETHINKING
DOGMAS
RETHINKING
DOGMAS

General introduction

General introduction

After colorectal tumors, inflammatory bowel disease (IBD) is the most common indication for bowel resection. However, compared to colorectal tumors, surgery plays a less prominent role in IBD guidelines. As, the optimization of IBD treatment is work in progress, now is the time to rethink developments. Should we progress in this way or do we already run into dogmas?

Inflammatory bowel disease (IBD) is a chronic auto-immune inflammatory disease of the gastrointestinal tract. The two most common types are Crohn's disease (CD) and ulcerative colitis (UC). Both CD and UC are usually diagnosed between the age of 15 and 35.[1] The exact cause of IBD is still unknown and no definite cure exists. The current treatment consists of a combination of medical and surgical approaches, both aiming to suppress symptoms and halting disease progression.[2] The medical therapy entails an armamentarium of immunosuppression drugs, which is applied in a step-up approach. Surgery can be an alternative to medication, while sometimes unavoidable because of disease progression or intolerance to medication. Due to its chronic character, living with IBD affects the quality of life, including lack of energy, declining work performance and less libido for many patients in the prime of their lives.[1,3]

To enhance the quality of life of IBD patients, research was conducted to optimize treatment outcomes. Before the implementation of randomised controlled trials (RCT), studies were dominated by expert opinions. To increase the scientific value of research one focused on the level of control (internal validity). During the 1980's this developed into generally accepted methodologic hierarchies, with case reports at the bottom and RCTs considered to be the senior methodology.[4] Evidence based medicine became the standard. Some of the most defining RCTs in the field showed promising results of anti-tumour necrosis factor α antibodies (anti-TNF) for the treatment of IBD.[5,6] However, surgery can be an alternative to the medical approach, as has been demonstrated by the LIR!C trial. But, apart from this study these two strategies are barely directly compared to each other. It is debatable whether the established RCT is the most optimal study design to compare medication versus surgical therapies. Currently, the principle of evidence-based medicine with a focus on internal validity could at times fall short for tailored IBD treatments. Food for thought, which motivated this research group to reflect on certain dogmas in research for the surgical treatment of IBD.

Perianal Crohn's disease

CD can occur anywhere in the gastrointestinal tract, including the distal rectum with the development of perianal fistulas. The lifetime risk of perianal fistula evolvement ranges from 14% to 38%.[7] Perianal CD fistulas has a significant impairment of daily activities due to pain, purulent discharge and perineal tissue destruction.[8] To date, the

three standard treatment options for high perianal fistulas are i) the surgical approach by chronic seton drain drainage, ii) the medical approach by anti-TNF and iii) surgical closure with or without anti-TNF treatment.[9,10] Looking at previous studies, the fistula closure rates seems comparable between these three treatment options, while it is suggested that the re-intervention rate is substantially lower with seton drainage compared to anti-TNF and surgical closure.[11–13] However, prior studies were flawed by a high risk of bias, had short follow-up, and none of the studies directly compared seton drainage to anti-TNF treatment and/or surgical closure. Therefore, the aim of **chapter 1** was to identify the optimal treatment of perianal Crohn's disease fistulas (PISA RCT).

Designing surgical trials

What is the Holy Grail; performing an RCT or striving for an unbiased answer to the research question? At the very least we should consider if an RCT is the 'Holy Grail' for each study setting. Bias due to treatment preference can be expected when treatment groups significantly differ between each other. Lessons are learned from the PISA study (medical vs. surgical treatment options), in which almost half of the patients declined enrolment to avoid being randomised to their non-preferred treatment arm. When a significant number of patients decline participation, the generalizability of RCT results to daily clinical practice can be affected, resulting in decreased external validity. Meanwhile, internal validity might also be affected due to randomisation of patients to their (non-) preferred strategy, potentially influencing treatment adherence and subjective study outcomes. A partially randomised patient preference trial has been developed to diminish the influence of patients' preference on study outcomes. The aim of **chapter 2** was to assess the validity of this alternative design for RCT's.

Ileocecal resection

CD most frequently affects the terminal ileum. The majority of these patients require surgery, making ileocecal resection the most common surgical procedure in CD patients. Unfortunately, a substantial proportion of patients will develop post-operative disease recurrence. In contrast to colorectal cancer surgery, current IBD guidelines do not specifically recommend performing a radical resection (i.e., avoid inflamed resection margins). Furthermore, these guidelines advise close bowel resection, leaving the mesentery in situ. The aim of **chapter 3** was to assess the predictive value of inflamed ileocecal resection margins for disease recurrence. The aim of **chapter 4** was to map the gradient of pro-inflammatory and regulatory macrophages in the mesentery, in order to find a rationale for additional resection of the mesentery during ileocecal resection.

Waiting list complications

The waiting list for colorectal surgery increases, for which patients are prioritised. Since it is mandatory to adhere to the newly implemented oncology quality- and volume

standards, oncological surgeries are given priority over 'benign' diseases.[14,15] However, due to the progressive character of IBD, this may result in severe 'waiting list complications' such as strictures and fistulas development, septic episodes, malnutrition or hospital admission. Therefore, it is debatable if current triage is justified. In **chapter 5** we highlight the potential consequences of a longer interval towards surgery for IBD patients.

Pouch surgery

In contrast to CD, UC is restricted to the large bowel. UC patients are primarily treated with medication. However, in up to 20% of patients a colectomy is required because of medical therapy refractory disease.[16,17] To avoid a permanent ileostomy, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) was introduced in the 1980's and has since become the treatment of choice.[18] Although IPAA offers bowel continuity restoration, it is also associated with significant surgical morbidity, including anastomotic leakage in up to 15% of patients.[19–21] Inadequately managed anastomotic leakage affects long-term pouch function and is the main cause of pouch failure (receiving an stoma after all).[21–23] The aim of **chapter 6 and 7** was to address the recently introduced minimal invasive transanal IPAA approach, and its influence on anastomotic leakage and long-term outcomes of IPAA surgery. Additionally, the treatment possibilities of anastomotic leakage have developed with the implementation of the Endo-sponge® assisted early surgical closure. **Chapter 8** aimed to address the long-term results of Endo-sponge® assisted early surgical closure. Furthermore, proctitis after subtotal colectomy is common for UC patients. However, the impact on pouch outcomes is unknown. The goal of **chapter 9** was to determine the extent of the relationship between proctitis and anastomotic leakage and pouchitis.

In conclusion, we have identified several common dogmas in daily IBD treatment, which we will try to address in this thesis.

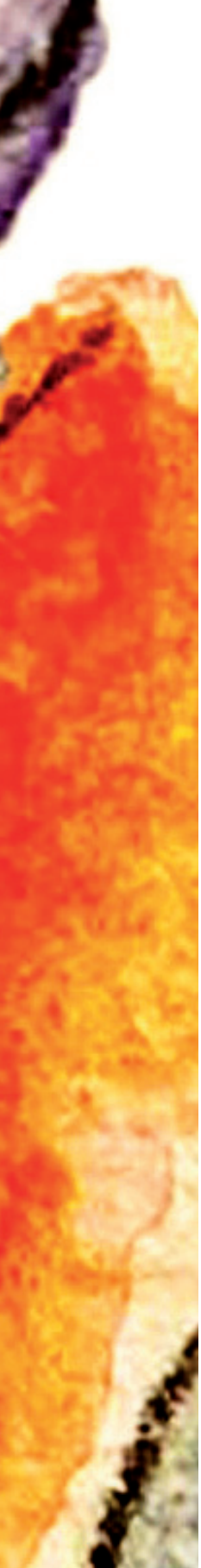
Research questions addressed in this thesis

1. With respect to re-interventions, is seton treatment superior to anti-TNF treatment and surgical closure combined with anti-TNF for patients with a high perianal Crohn's fistula?
2. Is a partially randomised patient preference trial a valid alternative to a randomised controlled trial regarding internal and external validity?
3. What is the predictive value of microscopic inflammation at ileocecal resections margins for postoperative Crohn's recurrence?
4. Is there an anatomical variation in mesenteric macrophage phenotypes that can guide surgical resection margins in Crohn's disease?
5. Is a longer waiting time for IBD surgery associated with 'waiting list complications'?
6. Is transanal versus transabdominal minimally invasive pouch surgery in UC beneficial regarding short-term morbidity?
7. Does transanal versus transabdominal minimally invasive pouch surgery in UC result in superior long-term pouch function?
8. Does Endo-sponge assisted early surgical closure of pouch leakage improve long-term pouch function?
9. What is the impact of rectal sump inflammation on anastomotic pouch leakage and pouchitis?

References

1. Torres, J., Mehandru, S., Colombel, J.-F. & Peyrin-Biroulet, L. Crohn's disease. Lancet 389, 1741–55 (2017).
2. Peyrin-Biroulet, L., Loftus, E. V, Colombel, J.-F. & Sandborn, W. J. The natural history of adult Crohn's disease in population-based cohorts. Am. J. Gastroenterol. 105, 289–97 (2010).
3. Ungaro, R., Mehandru, S., Allen, P. B., Peyrin-Biroulet, L. & Colombel, J.-F. Ulcerative colitis. Lancet (London, England) 389, 1756–70 (2017).
4. Jones, D. S. & Podolsky, S. H. The history and fate of the gold standard. Lancet 385, 1502–3 (2015).
5. Present, D. H. et al. Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease. N. Engl. J. Med. 340, 1398–405 (1999).
6. Targan, S. R. et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N. Engl. J. Med. 337, 1029–35 (1997).
7. Hellers, G., Bergstrand, O., Ewerth, S. & Holmström, B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut 21, 525–7 (1980).
8. Viganò, C., Losco, A., Caprioli, F. & Basilisco, G. Incidence and clinical outcomes of intersphincteric abscesses diagnosed by anal ultrasonography in patients with crohn's disease. Inflamm. Bowel Dis. 17, 2102–8 (2011).
9. Hakkaart- van Roijen L, Tan SS, B. C. Handleiding voor kostenonderzoek: methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen 2010.
10. de Groof, E. J. et al. Systematic review of evidence and consensus on perianal fistula: an analysis of national and international guidelines. Colorectal Dis. 18, O119-34 (2016).
11. Stellingwerf, M. E., van Praag, E. M., Bemelman, W. A. & Buskens, C. J. P426 Meta-analysis of endorectal advancement flap vs. ligation of the intersphincteric fistula tract for Crohn's and cryptoglandular high perianal fistulas. J. Crohn's Colitis 12, S320 (2018).
12. Soltani, A. & Kaiser, A. M. Endorectal Advancement Flap for Cryptoglandular or Crohn' s Fistula-in-Ano. Dis. Colon Rectum 53, 486–95 (2010).
13. de Groof, E. J. et al. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis. 18, 667–75 (2016).
14. Oncologie gaat voor, andere zorg in de verdrukking | medischcontact. Available at: https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/oncologie-gaat-voor-andere-zorg-in-de-verdrukking.htm#. (Accessed: 17th April 2019)
15. IKNL. Landelijke werkgroep Gastro Intestinal Tumoren. Colorectaal carcinoom. Landelijke richtlijn, versie 3.0, 2014. Oncoline.nl (2014).
16. Targownik, L. E., Singh, H., Nugent, Z. & Bernstein, C. N. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. Am. J. Gastroenterol. 107, 1228–35 (2012).
17. Sahami, S. et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. United Eur. Gastroenterol. J. 5, 554–62 (2017).
18. Parks, A. G. & Nicholls, R. J. Proctocolectomy without ileostomy for ulcerative colitis. Br. Med. J. 2, 85–8 (1978).
19. Sossenheimer, P. H. et al. Abnormal Pouchogram Predicts Pouch Failure Even in Asymptomatic Patients. Dis. Colon Rectum 1 (2018). doi:10.1097/DCR.0000000000001285
20. Santorelli, C., Hollingshead, J. & Clark, S. K. Clinical value of pouchogram prior to ileostomy closure after ileal pouch anal anastomosis. Tech. Coloproctol. 22, 541–4 (2018).
21. Sahami, S. et al. A Multicentre Evaluation of Risk Factors for Anastomotic Leakage After Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease. J. Crohns. Colitis 10, 773–8 (2016).
22. de Buck van Overstraeten, A. et al. Transanal Versus Transabdominal Minimally Invasive (Completion) Proctectomy With Ileal Pouch-anal Anastomosis in Ulcerative Colitis: A Comparative Study. Ann. Surg. 1 (2017). doi:10.1097/SLA.0000000000002395
23. Bartels, S. A. L. et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. Br. J. Surg. 102, 281–7 (2015).


RETHINKING
DOGMAS



PART 1

Crohn's disease – Innovative (surgical) strategies


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 1

Treatment of perianal fistulas in Crohn's disease, seton versus anti-TNF versus surgical closure following anti-TNF (PISA): a randomised controlled trial

Karin A Wasmann, E Joline de Groof, Merel E Stellingwerf, Geert R D'Haens, Cyriel Y Ponsioen, Krisztina B Gecse, Marcel G W Dijkgraaf, Michael F Gerhards, Jeroen M Jansen, Apollo Pronk, Sebastiaan A C van Tuyl, David D E Zimmerman, Karlien F Bruin, Antonino Spinelli, Silvio Danese, Jarmila D W van der Bilt, Marco W Mundt, Willem A Bemelman, Christianne J Buskens

JCC. 2020; 14(8): 1049-56

Abstract

Background and aims: Most patients with perianal Crohn's fistula receive medical treatment with anti-tumour necrosis factor (TNF), but the results of anti-TNF treatment have not been directly compared with chronic seton drainage or surgical closure. The aim of this study was to assess if chronic seton drainage for patients with perianal Crohn's disease fistulas would result in less re-interventions, compared with anti-TNF and compared with surgical closure.

Methods: This randomised trial was performed in 19 European centres. Patients with high perianal Crohn's fistulas with a single internal opening were randomly assigned to: i) chronic seton drainage for 1 year; ii) anti-TNF therapy for 1 year; and iii) surgical closure after 2 months under a short course anti-TNF. The primary outcome was the cumulative number of patients with fistula-related re-intervention(s) at 1.5 years. Patients declining randomisation due to a specific treatment preference were included in a parallel prospective PISA registry cohort.

Results: Between September 14, 2013 and November 20, 2017, 44 of the 126 planned patients were randomised. The study was stopped by the data safety monitoring board because of futility. Seton treatment was associated with the highest re-intervention rate (10/15, versus 6/15 anti-TNF and 3/14 surgical closure patients, $P = 0.02$). No substantial differences in perianal disease activity and quality of life between the three treatment groups were observed. Interestingly, in the PISA prospective registry, inferiority of chronic seton treatment was not observed for any outcome measure.

Conclusions: The results imply that chronic seton treatment should not be recommended as the sole treatment for perianal Crohn's fistulas.

The trial is registered with Trialregister.nl number NTR4137.

Introduction

The lifetime risk of fistula development in patients with Crohn's disease (CD) ranges from 14% to 38%.[1] Perianal CD fistulas cause pain, purulent discharge, and sphincter and perineal tissue destruction, resulting in a significant impairment of quality of life (QoL).[2] Also, the impact on health care resources is considerable, due to multiple surgical interventions and biologic drugs.[3] In daily clinical practice, no consensus has been reached on the optimal treatment of high perianal fistulas with a single internal opening.[4] Currently, the three standard treatment options are: i) surgical approach by chronic seton drain drainage; ii) medical approach by anti-tumour necrosis factor alpha antibodies (anti-TNFα); and iii) surgical closure with or without anti-TNF induction treatment. The choice of treatment is at the discretion of the patient, after shared decision making with the treating physician, preferably after discussion within a multidisciplinary team.

Since two randomised controlled trials (RCTs) reported increased fistula closure rates, reduced fistula discharge, and improved quality of life (QoL) following anti-TNF compared with placebo, most patients receive anti-TNF.[5,6] Nonetheless, the long-term effect of anti-TNF is not as favourable, due to high recurrence rates and serious side effects. Systematic reviews suggested similar fistula closure rates between these three treatment options (43–50%).[7–9] However, the surgical treatment options are generally less popular due to concerns regarding wound healing problems in CD.[4–6,10] The advantages of seton drainage include patency preservation of the fistula tract, preventing side branching of the tract and recurrent abscess formation. Subsequently, the reported re-intervention rates seemed substantially lower with seton drainage (10–20%) as compared with anti-TNF and surgical closure (30–50%).[7–9] However, rates varied widely, and no definite conclusion could be drawn. Previous studies were flawed by a high risk of bias, had short follow-up, and none of the studies directly compared seton drainage with anti-TNF treatment and/or surgical closure.

Therefore, we conducted an international, multicentre, prospective randomised controlled trial to identify the optimal treatment of Crohn's high perianal fistulas. It was hypothesised that chronic seton drainage for perianal fistulas in CD would be the most effective treatment approach, as it would reduce re-interventions in the short term when compared with anti-TNF and surgical closure following anti-TNF, and overall long-term closure rates would be comparable between the three groups.

Materials and methods

Study design

The PISA trial is an international, prospective multicentre, pragmatic, randomised, controlled, open-label, parallel group, superiority trial. The trial compared chronic seton drainage with anti-TNF and with surgical closure after anti-TNF induction. The study was conducted at 19 teaching hospitals and tertiary care centres in The Netherlands, Belgium, Spain, and Italy (seven centres were tertiary referral centres, five of which were in the Netherlands).

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial received central approval from the medical ethics committee at the Amsterdam UMC, location AMC, and from the corresponding committees in all participating centres. A data and safety monitoring board (DSMB) monitored the trial at predefined time points. Additionally, the study was monitored by the clinical research unit of the Amsterdam UMC, location AMC in accordance with the moderate risk classification of the Dutch federation of Academic Centres (NFU). The study protocol has been published previously.[11] This trial is registered at the Dutch Trial Registry (NTR4137).

Participants

Adult patients with a newly diagnosed or recurrent draining high tract (intersphincteric, transsphincteric or suprasphincteric) Crohn's perianal fistula located in the upper two-thirds of the external sphincter were screened for eligibility. Main exclusion criteria were: multiple internal fistula openings. based on magnetic resonance imaging (MRI) or inspection under anaesthesia (the number of external fistulas was not taken into account); proctitis (defined as any active mucosal inflammation or ulcer > 5 mm in the rectum); anorectal stenosis (defined as the impossibility of introducing a proctoscope); a rectovaginal fistula; a seton *in situ* for more than 3 months; anti-TNF treatment in the preceding 3 months; patients not eligible for anti-TNF treatment (e.g., due to previous anti-TNF treatment without any effect on perianal fistula(s); previously demonstrated allergy to anti-TNF medication; immunocompromised status); and presence of a stoma. All participants provided written informed consent.

Randomisation and masking

Patients were allocated (1:1:1) to chronic seton drainage, long-term anti-TNF, or surgical closure after anti-TNF induction. Random block randomisation with block sizes of six participants was performed by a central web-based system (ALEA Clinical B.V., The Netherlands) and was not stratified. Patients and study staff masking was not possible because of the differing nature of the interventions (medical versus surgical). Treatment preference, if explored at consultation before randomisation, was registered. In case this

was reason to decline participation in the trial, the patients were asked for consent to be prospectively included in the PISA registration study, to maintain external validity. These patients met the same inclusion criteria and were treated according to the same protocol as the patients included in the PISA RCT.

Interventions

The procedures have been published previously (Supplementary Figure S1.1).[11] Before randomization, all patients underwent seton insertion (vessel loop) under general anaesthesia in a day care setting and received a 2-week antibiotic course. Furthermore, 6-mercaptopurine (6MP) was added. Patients were followed for 1.5 years.

For patients allocated to chronic seton drainage, the seton was scheduled to be removed after 1 year.

For patients allocated to anti-TNF, the choice of infliximab or adalimumab was left to the discretion of the treating gastroenterologist. Anti-TNF treatment was continued for at least 1 year. Any dose adaptation was allowed. The seton was removed 6 weeks after start of anti-TNF treatment, as it has been demonstrated that seton removal before 2 months is associated with higher closure rates.[12] However, ultimately the decision of seton removal is at the discretion of the treating physician.

For patients allocated to surgical closure after anti-TNF induction, surgical closure was either performed by advancement flap or ligation of the intersphincteric tract (LIFT) procedure. The choice of treatment was left to the discretion of the treating surgeon. Surgical closure was performed in a day care setting and was combined with seton removal. Surgical closure was planned after completion of the anti-TNF induction, generally within 8–12 weeks after starting anti-TNF. Anti-TNF was stopped after 4 months. The procedure was performed by a specialised colorectal surgeon. When the participating centres lacked expertise, the patient was referred to the Amsterdam UMC, location AMC.

Outcomes

The primary outcome was the proportion of patients with fistula-related re-intervention(s), defined as surgical re-interventions and/ or (re)start of anti-TNF therapy due to suspicion of recurrent abscess or new fistula tract(s) within 1 year. This was assessed by the trial physician and derived from operation and medical reports. A planned seton change without a suspicion of an abscess, e.g., due to a knotless seton, or (re) start of anti-TNF for general CD symptoms, were not considered as a re-intervention. Secondary outcomes included: i) the proportion of patients with clinically relevant severe Perianal Crohn's Disease Activity Index (PCDAI > 7, as this is associated with the need of therapy[13]), evaluated by a physician at the outpatient clinic at Months 0, 6, 12,

and 18; ii) the proportion of patients with a closed fistula, defined as a fibrotic tract on MRI[14] after 1.5 years; iii) results of (disease-specific) quality of life (QoL) questionnaires (Inflammatory Bowel Disease Questionnaire (IBDQ) and EuroQol Visual Analogue Scale (EQ-VAS)); and iv) cost-effectiveness (including the EQ-5D-3L, antibiotic courses, number of sick leave or in-hospital days according to the health and labour questionnaire) assessed by questionnaires sent by email (LimeSurvey 2.6.7, Hamburg, Germany) or, if the patient preferred, by regular mail at Months 0, 3, 6, 9, 12, 15, and 18.

Patients were seen at the outpatient clinic at Months 6, 12, and 18 after inclusion. Patients were contacted by telephone every 3 months to verify adverse events, re-interventions, and any changes in medical therapy. Serious adverse events included those resulting in death or those that were life-threatening, requiring or prolonging admission to hospital, or resulting in persistent or substantial disability or incapacity. The local investigator and trial coordinator collected the data in an electronic database (Oracle Clinical 4.6.2, Redwood Shores, USA).

Statistical analyses

All analyses, including the analyses of the registry data, were based on the intention-to-treat principle. To detect a clinically relevant reduction of 30% of re-interventions (50% anti-TNF and surgical closure versus 20% seton drainage) with a power of at least 80% at a two-sided α level of 0.05 considering a 5% drop out rate, it was necessary to include 42 patients in each group (total target sample size of 126 patients). The 30% decrease in re-interventions was based on systematic reviews.[7–9] Chi square or Fisher's exact test was used as appropriate, to analyse differences between the proportion of patients with fistula-related re-intervention(s) and patients with severe perianal disease activity (PCDAI > 7) among the three treatment groups. The change in IBDQ and EQ-VAS over time in the three study arms was investigated using linear mixed models with repeated measures analysis of variance adjusted for baseline value. QoL data are presented as model-based estimated means and corresponding confidence interval (CI). A two-sided *P* value of less than 0.05 was considered significant. All statistical analyses were performed with SPSS software, version 24.0 (IBM Corp., Armonk, New York, USA).

Early termination of the trial

After an accrual of 33% of the total sample size, the (serious) adverse events per treatment group were reported to the DSMB as stipulated in the protocol. Most events entailed re-interventions (Supplementary Document S1.1). The proportion of patients with a re-intervention was highest in the chronic seton group. At the discretion of the DSMB, it was decided to perform an interim analysis. Conditional powers under the null trend (treatments are equally efficient) and the alternative trend (chronic seton is superior) were calculated to assess futility of continuing the trial. For both trends, the likelihood of showing superiority of the chronic seton arm at the completion of the

trial was less than 1%. In case of continuation of the trial with the remaining two arms (anti-TNF versus surgical closure after anti-TNF), the conditional power to observe a 30% difference (20% versus 50% re-interventions) between these arms was < 1% and 9% under the null and alternative hypothesis, respectively. The DSMB recommended termination of the trial due to futility (Supplementary Document S1.1). The PISA steering committee decided to follow the advice and the METC accepted this decision on notification. A meeting was organised to discuss the crucial aspects of small numbers.[15] As the chance of type 1 errors increased, the following decisions were made: to only statistically test the primary outcome at the original α level of 0.0; to complete the dataset by awaiting a minimal follow-up of 6 months; to report all outcome events till the end of study; and to evaluate the data of the registry patients. Because not all patients had completed the study, Kaplan-Meier analyses with log-rank testing to assess data for categorical outcomes were used. As described in the protocol, the study also intended to report fistula closure rates and a cost-effectiveness analysis. However, as closure of perianal fistula was only measured with MRI at 1.5 years, it was decided to await these data. Since chronic seton treatment was considered to be clinically too unfavourable, the cost-effectiveness analysis was considered no longer opportune. The funders shared that view.

Results

Between September 14, 2013 and November 20, 2017 (termination of the trial), 190 patients were screened for eligibility, of whom 96 were excluded; 44 patients were randomised and 50 patients were included in the PISA registry. Patients in the randomised trial were assigned to chronic seton drainage (n = 15), anti-TNF treatment (n = 15), or surgical closure after anti-TNF induction (n = 14). In the PISA registry, 20 patients chose chronic seton drainage, 21 anti-TNF treatment, and nine surgical closure after anti-TNF induction. Two patients in the registry, both in the surgical closure group, withdrew from the study within 1 month and were excluded from outcome analyses (Figure 1.1). The remaining 92 patients had a follow-up of at least 6 months, of whom 60 patients completed the 1.5-year follow-up.

Patient baseline characteristics of the RCT and the registry are shown in Tables 1.1 and 1.2. The mean age of the randomised patients, as well as of the registry patients, was 38 years (standard deviation (SD) 14 and 12, respectively). The baseline characteristics between the three treatment groups in the RCT, as well as in the registry, did not differ. In all groups, there were no differences in adherence to the protocol. At least 80% started with antibiotics and more than 80% were still on thiopurine at the end of follow-up. Also, the baseline characteristics between the patients in the RCT and the registry were comparable (Supplementary Table S1.1).

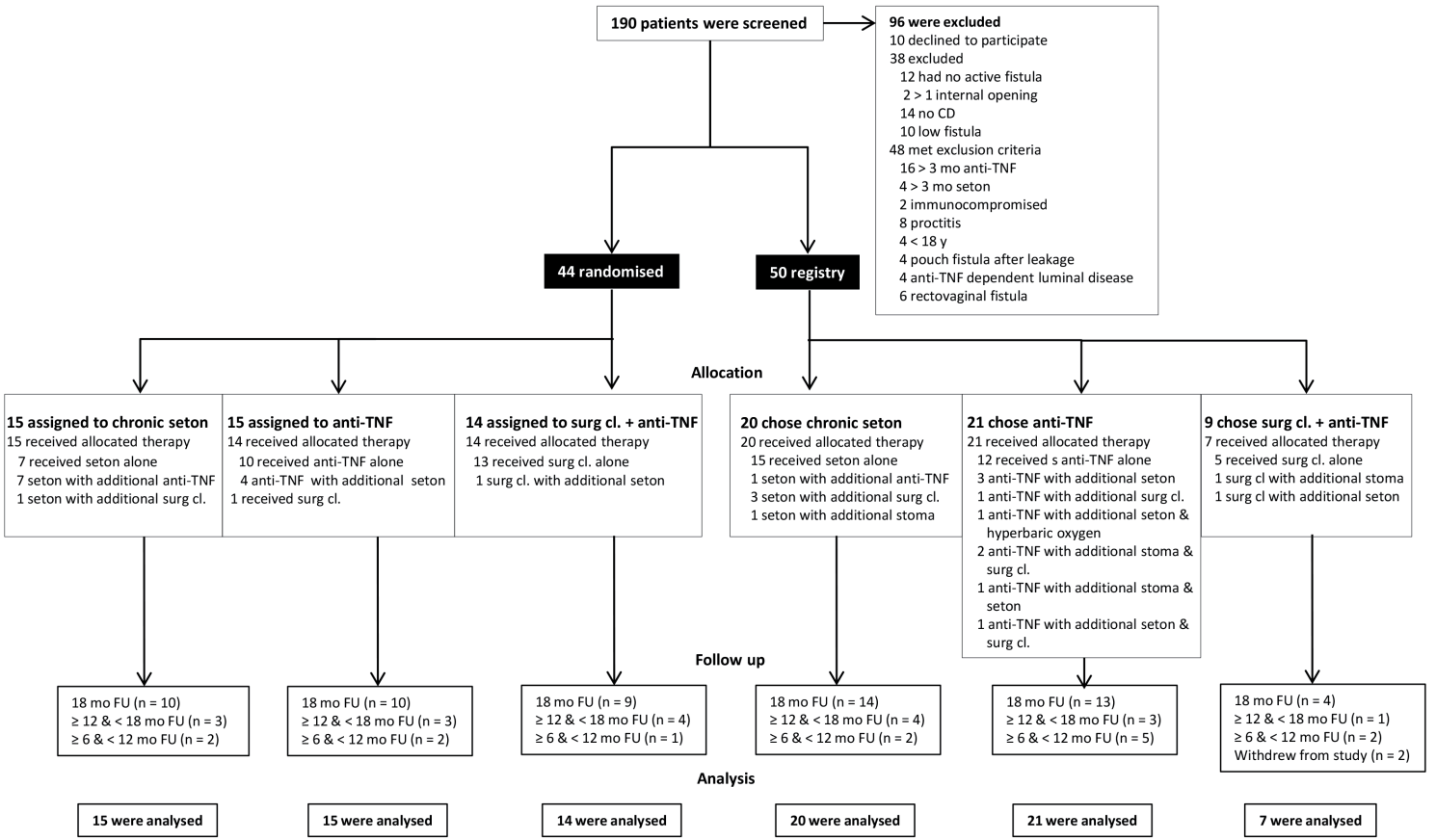


Figure 1.1. Trial profile according to the CONSORT diagram.
Surg cl, surgical closure; mo, months; FU, follow-up.

Table 1.1. Baseline characteristics of randomised patients

	Seton (n = 15)	Anti-TNF (n = 15)	Surgical closure (n = 14)
Age (mean, SD)	35 (13)	43 (15)	36 (15)
Female	11 (73%)	8 (53%)	8 (57%)
Smoking	5 (36%)	5 (33%)	2 (14%)
Luminal disease activity[a]	0 (0%)	2 (14%)	0 (0%)
Prior anti-TNF usage	1 (10%)	4 (29%)	6 (46%)
Disease years perianal fistula (median, IQR)	1 (1–4)	2 (1–8)	1 (1–5)
Number of previous fistula interventions (median, range)	1 (0–4)	1 (0–3)	2 (0–3)
Severe perianal disease activity (PDAI > 7)[b]	9 (64%)	7 (54%)	11 (79%)
IBDQ (max 224 points) (mean SD)[c]	151 (46)	148 (35)	146 (44)
EQ-VAS (mean, SD)[d]	61 (21)	59 (23)	60 (20)
Number external opening (median, range)	1 (0–2)	1 (0–3)	1 (0–2)
MRI imaging			
Number external fistula tracts > 1	12 (80%)	8 (5%)	5 (36%)
Rectal wall involvement	2 (15%)	4 (29%)	0 (0%)

TNF, tumour necrosis factor; SD, standard deviation; IQR, interquartile range; PCDAI, Perianal Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; MRI, magnetic resonance imaging. [a] Luminal disease activity requiring anti-TNF. Assessed by colonoscopy within 3 months prior to randomisation. [b] PDAI assessed 5 items: i) fistula production, ii) pain, iii) limitation of sexual activities, iv) type of perianal disease and v) severity of induration. Every category includes a scale ranging from 0 to 4 points, higher scores representing higher disease activity. The total score can range from 0 to 20 points. [c] IBDQ score consists of 32 questions; each with a 1–7 scale. The total score can range from 32 to 224 points with higher scores representing higher QoL. [d] The EQ-VAS is a generic, standardized measure of health-related quality of life over the preceding week consisting of the EQ-VAS descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-VAS is a vertical scale grading the overall health status ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

The proportion of patients with a fistula-related re-intervention(s) among the randomised patients was significantly associated with chronic seton drainage: 10 patients (74%) versus six patients (42%) in the anti-TNF group and three patients (23%) in the surgical closure after anti-TNF group, $P = 0.02$. In the registry patients, the proportion of patients with a re-intervention was similar between the groups, with eight patients (42%) in the chronic seton group versus nine patients (48%) in the anti-TNF group and two patients (44%) in the surgical closure after anti-TNF group, $P = 0.78$ (Table 1.3).

Re-interventions occurred earliest in the chronic seton group: for the randomised patients after a median of 4 months (interquartile range (IQR) 1–9) versus 6 months (3–8) in the anti-TNF group, and 11 months (IQR 10–11) in the surgical closure after anti-TNF group. For the registry patients, re-interventions occurred after a median of 2 months (IQR 1–11) in the chronic seton group versus 3 months (IQR 1–11) in the anti-TNF group and 13 months (IQR 8–13) in the surgical closure group. Re-interventions per group per time point are shown in Supplementary Figures S1.2 and S1.3.

Table 1.2. Baseline characteristics of registry patients

	Seton (n = 20)	Anti-TNF (n = 21)	Surgical closure (n = 9)
Age (mean, SD)	42 (13)	36 (9)	31 (9)
Female	13 (68%)	9 (45%)	4 (44%)
Smoking	5 (25%)	4 (22%)	6 (67%)
Luminal disease activity	3 (19%)	2 (13%)	1 (17%)
Prior anti-TNF usage	8 (42%)	7 (41%)	5 (71%)
Disease years perianal fistula (median, IQR)	1 (0–9)	2 (0–5)	2 (1–6)
Number of previous fistula interventions (median, range)	1 (0–9)	0 (0–5)	2 (0–4)
Severe perianal disease activity (PDAI > 7)	13 (81%)	12 (67%)	4 (57%)
IBDQ (max 224 points) (mean SD)	140 (45)	143 (28)	142 (45)
VAS	54 (24)	54 (23)	59 (23)
Number external opening (median, range)	1 (0–2)	1 (0–2)	1 (0–2)
MRI imaging			
Number external fistula tracts > 1	9 (45%)	14 (67%)	5 (56%)
Rectal wall involvement	2 (11%)	2 (13%)	0 (0%)

* None of the parameters were significantly different. TNF, tumour necrosis factor; SD, standard deviation; IQR, interquartile range; PCDAI, Perianal Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; MRI, magnetic resonance imaging.

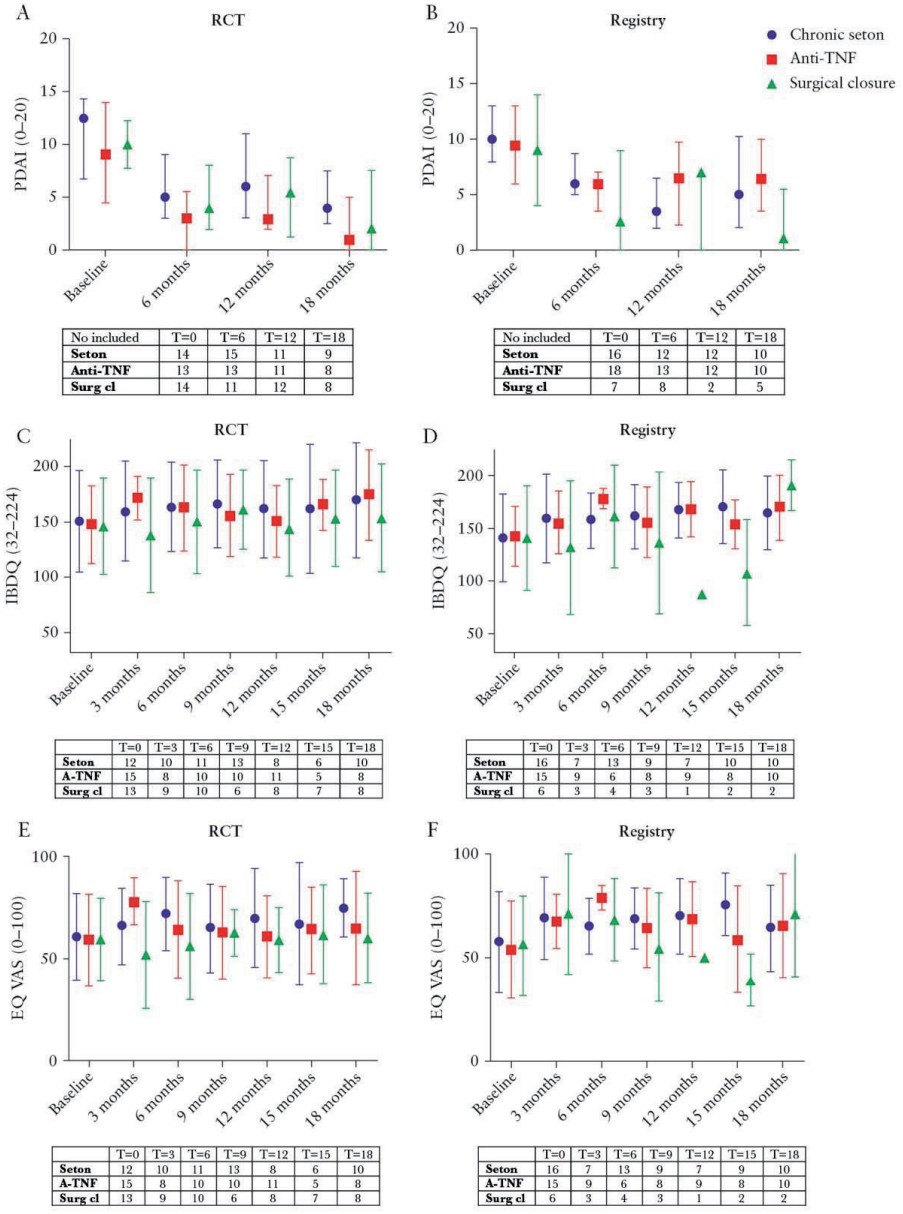
Table 1.3. Re-interventions in RCT and registry patients till end of study assessed using Kaplan-Meier analyses

Re-interventions	Seton drainage n (%)	Anti-TNF n (%)	Surgical closure n (%)
RCT*	10 (74%)	6 (42%)	3 (23%)
Registry	8 (42%)	9 (48%)	2 (44%)

* Re-interventions till end of study was significantly higher in the seton group of the randomised patients (Plog-rank = 0.02). RCT, randomised controlled trial; TNF, tumour necrosis factor.

Baseline PCDAI was comparable for the three treatment groups in both the RCT and the registry (Tables 1.1 and 1.2). The PCDAI improved in all groups (Figure 1.2a and b). In the RCT, the number of patients per group with severe perianal disease activity (score > 7) till end of study included five patients (40%) in the chronic seton group, two patients (19%) in the anti-TNF group, and three patients (31%) in the surgical closure after anti-TNF group. In the registry, severe perianal disease activity till end of study was: five patients (40%) in the chronic seton group, five patients (44%) in the anti-TNF group, and one patient (20%) in the surgical closure after anti-TNF group. For one patient in the RCT and nine patients in the registry, the PCDAI was not assessed during follow-up.

Baseline disease-specific QoL and general QoL were both comparable between the three treatment groups in both the RCT and the registry (Tables 1.1 and 1.2). The QoL is shown in Supplementary Table S1.2, and in Figure 1.2 c–f. In the RCT, the disease-specific



No included	T=0	T=6	T=12	T=18
Seton	14	15	11	9
Anti-TNF	13	13	11	8
Surg cl	14	11	12	8

No included	T=0	T=6	T=12	T=18
Seton	16	12	12	10
Anti-TNF	18	13	12	10
Surg cl	7	8	2	5

	T=0	T=3	T=6	T=9	T=12	T=15	T=18
Seton	12	10	11	13	8	6	10
A-TNF	15	8	10	10	11	5	8
Surg cl	13	9	10	6	8	7	8

	T=0	T=3	T=6	T=9	T=12	T=15	T=18
Seton	16	7	13	9	7	10	10
A-TNF	15	9	6	8	9	8	10
Surg cl	6	3	4	3	1	2	2

	T=0	T=3	T=6	T=9	T=12	T=15	T=18
Seton	12	10	11	13	8	6	10
A-TNF	15	8	10	10	11	5	8
Surg cl	13	9	10	6	8	7	8

	T=0	T=3	T=6	T=9	T=12	T=15	T=18
Seton	16	7	13	9	7	9	10
A-TNF	15	9	6	8	9	8	10
Surg cl	6	3	4	3	1	2	2

Figure 1.2. PCDAI, IBDQ, EQ-VAS over time (from baseline to 18 months) in RCT and registry patients. Blue represents the chronic seton group, red the anti-TNF group, and green the surgical closure after anti-TNF group. A lower PCDAI characterises less perianal disease activity. Higher IBDQ and EQ-VAS scores indicate a better quality of life (QoL). The change in IBDQ and EQ-VAS over time of the three study arms was investigated using linear mixed-models with repeated measures analysis of variance adjusted for baseline value. QoL data are presented as model-based estimated means and corresponding confidence intervals (CIs). The arrows represent a re-intervention of a treatment of the other treatment group (seton placement, start anti-TNF therapy of surgical closure). Stripes without any specification are re-interventions that are the same as the original treatment. TNF, tumour necrosis factor; PCDAI, Perianal Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; EQ-VAS, EuroQol Visual Analogue Scale.

QoL till end of study was higher in the anti-TNF group compared with the other two groups, whereas the general QoL was lower in the surgical closure after anti-TNF group. The registry showed no considerable differences for disease-specific and/or general QoL. The disease-specific QoL (IBDQ) and general QoL (EQ-VAS) could be assessed for 39 (89%) patients in the RCT and in 34 (71%) patients in the registry.

Discussion

This study is the first prospective randomised controlled trial comparing surgical treatment options with anti-TNF for Crohn's disease high perianal fistulas. After the first interim analysis, the trial was terminated based on futility. Refuting the original hypothesis, the trial showed an inferior outcome of chronic seton treatment with respect to re-interventions in the randomised patients. None of the secondary outcomes in the RCT group demonstrated results favouring chronic seton drainage. Continuation of the study with the remaining two treatment arms would also be futile, as the re-intervention rates in these arms were lower than expected. The outcomes of this study should be interpreted with caution, since both the number of included patients and the number of events (re-interventions) were considerably smaller than the minimum required sample size for sufficient power. Therefore, it is uncertain as to what extent over- or underestimation of treatment effects may have occurred. Consequently, not the exact reported numbers and rates of the treatment effects, but rather the relative differences between the treatments arms have potential value for drawing conclusions.[16] In addition, the discrepancies found between the RCT and registry results make it hard to draw firm conclusions.

The unexpected differences in re-intervention rates per treatment group in the randomised patients can be explained by various factors. The original hypothesis was based on retrospective studies with different inclusion criteria with a rather short duration of follow-up, especially for seton treatment.[9] As a result, these studies might have been prone to bias, leading to under-reporting of re-interventions after seton treatment. In contrast, the number of re-interventions in the anti-TNF group and surgical closure after anti-TNF group were lower than previously described. In the anti-TNF group, all patients were treated with seton drainage before the start of anti-TNF, in order to prevent recurrent abscess formation. In previous studies this was not done on a consistent basis, which could explain the low re-intervention rate in our study.[9] Furthermore, during the PISA trial, most surgical closures were LIFT procedures. Previous study results are probably outdated, as they generally describe the treatment effect of an advancement flap and reported outcomes without concomitant anti-TNF.[7,8] It is hypothesised that a LIFT procedure combined with anti-TNF may account for the superior results observed in this study.

In our RCT, the disease-specific QoL was highest in the anti-TNF group. This can be expected, as anti-TNF may also have a favourable effect on the overall disease burden in CD.[5] The general QoL was lower in the surgical closure group. Since the surgical intervention is only applied after some months, awaiting a complete follow-up will probably improve these results.

As the results of the PISA RCT were different from those expected and the baseline characteristics of the PISA registry patients were not different from those of randomised patients, it seemed justified to compare these results. In the registry data, chronic seton drainage was not associated with significantly more re-interventions. This was a somewhat striking finding, especially as severe perianal disease activity between the randomised and registry chronic seton treatment group was comparable at each point in time. Seton is known to be an uncomfortable treatment. Patients who consciously chose seton treatment in the registry, might have preferred to avoid surgery or the side effects of biologicals. In contrast, patients randomised to chronic seton treatment might be more disappointed about the discomfort, especially as it takes considerable time for seton stability to be achieved. This is further emphasised by the fact that most of the re-interventions occurred within 6 months in the seton group. Discomfort discussed at the outpatient clinic could lead to inspection under anaesthesia in daily clinical practice. These events count as a re-intervention, even in the absence of an abscess. It is argued that a seton procedure was tolerated more by patients who chose chronic seton drainage willingly as opposed to patients who were randomly allocated to it. Consequently, the primary endpoint re-intervention (which was thought to be an objective endpoint) is likely influenced by patient preference. This could explain the different results between the RCT and preference groups.

This was the first RCT comparing the three different treatment options head to head. Initially, the conclusion based on the PISA RCT was very clear; instead of showing superiority, chronic seton drainage was significantly associated with inferior results. Upon PISA counselling, strong patient preference was noted and was followed by a low inclusion ratio. Therefore, we also initiated the PISA registry parallel to the RCT. In accordance with the RCT, the PISA registry results did not suggest superiority of chronic seton treatment. However, it did not confirm inferiority of chronic seton treatment. Hence, if a patient chooses chronic seton treatment, it might still be a valid alternative. Interestingly, the registry data also revealed that relatively few patients chose surgery. It touches upon a more extensive problem that patients may not be well informed about the surgical treatment options. A fundamental factor driving this situation is probably that the majority of Crohn's fistula patients have a long medical history with a gastroenterologist who might be less aware of the surgical treatment options and outcomes to be able to support thorough shared decision making.

Apart from interesting clinical data (albeit small numbers), we learned that a classical RCT might not be the optimal design for trials which compare treatments with substantially different characteristics (medical versus surgical).[17] This type of study design, with a high internal validity due to homogeneity (including unknown confounders) between the study groups and the possibility of blinding, was originally designed to compare medical versus placebo therapy.[18] However, when performing an RCT which compares treatments of substantially different natures, patient treatment preferences can be expected. In such cases, only presenting the RCT data will inevitably result in a less representative study group, which would not be in accordance with the transparency statement. We are aware that this might introduce a bias in the registry data, but withholding this information could result in an unbalanced and possibly unjustified conclusion. This study provided valuable lessons learned when designing future studies.

A limitation of the study is lack of patient involvement in trial design, particularly relating to design of the intervention to be included: the major pitfall of this study is that we did not consider patient preferences in the original design. A key lesson learned is that trial participants are not passive recipients of interventions. As described above, results of the RCT are likely to be influenced by patient preference. The influence of this occurrence can be mitigated by applying a more pragmatic design, such as a patient preference design or alternatively a cohort-embedded RCT (also known as TWICS).[19,20] These designs incorporate patient preference instead of excluding patients with a distinct treatment preference, resulting in a higher external validity. These designs have their own limitations. However, modern research should try to find a fine balance between the focus on limiting bias for study results (mainly concerning internal validity) and at the same time drawing externally valid conclusions that also take into account the applicability of study results. In conclusion, chronic seton treatment as the sole treatment is not the superior treatment for patients with perianal Crohn's fistulas.

Acknowledgements

We would like to thank E.J.M. Nieveen van Dijkum, M.W.T. Tanck and J.J.G.H.M. Bergman for their participation in the Data Safety Monitoring Board, P.J. Tanis for his participation as independent expert, all staff at the participating centres of the PISA trial for their efforts, the Dutch Initiative on Crohn's and Colitis, F.A.B.M. Wasmann for linguistics editing, and especially the patients for participating in the trial.

Funding

The work was supported by The Netherlands Organization for Health Research and Development [ZonMw, grant number 837002002] and the Crohn and Colitis Foundation [grant number 210270]. The funders of the study had no role in the study design, data collection, analysis, interpretation, or writing of the report.

References

1. Hellers G., Bergstrand O., Ewerth S., Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut 1980;21(6):525–7.
2. Viganò C., Losco A., Caprioli F., Basilisco G. Incidence and clinical outcomes of intersphincteric abscesses diagnosed by anal ultrasonography in patients with crohn's disease. Inflamm Bowel Dis 2011;17(10):2102–8. Doi: 10.1002/ibd.21596.
3. Hakkaart- van Roijen L, Tan SS BC. Handleiding voor kostenonderzoek: methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen 2010. n.d.
4. de Groof EJ., Cabral VN., Buskens CJ., Morton DG., Hahnloser D., Bemelman WA., et al. Systematic review of evidence and consensus on perianal fistula: an analysis of national and international guidelines. Colorectal Dis 2016;18(4):O119-34. Doi: 10.1111/codi.13286.
5. Present DH., Rutgeerts P., Targan S., Hanauer SB., Mayer L., van Hogezand RA., et al. Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease. N Engl J Med 1999;340(18):1398–405. Doi: 10.1056/NEJM199905063401804.
6. Lichtiger S., Binion DG., Wolf DC., Present DH., Bensimon AG., Wu E., et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther 2010;32(10):1228–39. Doi: 10.1111/j.1365-2036.2010.04466.x.
7. Stellingwerf ME., van Praag EM., Bemelman WA., Buskens CJ. P426 Meta-analysis of endorectal advancement flap vs. ligation of the intersphincteric fistula tract for Crohn's and cryptoglandular high perianal fistulas. J Crohn's Colitis 2018;12(supplement_1):S320–S320. Doi: 10.1093/ecco-jcc/jjx180.553.
8. Soltani A., Kaiser AM. Endorectal Advancement Flap for Cryptoglandular or Crohn's Fistula-in-Ano. Dis Colon Rectum 2010;53(4):486–95. Doi: 10.1007/DCR.0b013e3181ce8b01.
9. de Groof EJ., Sahami S., Lucas C., Ponsioen CY., Bemelman WA., Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis 2016;18(7):667–75. Doi: 10.1111/codi.13311.
10. Tanaka S., Matsuo K., Sasaki T., Nakano M., Sakai K., Beppu R., et al. Clinical advantages of combined seton placement and infliximab maintenance therapy for perianal fistulizing Crohn's disease: when and how were the seton drains removed? Hepatogastroenterology n.d.;57(97):3–7.
11. de Groof EJ., Buskens CJ., Ponsioen CY., Dijkgraaf MGW., D'Haens GRAM., Srivastava N., et al. Multimodal treatment of perianal fistulas in Crohn's disease: seton versus anti-TNF versus advancement plasty (PISA): study protocol for a randomized controlled trial. Trials 2015;16(1):366. Doi: 10.1186/s13063-015-0831-x.
12. Gaertner WB., Decanini A., Mellgren A., Lowry AC., Goldberg SM., Madoff RD., et al. Does Infliximab Infusion Impact Results of Operative Treatment for Crohn's Perianal Fistulas? Dis Colon Rectum 2007;50(11):1754–60. Doi: 10.1007/s10350-007-9077-3.
13. Peyrin-Biroulet L., Panés J., Sandborn WJ., Vermeire S., Danese S., Feagan BG., et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clin Gastroenterol Hepatol 2016;14(3):348-354.e17. Doi: 10.1016/j.cgh.2015.06.001.
14. Van Assche G., Vanbeckevoort D., Bielen D., Coremans G., Aerden I., Noman M., et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. Am J Gastroenterol 2003;98(2):332–9. Doi: 10.1111/j.1572-0241.2003.07241.x.
15. Lachin JM. A review of methods for futility stopping based on conditional power. Stat Med 2005;24(18):2747–64. Doi: 10.1002/sim.2151.
16. Viele K., McGlothlin A., Broglio K. Interpretation of Clinical Trials That Stopped Early. JAMA 2016;315(15):1646–7. Doi: 10.1001/jama.2016.2628.
17. Preference Collaborative Review Group. Patients' preferences within randomised trials: systematic review and patient level meta-analysis. BMJ 2008;337(oct31 1):a1864. Doi: 10.1136/bmj.a1864.
18. Bothwell LE., Greene JA., Podolsky SH., Jones DS. Assessing the Gold Standard — Lessons from the History of RCTs. N Engl J Med 2016;374(22):2175–81. Doi: 10.1056/NEJMms1604593.
19. K.A. Wasmann, MD1, P.C. Wijsman 2, MD, S. van Dieren3, MD, W.A. Bemelman 1 and CJB. Using patient's preference in randomized controlled trials. Abstr ESCP 2018.

20. Ahmed HU., Berge V., Bottomley D., Cross W., Heer R., Kaplan R., et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol 2014;11(8):482–91. Doi: 10.1038/nrclinonc.2014.44.

Supplementary Table S1.1. Baseline characteristics for the RCT and registry patients

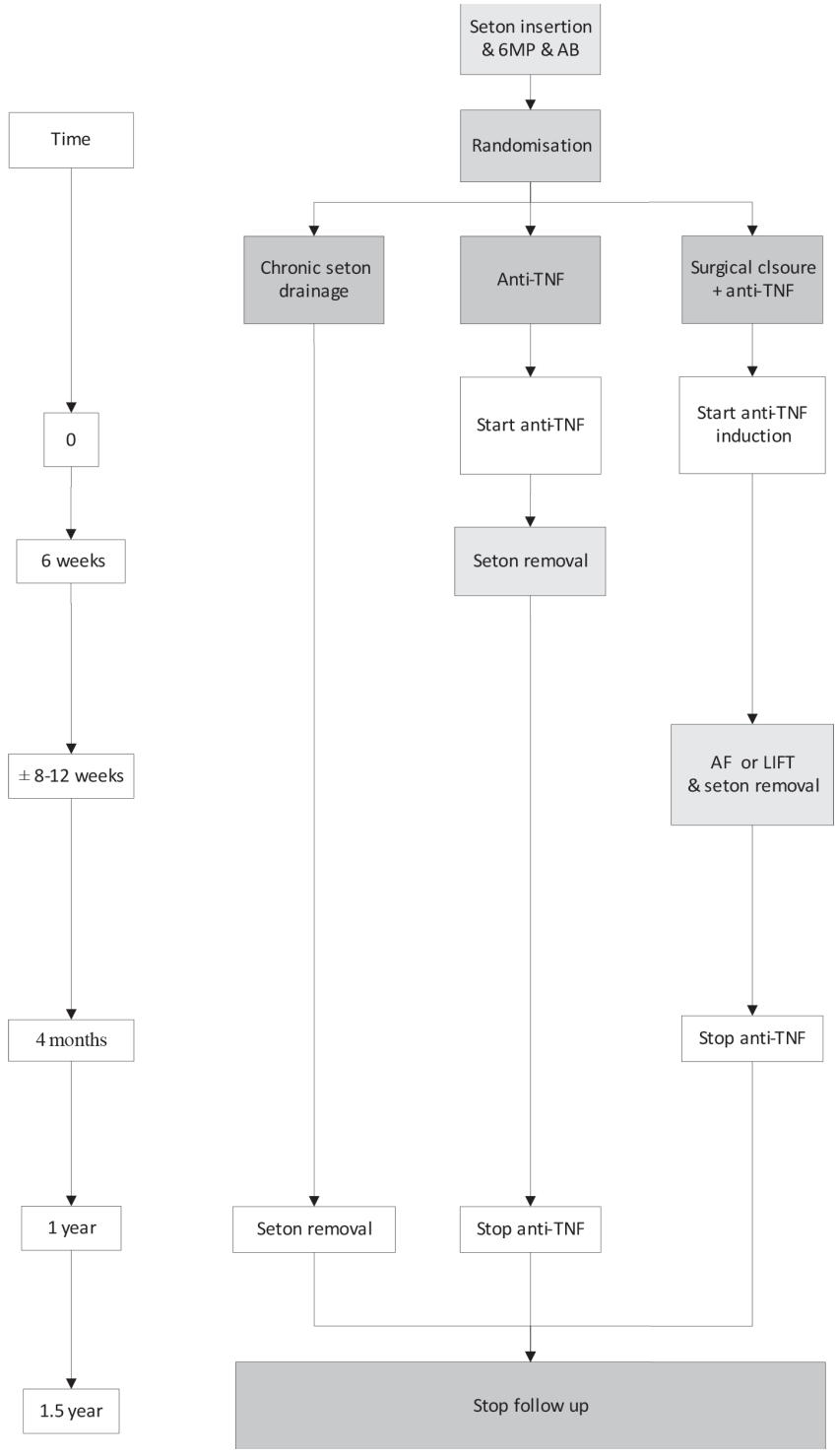
	RCT (n = 44)	Registry (n = 50)
Age (mean, SD)	38 (14)	38 (12)
Female (n, %)	27 (61)	26 (54)
Smoking (n, %)	12 (28)	15 (32)
Luminal disease activity* (n, %)	2 (5)	6 (16)
Prior anti-TNF usage (n, %)	11 (30)	20 (47)
Disease years perianal fistula (median, IQR)	2 (1–6)	1 (0–6)
Number of previous fistula interventions (median, range)	1 (0–4)	2 (0–9)
Severe perianal disease activity (PDAI > 7)	27 (66)	29 (71)
IBDQ (mean, SD)	148 (40)	141 (37)
EQ VAS (mean, SD)	60 (21)	55 (23)
Number external opening (median, range)	1.3 (1–3)	1.2 (1–2)
MRI imaging		
No patients with > 1 external fistula tract (n, %)	25 (60)	28 (64)
Rectal wall involvement (n, %)	6 (15)	4 (9)

* None of the parameters were significantly differed.

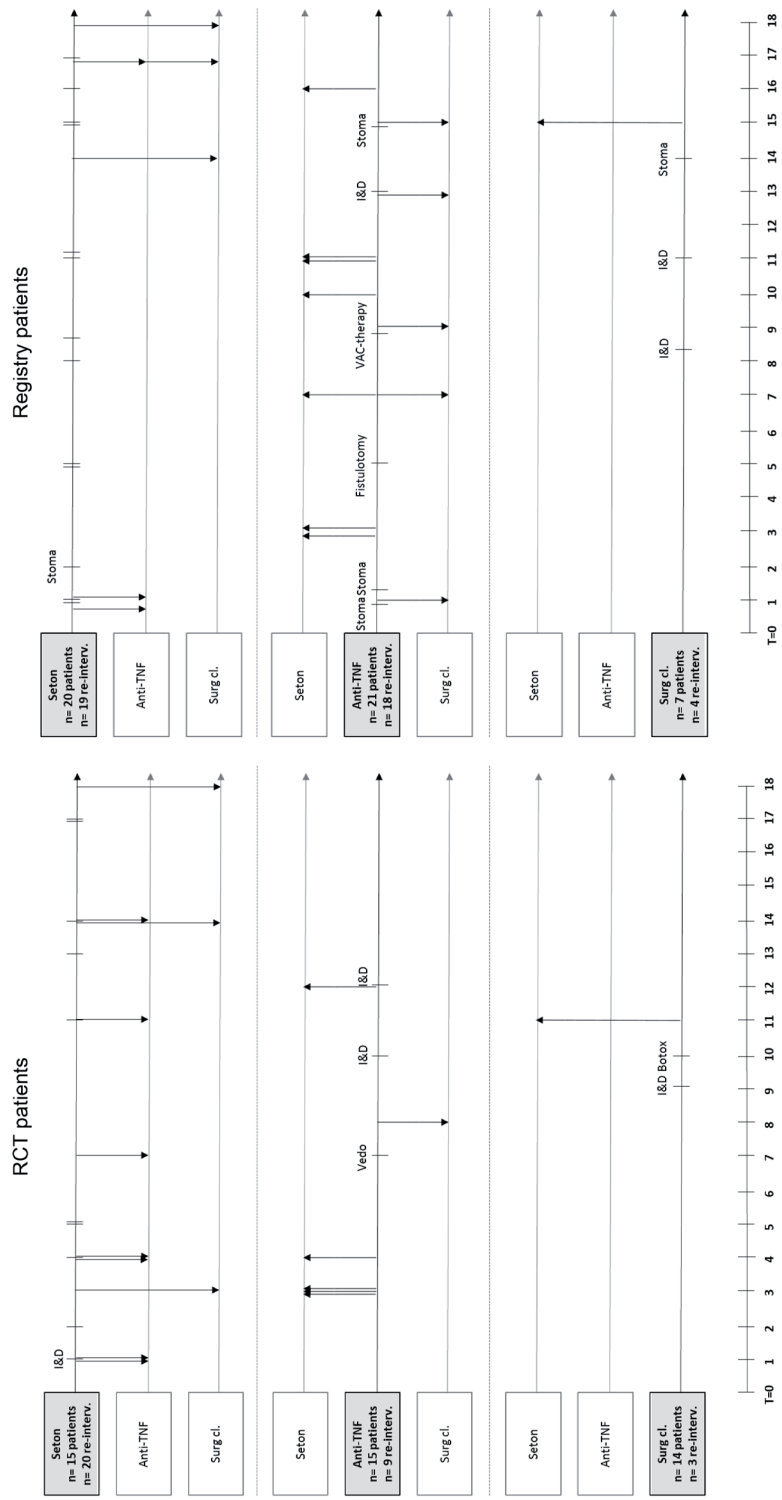
Supplementary Table S1.2. Disease specific and general QoL estimated means till end of study

	Seton Mean (95% CI)	Anti-TNF Mean (95% CI)	Surgical closure Mean (95% CI)
IBDQ RCT	158.7 (150.8–166.6)	168.6 (161.3–176.0)	149.3 (141.5–157.2)
IBDQ registry	152.7 (143.8–161.5)	164.2 (154.0–174.3)	165.5 (151.3–179.6)
EQ VAS RCT	68.9 (63.8–74.1)	68.6 (63.8–73.5)	57.7 (52.5–62.8)
EQ VAS registry	67.5 (62.9–72.2)	68.4 (63.0–73.8)	67.5 (59.9–75.1)

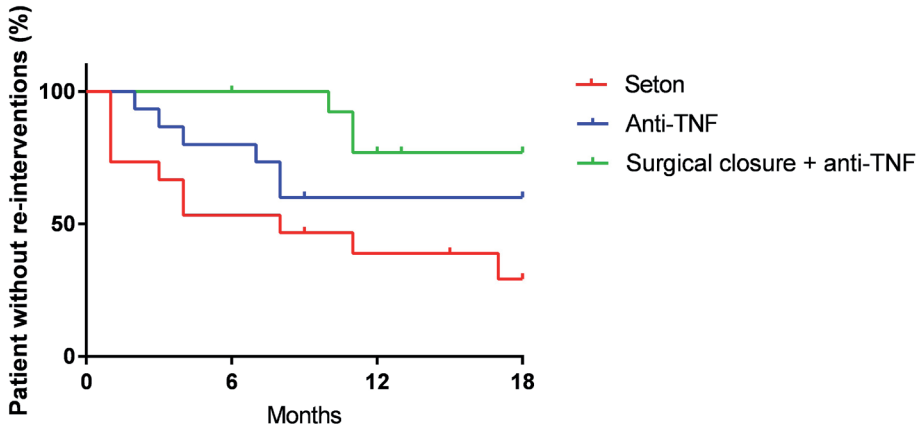
IBDQ, disease specific quality of life; EQ VAS, general quality of life.



Supplementary Figure S1.1. Flow chart study procedures.



Supplementary Figure S1.2. Re-interventions over time in RCT and registry patients.
Re-interv., re-interventions; Surg cl, surgical closure; I&D, incision and drainage; Vedo, Vedoluzimab; Botox, Lidocaine injection; VAC-therapy, Endo-sponge® insertion in fistula tract. The arrows represent a re-intervention of a treatment of the other treatment group (seton placement, start anti-TNF therapy of surgical closure). Stripes without any specification are re-interventions that are the same as the original treatment.



Supplementary Figure S1.3. Kaplan-Meier figure of the re-intervention over time in the RCT group.

Supplementary Document S1.1. DSMB report interim review PISA trial after 42 included patients

Aim of the study

Evaluate the number of patients that need a re-intervention due to a fistula-related complication within 12 months. Patients will be randomized and receive one of the three standard treatment approaches that are currently used for fistula treatment (Seton, anti-TNF and Surgery). The percentage re-interventions in the anti-TNF and surgery arms are expected to be 50% and the trial is powered to show a 30% reduction to 20% re-interventions in the Seton arm. (Superiority of Seton compared to other two arms).

A total of 126 patients are to be included in the randomized clinical trial and interim reviews are performed after inclusion of 42 and 84 patients, respectively. The number of serious (SAE) and adverse events (AE, i.e. re-interventions) that occurred after inclusion of 42 patients is shown in Table D1.1.

Table D1.1. Number of serious adverse events (SAE) and adverse events (AE) in the three arms of the PISA trial

Arm	SAE, n (%)	AE, n (%)
Seton (n = 14)	3 (21%)	7 (50%)
Anti-TNF (n = 14)	5 (36%)	1 (7%)
Surgery (n = 14)	1 (7%)	2 (14%)
Total	9 (21%)	10 (24%)

There is a skewed distribution of the AE between the groups with the highest percentage (50%) occurring in the Seton arm. This percentage is not only higher than expected in this arm, but also significantly higher ($P_{\text{fisher exact}}$: 0.046) than the percentages in the other two arms.

The study was intended to show superiority of the Seton arm with respect to re-interventions, but the data obtained so far indicate inferiority. The DSMB assessed the futility of continuing the trial given the likelihood that the trial will fail to show evidence of the improved efficacy of the Seton arm. Conditional powers were calculated under the null trend (treatments are equally efficient) and the alternative trend (Seton is superior (20 vs. 50% re-interventions). For both trends, the conditional power to show superiority of the Seton arm at the completion of the trial was less than 1%.

In case of a two-arm trial (Surgery vs. Anti-TNF), the conditional power to observe a 30% difference (20 vs. 50% re-interventions) between these arms is < 1% and 9% under the null and alternative hypothesis, respectively.

Recommendations

- Because of the inferiority of the Seton treatment, we recommend stopping this arm of the trial.
- Because of futility, we do not recommend to continue the trial with the remaining two arms (Anti-TNF and Surgery). Furthermore, with the present advanced knowledge, we recommend other primary outcome measures for a comparison of the Anti-TNF and Surgery arms.

Response of authors

After supplying the safety data to the DSMB, including all 10 AEs consisting of surgical re-interventions, at the discretion of the DSMB it was decided to convert into an interim analysis. However, for an appropriate interim analysis it has to be underlined that the number of re-interventions till one year (primary outcome) instead of till one and a half year (as used for a safety analysis) should be used. Therefore, we performed additional power calculations of the re-interventions till one year. The number of re-interventions were 5 in the chronic seton group, 1 in the anti-TNF group and 2 in the surgical closure group (Table D1.2). Consequently, the data still indicates inferiority instead of superiority of the chronic seton arm. The futility of continuing the trial given the likelihood that the trial will fail to show evidence of the improved efficacy of the chronic seton arm was assessed again. Conditional powers were calculated under the null trend (treatments are equally efficient), current trend and the alternative trend (chronic seton is superior (20 vs. 50% re-interventions). For all trends but one, the conditional power to show superiority of the chronic seton arm at the completion of the trial was less than 1%. Only the alternative trend for superiority of chronic seton over surgical closure was less than < 6%. Moreover, all powers were far below the general accepted 20% threshold to reject futility.

Table D1.2. Number of re-interventions (0–12 months) in the three arms of the PISA trial

Arm	Re-interventions n
Seton (n = 14)	5
Anti-TNF (n = 14)	1
Surgery (n = 14)	2

Response of the DSMB

Based on the correct data and after verifying the power analyses, it was decided that the recommendations were still justified.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 2

Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses

Karin A Wasmann, Pieta C Wijsman, Susan van Dieren, Willem A Bemelman, Christianne J Buskens

BMJ Open. 2019;9:e031151

Abstract

Objective: Randomised controlled trials (RCT) are the gold standard to provide unbiased data. However, when patients have a treatment preference, randomisation may influence participation and outcomes (e.g., external and internal validity). The aim of this study was to assess the influence of patients' preference in RCTs by analysing partially randomised patient preference trials (RPPT); an RCT and preference cohort combined.

Design: Systematic review and meta-analyses.

Data sources: MEDLINE, Embase, PsycINFO and the Cochrane Library.

Eligibility criteria for selecting studies: RPPTs published between January 2005 and October 2018 reporting on allocation of patients to randomised and preference cohorts were included.

Data extraction and synthesis: Two independent reviewers extracted data. The main outcomes were the difference in external validity (participation and baseline characteristics) and internal validity (lost to follow-up, crossover and the primary outcome) between the randomised and the preference cohort within each RPPT, compared in a meta-regression using a Wald test. Risk of bias was not assessed, as no quality assessment for RPPTs has yet been developed.

Results: In total, 117 of 3734 identified articles met screening criteria and 44 were eligible (24 873 patients). The participation rate in RPPTs was > 95% in 14 trials (range: 48%–100%) and the randomisation refusal rate was > 50% in 26 trials (range: 19%–99%). Higher education, female, older age, race and prior experience with one treatment arm were characteristics of patients declining randomisation. The lost to follow-up and cross-over rate were significantly higher in the randomised cohort compared with the preference cohort. Following the meta-analysis, the reported primary outcomes were comparable between both cohorts of the RPPTs, mean difference 0.093 (95% CI -0.178 to 0.364, $P = 0.502$).

Conclusions: Patients' preference led to a substantial proportion of a specific patient group refusing randomisation, while it did not influence the primary outcome within an RPPT. Therefore, RPPTs could increase external validity without compromising the internal validity compared with RCTs.

Trial registration: CRD42019094438.

Introduction

Randomised controlled trials (RCT) are suggested to provide the most reliable evidence for treatment efficacy.[1] However, participants are no passive recipients of interventions. Patients with a treatment preference may decline enrolment to avoid being randomised to their non-preferred treatment. Consequently, treatment preferences can decrease the generalisability of RCT results to the clinical population (i.e., reduce external validity). Additionally, trials comparing experimental versus standard treatment are likely to include patients preferring experimental treatment, as trial participation is not needed for patients preferring standard treatment, further reducing external validity. Internal validity may be reduced, as randomisation to the (non-) preferred strategy could influence adherence to treatment protocol and study outcomes. Subjective study outcomes can directly be affected by treatment preference, whereas objective outcomes are most likely affected indirectly via adherence (so-called reluctant acquiescence phenomenon). Especially for an unblinded trial comparing treatments of significant different nature (e.g., medical vs. surgical) the RCT could be an inappropriate design. Throughout the years, several approaches using various names have been proposed as alternative designs to diminish the influence of patients' preference on validity: a partially randomised patient preference trial (RPPT), a comprehensive cohort trial, a patient preference trial, and more.[2] In general, the aim of these designs is to treat patients with a preference for treatment strategies accordingly, whereas only those patients without a distinct preference will be randomised in the usual way.[3] In the era of patients becoming more active participants in research, the use of RPPTs increases. The two previous systematic reviews addressing influence of preference on validity concluded that this influence was limited.[4,5] However, one review only included studies addressing psychotherapy, and the other dates from 2005. So far, the value of the RPPT remains unclear, nor has it been addressed in the Oxford Levels of Evidence (Centre for Evidence-Based Medicine).[6]

The aim of the study was to assess the influence of patients' preference following randomisation in current daily clinical practice, by comparing randomised cohorts with preference cohorts within all RPPTs published since 2005. Two hypotheses were tested: (1) Patients' preference will negatively influence participation in RCTs, decreasing external validity. Therefore, the external validity of an RPPT will be higher. (2) Patients' preferences will influence adherence and outcomes in RCTs, decreasing internal validity. However, as only the remaining indifferent patients will be included in the RCT cohort of an RPPT, this RCT cohort can be considered as the true gold standard for internal validity.

Methods

Design

A systematic review and meta-analyses of RPPTs was conducted. This study is reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[7] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (online supplementary material 1).[8] The study protocol is available in online supplementary material 2.

Data sources and searches

A search in PubMed, Embase, PsycINFO and the Cochrane Library for RPPTs published between 1 January 2005 and 5 October 2018 was executed without language restriction with the assistance of a librarian. The subject in the search strategy was RPPT and possible aliases of RPPT (see the PubMed Search Strategy). Database searches were supplemented by hand searching reference lists of relevant articles. Additionally, authors were contacted to seek for data from unpublished studies identified. Non-English language articles were translated for possible inclusion.

PubMed search strategy

5 October 2018

(patient preference design*[tiab] OR patient preference model*[tiab] OR patient preference trial*[tiab] OR patient preference method*[tiab] OR comprehensive cohort stud*[tiab] OR comprehensive cohort design*[tiab] OR patient preference group[tiab] OR patient preference allocation arms[tiab] OR preference allocation[tiab] OR randomized preference trial*[tiab] OR randomised preference trial*[tiab] OR preference arms[tiab] OR preferences[ti] OR treatment preference basis[tiab] OR (patient preference*[tiab] AND random*[ti]) OR (prefer*[ti] AND random*[ti]) OR (registry patient*[tiab] AND randomized[tiab])) AND ("Clinical Trial"[pt] OR trial[ti] OR preference trial[tiab]) AND ("2004/09"[Date - Publication] : "3000"[Date - Publication])

And

((patient preferences[ti] AND clinical trials[ti]) OR nonrandomized[ti] OR (patient preference[ti] AND randomization[ti]) OR (random[ti] AND nonrandom assignment[ti]) OR (randomized[ti] AND non-randomized[ti]) OR (nonrandom assignment[ti]) OR (randomized[ti] AND nonrandomized[ti]) OR (randomi*[tiab] AND preference arm) OR (partially randomized study[tiab] AND "Randomized Controlled Trial"[pt]) OR (unwilling to be randomized[tiab] AND "Randomized Controlled Trial"[pt]) OR (choice[tiab] AND randomisation[tiab] AND "Randomized Controlled Trial"[pt])) AND (random*[tiab]) AND ("Clinical Trial"[pt] OR trial[ti] OR clinical trials[ti]) AND ("2004/09"[Date - Publication] :

"3000"[Date - Publication])"comprehensive cohort*"[tiab] AND ("2004/09"[Date - Publication] : "3000"[Date - Publication])

Study selection

RPPTs describing results of both the randomised and preference cohorts, as long as in both cohorts patients met the same inclusion and exclusion criteria and were treated according to the same treatment protocol, were included. Trials in which a two-stage randomised design was conducted, allocation was based on doctors' preference, without available separate data for the randomised and preference cohorts, with economic primary outcomes, or with non-clinical populations were excluded. Furthermore, it was decided not to include older RPPTs (before 2005), as it is important to consider the value of this design for current daily practice. A previous systematic review addressing on the value of RPPTs was published in 2005, which can be used to interpret results from older studies.[4]

Data extraction

The two first authors independently screened the citations and abstracts for eligible articles using a prepiloted standardised data form (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia). Disagreements were discussed at steering group meetings.

The same two authors extracted data with the use of the same data form. Multiple publications reporting on the same trial were considered as one single trial for these analyses.

The level of sought data was summary estimates. Authors were contacted for further information when necessary. In case they were not forthcoming, the study was included in the review, but excluded from our reanalysis and/or meta-analyses.

Risk of bias assessment

Quality assessment of the trials was not performed, as no quality assessment for RPPTs has yet been developed and current criteria predominantly relate to concealment of randomisation (e.g., Risk of Bias in Non-Randomized Studies-I and Cochrane Risk of Bias); consequently quality assessment and variability between trials were not applicable.[9,10] Since the outcomes of each trial greatly differed, also the risk of bias assessment for systematic reviews (e.g., Grading of Recommendations, Assessment, Development and Evaluations) was not applicable.[11]

Outcomes

The primary outcomes were external and internal validity between randomised and preference cohorts within RPPTs. To analyse whether patients' preference influenced external validity, data were extracted on participation rates in the randomised and

preference cohorts. To assess if a specific patient group accepted randomisation, data were extracted on baseline characteristics of the randomised and preference cohorts of an RPPT separately. These characteristics were categorised into sociodemographic and clinical factors. Subsequently, these factors were compared between the randomised and preference cohorts of RPPTs.

To analyse whether patients' preference influenced internal validity, data were extracted on lost to follow-up, crossovers and primary outcomes of the randomised and preference cohorts of an RPPT separately. Subsequently, these outcomes were compared between the randomised and preference cohorts within RPPTs. The primary outcomes of RPPTs were identified through explicit statements, study hypotheses, reported power analyses, and were checked on similarity with the study protocol. If this was not sufficient, the most likely primary outcome was chosen by consensus (KAW and SvD), or the study was excluded. To compare the primary outcomes between the randomised and preference cohorts within RPPTs, the outcome effects were compared between the randomised cohort and the preference cohort. It is emphasised that comparisons of outcome between randomised and preference cohorts are subject to bias, and if not done by the study itself, it was not possible to adjust for confounding factors. If in studies the adjusted and non-adjusted primary outcomes were available, the adjusted outcomes were used. Subsequently, separate analyses on adjusted and non-adjusted primary outcomes were performed.

Statistical analysis

The randomisation rate, participation rate and difference in baseline characteristics between the randomised and preference cohorts were explored and described, but not compared using statistics. To assess differences in baseline characteristics, mean and SDs were compared. If median IQRs were reported, it was converted to mean and SDs.[12] When baseline characteristics were presented per experimental and control group, the sum of mean and SDs of these two groups was calculated for the randomised and preference cohorts using a weighted *t*-test. The lost to follow-up and cross-over rates were compared using a random effects model meta-analysis for proportions.

To realise the comparison of the primary outcomes of randomised and preference cohorts, a reanalysis was conducted. Because the trials involved a range of diseases, outcome measures and sample sizes, different treatment effect scales were converted into standardised effect sizes in the reanalysis. Treatment effects were calculated directly for continuous outcome variables as standardised mean differences (difference in means divided by the pooled SD). For binary outcomes, log ORs were calculated and converted into standardised effect size differences.[13] In case none of the patients in the preference cohort chose the control treatment, the treatment effect of the experimental treatment was compared with the control treatment of the randomised

cohort. Only trials for which a 'net' effect (primary outcome minus baseline value of the primary outcome) could be calculated were included in the meta-analyses. In case the 'net' effect was missing, but baseline values and primary outcomes were available, the SD was estimated.[14] Heterogeneity was not assessed as trial outcomes were different for each study included. Meta-analysis of randomised versus preference cohort was performed using a random effects model with an inverse variance weighting. A final meta-regression was performed using a Wald test to compare the standardised treatment effects.

A $P < 0.05$ was considered a significant difference. R's programming environment was used (V.3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There was no direct involvement of patients or the public in the development of the research question, selection of the outcome measures, design and implementation of the study, or interpretation of the results.

Results

In total, 117 out of 3734 records identified were full text screened. Fifty-eight partially RPPTs from 2005 onwards were found, of which 44 (including 24 873 patients) were eligible for at least basic data extraction (Table 2.1), and 20 could be included in the meta-analyses (PRISMA flow chart, Figure 2.1).[15–72] Exclusion reasons for the meta-analyses were: no availability of both treatment outcomes in the randomised and preference cohorts separately in 14 trials,[15,16,18,19,23,24,27,30,31,34,39,41,42,63] no availability of SDs, which could also not be converted from other available data in five trials,[21,29,49,52,62] and the number of events or the power of one or both cohort(s) was too low to perform separate randomised and preference analyses in five trials.[25,28,40,55,72] The trials covered a wide range of clinical areas and interventions. The main areas were gynaecology (n = 11), orthopaedics (n = 10) and psychiatry (n = 5). Of the 44 included trials, 32 compared an intervention versus conservative treatment, including 16 surgical interventions (Table 2.1). In all trials but one, if patients refused randomisation they received their preference treatment (Figure 2.2). In the other study, a Zelen randomisation was performed, randomising all eligible patients and afterwards asking for their consent to participate in the randomised arm or if they preferred the other intervention.[34] Parental preference was relevant in five trials involving children, as permission of parents was required and the preference between patients and parents could not be distinguished.[24,29,42,56,63]

Table 2.1. Partially randomised patient preference trials included in the review

Source	Population	No. R.	P.	Field	Intervention and comparison groups	Prim. outcome(s)
Ashok et al., 2005[15]	Woman presenting for termination of pregnancy	400	86	Gynaecology	Medical vs. surgical termination^+	Acceptability at 2 wk
Barnard et al., 2016[16]	Premenopausal women with symptomatic uterine fibroids	59	34	Gynaecology	UAE vs. MRgFUS^+	Perioperative outcomes at 3 mo
Bergk, J. et al., 2011[18]	Patients with DSM-IV disorder	27	81	Psychiatry	Mechanical restraint vs. seclusion	CES at 4 wk
Boers et al., 2017[19]	Pregnant women with disproportional intrauterine growth	650	452	Gynaecology	Induction vs. expectative monitoring^	(S)AE neonate at discharge
Brinkhaus et al., 2017[20] *	Patients with allergic asthma	357	1088	Social medicine	Acupuncture vs. control^	AQLQ at 3 mo
Brinkhaus et al., 2008[21]	Patients with allergic rhinitis	981	4256	Social medicine	Acupuncture vs. control^	RQLQ at 30 d
Buhagiar et al., 2017[22] *	Patients after total knee arthroplasty	165	87	Orthopaedics	Home based vs. inpatients recovery	Walking distance at 36 wk
Chekerov et al., 2017[23]	Elderly with ovarian cancer receiving chemotherapy	3	116	Gynaecology	Oral vs. iv treosulfan	DFS at 2 y
Creutzig et al., 2014[24]	Paediatric patients with relapsed AML	101	54	Haematology	L-DNR/Flag vs. Flag	OS at 4 y
Crowther et al., 2012[25]	Pregnant women with one prior caesarean	22	2323	Gynaecology	Caesarean vs. vaginal birth^+	Death and SAE at 30 d
Dalal et al., 2006[26] *	Participants in cardiac rehabilitation after acute MI	104	126	Cardiology	Home based vs. hospital recovery	HAD at 9 mo
Ejlertsen et al., 2008[27]	Premenopausal patients with breast cancer	525	1628	Oncology	Chemotherapy vs. ovarian ablation^+	DFS at 10 y
Erkan et al., 2007[28]	Patients with positive aPL but no vascular and/or pregnancy events.	98	74	Internal medicine	Aspirin vs. placebo or no aspirin^	Acute thrombosis per 100-patients y
Fong et al., 2015[29]	Patients with adolescent idiopathic scoliosis	19	50	Orthopedics	Brace vs. observational^	Recruitment feasibility
Gall et al., 2007[30]	Patients undergoing colon cancer surgery	203	135	Surgery	GP – vs. surgeon follow-up	PCS score at 24 mo
Glazener et al., 2016[31]	Patients with vaginal wall prolapse	1348	1126	Gynaecology	Mesh vs. no mesh^+	POPSS at 12 mo

Grant et al., 2008[32] *	Patients with gastro-oesophageal reflux disease	357	453	Upper GI	Surgery vs. medication^+	Reflux QOL at 1 y
Hatcher et al., 2005[34]	Patients presenting with self-harm	552	542	Psychiatry	PST plus standard care vs. standard care^	Repeated self-harm at 1 y
Howard et al., 2010[35] *	Women requiring voluntary psychiatric admission	42	61	Psychiatry	Crisis houses vs. psychiatric wards	Functioning (GAF) at 12 wk
Hubacher et al., 2017[36] *	Women 18-29 years who were seeking a short -acting method	382	524	Gynaecology	Long-acting vs. short-acting contraceptive^	Continuation rate at 1 y
Jones et al., 2011[37] *	Palliative cancer patients	41	36	Oncology	Advance vs. usual care^	VAS (S) at 8 wk
Karlsen et al., 2007[39]	Patients with proximal ureter stones	50	21	Urology	Shock wave vs. ureteroscopy^+	Stone free rate at 3 mo
Kearney et al., 2011[40]	Patients with an acute Achilles tendon rupture	20	29	orthopedics	Surgery vs. conservative^+	Disability rating index at 9 mo
Kroz et al., 2017[41]	Patients with breast cancer - related fatigue	65	61	Oncology	Multimodel combined program vs. aerobic training^	PSQI at 10 wk
Lock et al., 2010[42]	Children with recurrent sore throats	268	461	Children Surgery	Surgery vs. medication^+	No. episodes of sore throats at 2 y
Majumdar et al., 2010[43] *	Patients with lower urinary tract symptoms (LUTS)	99	210	Urology	Urodynamics vs. conservative^+	Kings QOL at 6 mo
Mittal et al., 2017[46] *	Patients with type B ankle fracture	160	276	Orthopedics	Surgery vs. no surgery^+	FAOQ and PCI at 12 mo
Prescott et al., 2007[49]	Women after breast conserving surgery	255	100	Oncology	Non- vs. radiotherapy^	QoL after 5 y
Purepong et al., 2015[50] *	Office workers suffering from low back pain (LBP)	64	37	Physical therapy	Backrest vs. no intervention^	VAS at 3 mo
Raue et al., 2011[52]	Patients operated for diverticulitis	149	294	Surgery	Laparoscopic vs. open approach	QoL at 30 d
Robson et al., 2009[53] *	Termination of pregnancy less than 14 weeks gestation	349	1528	Gynaecology	Medicine vs. surgery TOP^+	Acceptability TOP at 2 wk
Schweikert et al., 2009[55]	Patient for cardiac rehabilitation	4	163	Cardiology	Out-patient vs. in-patient recovery	EQ-5D at 12 mo
Shi guang et al., 2014[58] *	Patients with vascular dementia	48	20	Alternative medicine	Acupuncture vs. training^	SDSVD at

Table 2.1 continues on next page

Table 2.1. ***Continued***

Source	Population	No. R.	P.	Field	Intervention and comparison groups	Prim. outcome(s)
Sinclair et al., 2017[59] *	Patients with severe lung disease	67	82	Pulmonology	Advance care planning vs. standard	ACP uptake at 6 mo
Schwieger et al., 2016[56] *	Adolescent with idiopathic scoliosis (AIS)	132	187	Orthopaedics	Brace vs. observation^	QOL at 2 y
Underwood et al., 2008[60] *	Older patients with chronic knee pain	282	303	Orthopaedics	Topic vs. oral ibuprofen	WOMAC at 12 mo
van der Kooij et al., 2013[62]	Uterine fibroids	177	103	Gynaecology	Embolization vs. hysterectomy^+	HRQoL at 12 mo
Van Heest et al. 2015[63]	Children with upper extremity cerebral palsy	29	10	Orthopedics	Surgery vs. botuline therapy^+	SHUEE at 24 wk
Weinstein et al. 2006[65] *	Patients with spondylolisthesis	304	303	Orthopaedics	Surgical vs. non-surgical^+	Physical functioning (SF-36 Phys) at 2 y
Weinstein et al. 2008[64] *	Patients with spinal stenosis	289	365	Orthopaedics	Surgical vs. non-surgical^+	Physical functioning (SF-36 Phys) at 2 y
Witbrodt, 2007 [67]*	Addicted people	293	321	Social medicine	Community residential vs. day hospital^	Abstinence at 12 mo
Witt el al., 2006[68] *	Patients with chronic low back pain	2841	8537	Rheumatology	Acupuncture vs. control^	HFAQ at 3 mo
Witt et al., 2006[69] *	Patients with osteoarthritis	712	2921	Rheumatology	Acupuncture vs. control^	Osteoarthritis index (WOMAC) at 3 mo
Woodward et al., 2004[72]	Pregnant women	60	20	Gynaecology	Water- vs. land birth	Baby condition at 6 wk

* These 20 trials could be used to calculate standardised effect sizes of the randomised- and preference cohort separately, and were included in our reanalysis on the effect of preference on outcome. ^ These 32 trials compared interventions versus conservative treatment. + These 16 trials compared surgical interventions versus conservative treatment. *Abbreviations:* Wk, week; mo, months; y, year; MRgFUS, magnetic resonance imaging-guided focused ultrasound surgery; UAE, uterine artery embolization; HRQoL, Health related Quality of Life; CES, Coercion Experience Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HFAQ, Hannover Functional Ability Questionnaire; AQLQ, Astma Quality of Life; SAE, Serious adverse event; HAD, Hospital Anxiety Depression scale; GAF, Global assessment of functioning; BPRS, Brief psychiatric rating scale; VAS, Visual analogue scales; FAOQ, Foot and Ankle outcomes questionnaire; PCI, Physical component score; RMDQ, Roland-Morris Disability Questionnaire; TOP, Termination of pregnancy; SVSVD, Scale of differentiation of syndromes of vascular dementia; ACP, Advance care planning; DFS, disease free survival; OS, overall survival; PCS, peritoneal cancer score; PST, problem solving therapy; RQLQ, Rhinitis Quality of life questionnaire; L-DNR, liposomal daunorubicin; FLAG, fludarabut; POPSS, Pelvic organ prolapse symptom score; SHUEE, Shriners Hospital Upper Extremity Evaluation; SF-36 Phys, short-from 36 scale physical functioning; PSQI, Pittsburg sleep Quality index; R, randomised; P, preference.

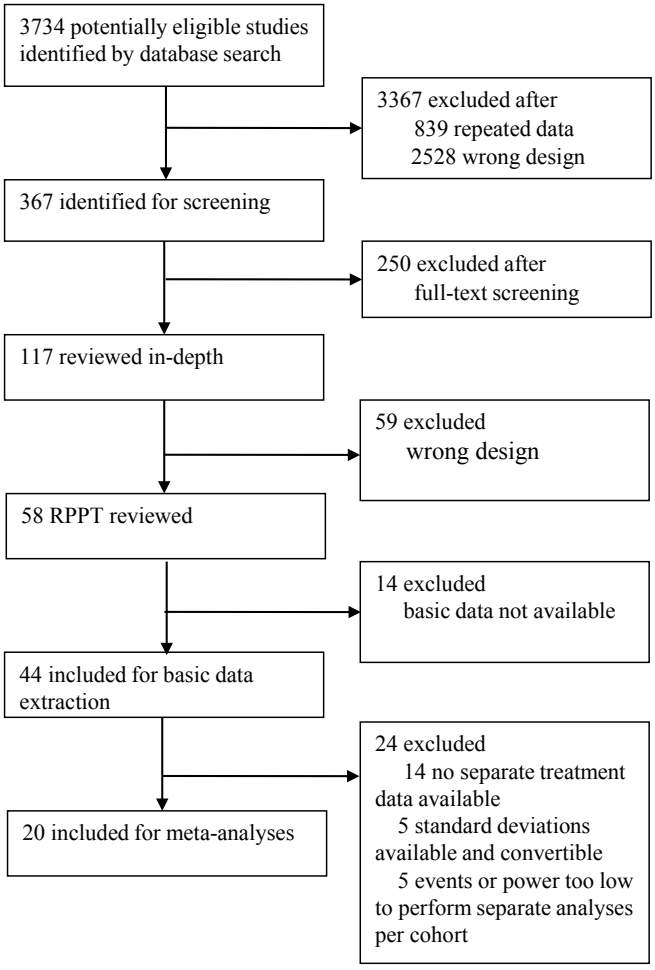


Figure 2.1. Study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
RPPT, randomised patient preference trial.

External validity

The following results concern the influence of patients' preference on external validity. Information on the number of eligible patients who agreed to participate (in either the randomised or preference cohort) was available in 39 out of the 44 RPPTs. The participation rate of eligible patients in the RPPTs ranged from 48% to 100%, in which 16 RPPTs reported a participation rate higher than 80%, and 14 RPPTs with a participation rate higher than 95%. Of these included participants in the 44 RPPTs, 18%–99% declined randomisation (hence these patients were included in the preference cohort). The randomisation refusal rate was more than 50% in 26 RPPTs.

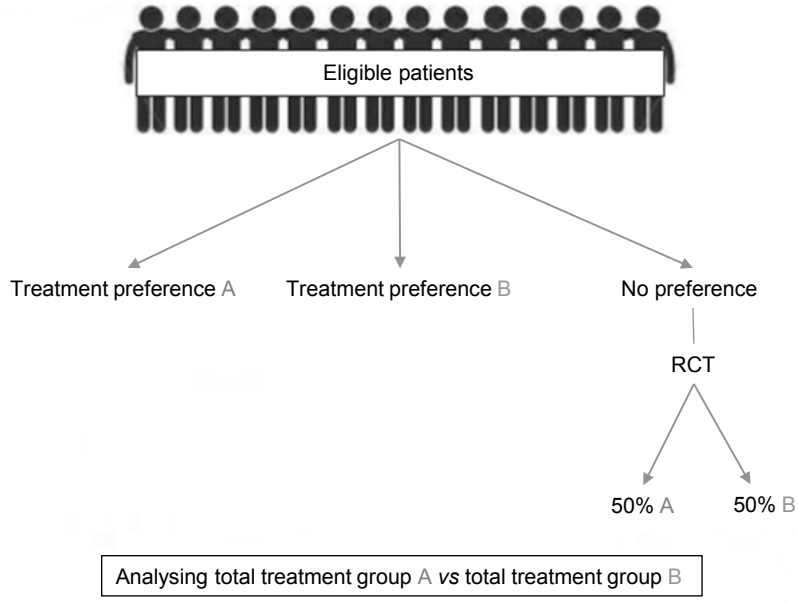


Figure 2.2. A randomised patient preference trial.
RCT, randomised controlled trial.

To assess if a specific patient group accepted randomisation, 35 of the 44 RPPTs reported at least one comparison between randomised and preference cohorts on baseline sociodemographic factors. At least one significant difference between randomised and preference cohorts was found in 20 of the 35 trials. Overall, 38 significant differences were found in 161 sociodemographic comparisons (24%). The proportion of significant findings was not dependent on sample size (smaller trials n < 300; 19/85, 22% and larger trials n ≥ 300; 19/76, 25%). Patients with a preference compared with those accepting randomisation were more likely to be older, female, with higher education, employed, Caucasian, not obese, non-smokers, unmarried and experienced with one treatment arm (Supplementary Table S2.1).

Thirty-four of the 44 RPPTs reported at least one comparison between randomised and preference cohorts on clinical baseline characteristics. At least one significant difference was found in 20 of the 34 trials. Overall, 36 significant differences were found in 220 clinical comparisons (16%). The proportion of significant findings was not dependent on sample size (smaller trials n < 300; 12/78, 15% and larger trials n ≥ 300; 24/142, 17%). Patients with a preference had more severe clinical problems in seven trials and less severe clinical problems in 10 trials, while in the remaining three trials no consistent pattern could be found (Supplementary Table S2.1).

Internal validity

The following results concern the influence of patients' preference on internal validity. Information on lost to follow-up in both the randomised and preference cohorts was available in 33 of the 44 RPPTs. For the randomised cohorts, the proportion of individuals lost to follow-up was < 10% in 14 trials, 10% to < 20% in 9 trials and ≥ 20% in 10 trials. For the preference cohorts the corresponding numbers of trials were 17, 9 and 7. The mean percentage of participants lost to follow-up was significantly higher in the randomised cohorts (16.1%, SD 16.8%) compared with the preference cohorts (13.3%, SD 14.7%), relative risk (RR 1.3) (95% CI 1.0 to 1.6, $P = 0.03$).

Information on crossovers in both the randomised and preference cohorts was available in 20 of 44 RPPTs. For the randomised cohorts, the proportion of individuals who crossed over to the other study treatment was < 10% in 11 trials, 10% to < 20% in 5 trials and ≥ 20% in 4 trials. For the preference cohorts the corresponding numbers of trials were 14, 5 and 1. The mean percentage of crossovers was significantly higher in the randomised cohorts (14.5%, SD 16.9%) compared with the preference cohorts (6.3%, SD 11.5%), RR 2.6 (95% CI 1.7 to 3.9, $P < 0.001$).

To assess the influence of patients' preference on primary outcomes, for 20 of the 44 RPPTs it was possible to perform reanalyses using standardised effect sizes (Figure 2.1).

Figure 2.3 shows the magnitude of the experimental treatment effect over the control treatment effect of the randomised and preference cohorts separately using standardised effect sizes. The trials are listed by sample size. A positive experimental treatment effect was seen in 13 trials. The influence of patients' preference on primary outcomes according to different standardised treatment effects between randomised and preference cohorts was small; in 13 of the 20 trials (65%) this was 0.2 or less (scale -2 to 2), in 5 trials (25%) between 0.21 and 0.5, and in 2 trials (10%) higher than 0.5. Of the 20 RPPTs, the overall mean difference in primary outcome between randomised and preference cohorts was not significantly different, 0.093 (95% CI -0.178 to 0.364, $P = 0.502$) (Figure 2.2). Only two trials showed a significant different treatment effect between the randomised and preference cohorts.[68,69] In both trials the experimental treatment effect was favourable over the control treatment effect in both the randomised and preference cohorts, but the favourable effect of the experimental treatment was significantly greater in the preference cohort. Both RPPTs compared acupuncture versus conservative treatment. In one trial the improvement of the osteoarthritis index in patients with osteoarthritis of the knee or hip was assessed, the other trial assessed the functional ability score in patients with chronic low back pain.

In 7 of these 20 trials, an adjusted primary outcome for baseline confounders was available.[22,32,35,37,60,64,65] In these trials, the mean difference in primary outcome between randomised and preference cohorts was even smaller, -0.026 (95% CI -0.263 to 0.211,

P = 0.832). In 18 trials (also) a non-adjusted primary outcome was available. Using these outcomes, the mean difference in primary outcomes was 0.228 (95% CI -0.117 to 0.572, *P* = 0.196) (Figures 2.4 and 2.5).

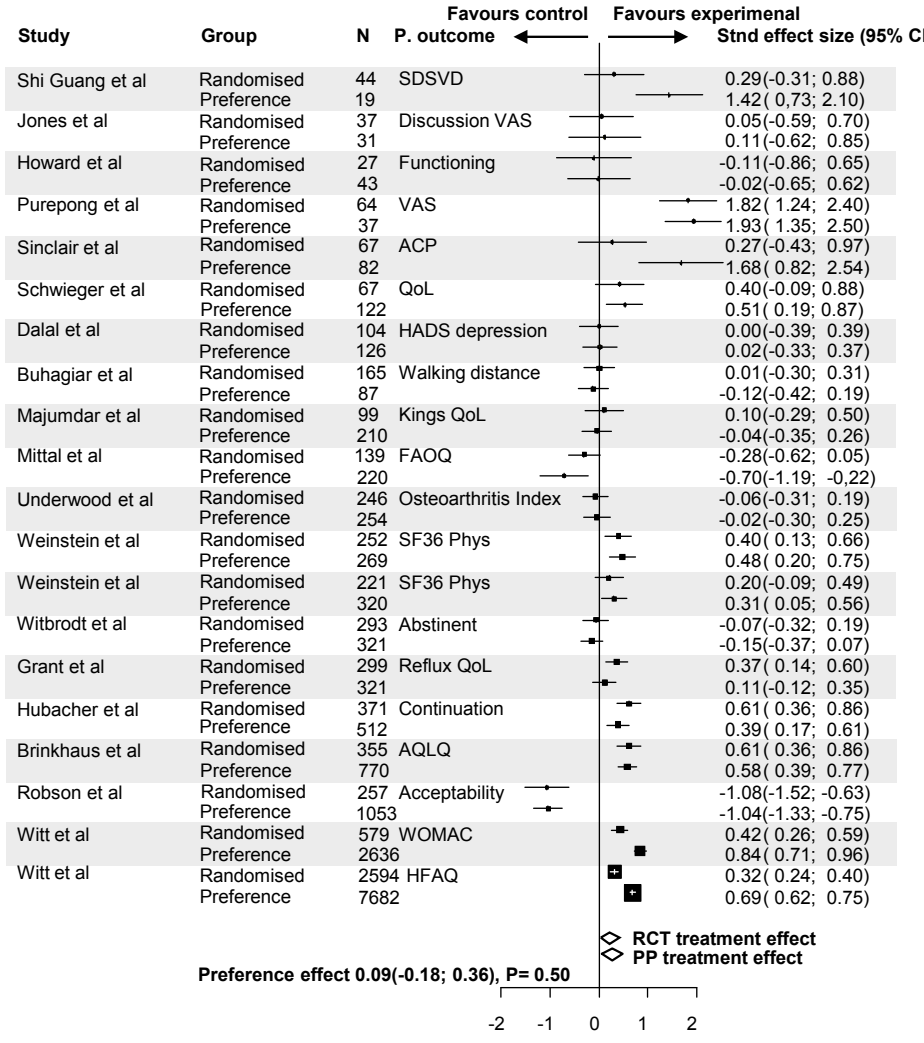


Figure 2.3. Forest plot of the preference effect on the primary outcome between the randomised and preference cohort, by comparing the overall treatment effect (standardized effect size) within the randomised cohorts versus the overall treatment effect within the preference cohorts.

ACP, advance care planning; AQLQ, Asthma Quality of Life Questionnaire; FAOQ, Foot and Ankle Outcomes Questionnaire; HADS, Hospital Anxiety Depression Scale; HFAQ, Hannover Functional Ability Questionnaire; PP, Patients' preference cohort; QoL, quality of life; RCT, randomised controlled trial; SDSVD, scale of differentiation of syndromes of vascular dementia; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

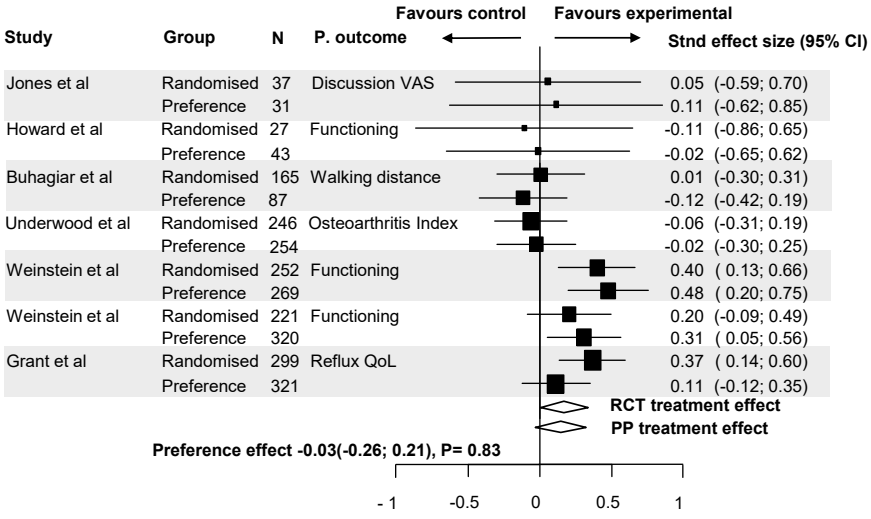


Figure 2.4. Forest plot of the preference effect on the primary outcome between the randomised and preference cohorts of trials in which the primary outcome is adjusted for confounders.
The overall treatment effect (standardised effect size) within the randomised cohorts was compared with the overall treatment effect within the preference cohorts. QoL, quality of life; RCT, randomised controlled trial; PP, Patients' preference cohort; VAS, visual analogue scale.

Discussion

These study results challenge the current consensus about the hierarchy of study designs. Our results indicate that patients' preference led to a substantial proportion of patients refusing randomisation (refusal of randomisation was more than 50% in 26 trials), while it did not affect the primary outcome of an RPPT.

Regarding our first hypothesis, it can be concluded that patients' preference does negatively influence participation to RCTs, as demonstrated by the low participation to the randomised cohort in RPPTs. The participation in the RPPTs was remarkably high (ranging from 48% to 100%), improving external validity when compared with the classic RCT (ranging from < 0.001% to 40%).[73] Cautiously, it could be argued that a typical patient group characterised by, for example, higher education, Caucasian race and non-obese individuals are more likely to refuse randomisation. In contrast, differences in clinical characteristics showed no consistent pattern in the randomised or preference cohorts. Therefore, not including a patient's preference cohort in a trial could result in a potential loss of inclusions of a specific patient group, further decreasing external validity.

Regarding our second hypothesis, it can be concluded that patients' preference does not significantly affect the primary outcome of an RPPT, as the primary outcomes of patients in the randomised and preference cohorts were similar. Since the aim of an RPPT is to treat patients according to their preference, it can be assumed that the

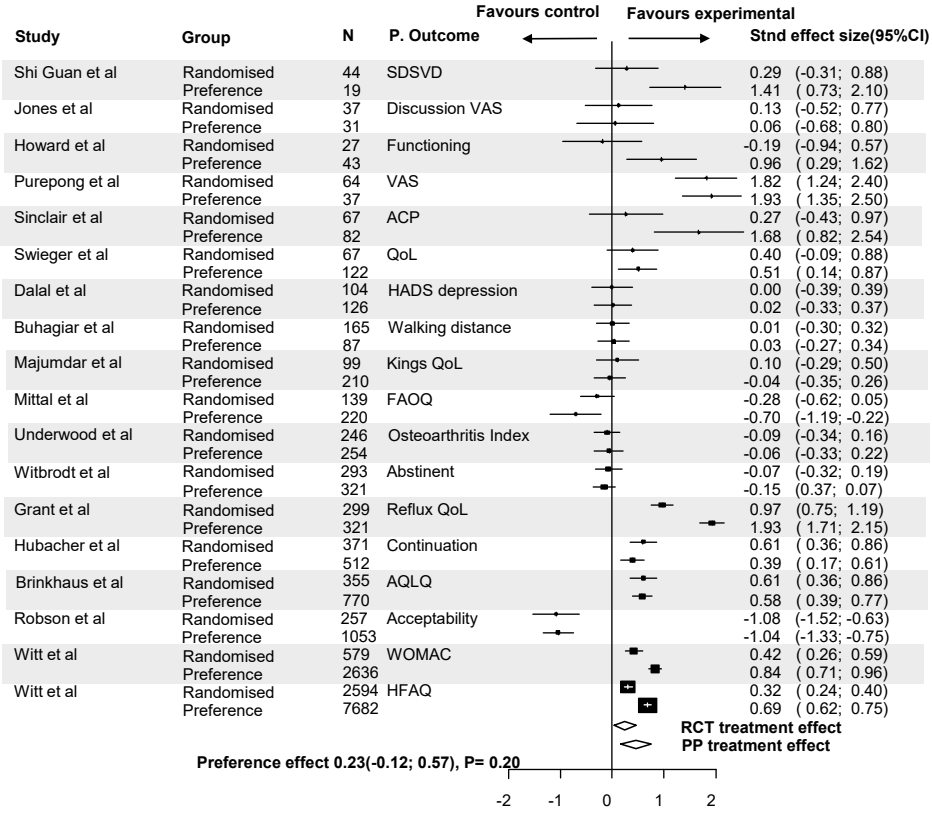


Figure 2.5. Forest plot of the preference effect on the primary outcome between the randomised and preference cohorts of trials in which the primary outcome is not adjusted for confounders.
The overall treatment effect (standardised effect size) within the randomised cohorts was compared with the overall treatment effect within the preference cohorts. ACP, advance care planning; AQLQ, Asthma Quality of Life Questionnaire; FAOQ, Foot and Ankle Outcomes Questionnaire; HADS, Hospital Anxiety Depression Scale; HFAQ, Hannover Functional Ability Questionnaire; PP, Patients' preference cohort; QoL, quality of life; RCT, randomised controlled trial; SDSVD, scale of differentiation of syndromes of vascular dementia; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

randomised cohort of an RPPT includes patients indifferent to the type of treatment. Subsequently, it is unlikely that outcomes of randomised patients will be biased by treatment preference. Hence, they could be seen as the gold standard. Lost to follow-up and crossovers were significantly higher in the randomised cohort compared with the preference cohort. As a result, the data of the preference cohort could be interpreted more easily than the randomised data. Perhaps, consciously choosing a treatment ensures a certain dedication and tolerance for the treatment.

Our results are strengthened by the previous systematic review of King et al., including RPPTs from 1966 to 2004. Based on their results, they also postulated that treatment

preference influences the willingness to accept randomisation, and that the evidence of its significant effect on internal validity is low.[4] A possible limitation of their study is that they did not measure patients' preference as specifically as in our analyses, since they also included a minority of two-stage randomised trials, as physician preference.

An RCT is once designed to reliably compare medication to placebo.[74] In the hierarchy of research designs, the results of RCTs are considered to be evidence of the highest grade. Lessons learnt from the history of RCT, and early studies from 1970s and 1980s suggested that observational studies suffer too much from confounders and frequently result in overestimation of treatment effects compared with RCTs.[75,76] Consequently, many experts advocated that results of observational studies should not be used for defining evidence-based medical care: '*If the study wasn't randomized, we suggest that you stop reading it and go on to the next article*.'[77] However, two updates of this work including studies between 1985 and 1995 found little evidence that estimates of treatment effects in observational studies are consistently larger than those obtained in RCTs.[78,79] It is suggested that observational studies have methodologically improved over time with the use of a control group, carefully defining inclusion and exclusion criteria, and by better understanding confounders. The fundamental criticism of the RPPT could be that within the preference cohort the unrecognised confounding factors may distort the results. Yet, our results showed that preference cohorts provide valid information comparable with the randomised results.

Today, the classic levels of evidence are subject of debate, as the disadvantages of RCTs have become more insightful in modern practice. In general, patients participating in RCTs are highly selected. Less than 10% of patients participate in trials, partly due to exclusion of patients with a specific treatment preference.[80] This limits the extrapolation of RCT results to patients seen in routine practice. Another consequence is that the majority of trials take several years to be completed. This causes a burden on health research costs, and results in a questionable ethical dilemma. Developments are fast and the relevance of trials may therefore change over time. Consequently, if an RCT is optimally designed but takes too long, the results will be outdated.

This especially applies when designing a trial in which it can be foreseen that patients' preference will be a prominent factor, for example, in trials comparing treatments of significant different nature (medical vs. surgical). Anticipation on the expected patients' preference by eliminating this factor is at the expense of the validity of a lot of RCTs. Especially when patient-centred outcomes are used, one should consider whether the most important patient group has been excluded. Trials must be internally valid, but lack of consideration of external validity causes the widespread underuse of treatments—that showed superiority in RCTs—in routine practice. Moreover, in these situations an RPPT could be the superior design over an RCT.

RPPTs provide unique data on external and internal validity as the patients in the preference cohort are followed according to the same conditions as the patients in the randomised cohorts. A limitation of our review is that interventions and settings between RPPTs were very diverse. On the other hand, because of this diversity, it could also be stated that randomised and preference data often produce similar results in all kinds of settings. Concerning the assessment of external validity, it should be noted that in only a minority of trials the differences in sociodemographic and clinical parameters between the cohorts of an RPPT were evident. Furthermore, in some cases none of the patients in the preference cohort choose the control treatment. In these cases, the treatment effect of the experimental treatment was compared with the control treatment of the randomised cohort. These are not optimal comparisons, but considered to be more appropriate than excluding these data. Moreover, as the idea of RPPTs is a relatively new concept, various terms were used in the inclusion period of this systematic review. In the publication of Walter et al. in 2017, different concepts were compared and they clearly defined the terms fully randomised patient preference trial and partially randomised patient preference trial. To achieve a 'fully randomised patient preference trial', the preference of all participants should be identified. Therefore, uniform counselling is of crucial importance in RPPTs. The majority of included studies claim to be RPPTs. However, in most of currently included studies, the details of how patients were counselled have not been addressed. As we cannot guarantee that a study identified the preference of all eligible patients, we decided to use the term partially randomised patient preference trials. Another result of the novelty of such a design is that it was not possible to objectively establish the quality of included trials, as there is currently no valid critical appraisal tool to apply for an RPPT. Consequently, our results may have been influenced by the inclusions of flawed trials.

In conclusion, RPPTs seem to be a reliable alternative for RCTs, especially in trials comparing treatments of vastly different nature (e.g., medical vs. surgical) or using patient-centred outcomes. In case patients' preference can be assumed, RPPT enables faster inclusion of a more representative population improving external validity without compromising internal validity.

References

1. Effectiveness. NC for R and DU systematic reviews of research on. Centre for Reviews and Disseminationt's Guidance for Those Carrying Out or Commissioning Reveiws. York, Engl Univ York 2001;Report 4.
2. Walter SD, Turner RM, Macaskill P, et al. Estimation of treatment preference effects in clinical trials when some participants are indifferent to treatment choice. BMC Med Res Methodol 2017;17:29. doi:10.1186/s12874-017-0304-x
3. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. Br Med J 1989;299:313–5. doi:10.1136/bmj.299.6694.313
4. King M, Nazareth I, Lampe F, et al. Impact of Participant and Physician Intervention Preferences on Randomized Trials. JAMA 2005;293:1089. doi:10.1001/jama.293.9.1089
5. Swift JK, Callahan JL. The impact of client treatment preferences on outcome: a meta-analysis. J Clin Psychol 2009;65:368–81. doi:10.1002/jclp.20553
6. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009) - CEBM. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed 3 Jul 2019).
7. Higgins JPT GS (Eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Cochrane Collab Oxford; Published Online First: 2011.http://handbook-5-1.cochrane.org/
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535–b2535. doi:10.1136/bmj.b2535
9. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. doi:10.1136/bmj.i4919
10. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928–d5928. doi:10.1136/bmj.d5928
11. Guyatt GH, Ebrahim S, Alonso-Coello P, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. J Clin Epidemiol 2017;87:14–22. doi:10.1016/j.jclinepi.2017.05.005
12. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. doi:10.1186/1471-2288-14-135
13. MW Lipsey DW. Practical meta-analysis. Thousan Oaks, Calif Sage Publ 2001.
14. 16.1.3.2 Imputing standard deviations for changes from baseline. http://handbook-5-1.cochrane.org/chapter_16/16_1_3_2_imputing_standard_deviations_for_changes_from_baseline.htm (accessed 10 Jul 2018).
15. Ashok PW, Hamoda H, Flett GM, et al. Patient preference in a randomized study comparing medical and surgical abortion at 10-13 weeks gestation. Contraception 2005;71:143–8. doi:10.1016/j.contraception.2004.08.013
16. Barnard EP, AbdElmagied AM, Vaughan LE, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. Am J Obstet Gynecol 2017;216:500.e1-500.e11. doi:10.1016/j.ajog.2016.12.177
17. Barnestein-Fonseca P, Vazquez-Alarcon R, Leiva-Fernandez F, et al. Inhalation Technique Evolution After Training in Copd. The Role of the Device. Value Heal 2014;17:A600. doi:10.1016/j.jval.2014.08.2076
18. Bergk J, Einsiedler B, Flammer E, et al. A randomized controlled comparison of seclusion and mechanical restraint in inpatient settings. Psychiatr Serv 2011;62:1310–7. doi:10.1176/ps.62.11.pss6211_1310
19. KE Boers, L van Wyk, JAM van der Post, A Kwee, MG van Pampus, HA Bremer, FMC Delemarre, KWM Bloemenkamp, S le Cessie, FME Roumen, JG Thornton, JMM van Lith, BW J Mol SS. Comparison of participants and non-participnatns in a trial of induction of labour versus expectant monitoring for intrauterine growth restriction at term (teh DIGITAT trial); a prospective cohort study. 2012.https://openaccess.leidenuniv.nl/bitstream/handle/1887/18948/06.pdf?sequence=12
20. Brinkhaus B, Roll S, Jena S, et al. Acupuncture in Patients with Allergic Asthma: A Randomized Pragmatic Trial. J Altern Complement Med 2017;23:268–77. doi:10.1089/acm.2016.0357
21. Brinkhaus B, Witt CM, Jena S, et al. Acupuncture in patients with allergic rhinitis: a pragmatic randomized trial. Ann Allergy, Asthma Immunol 2008;101:535–43.http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=105590802&lang=nl&site=ehost-live&scope=site

22. Buhagiar MA, Naylor JM, Harris IA, et al. Effect of Inpatient Rehabilitation vs a Monitored Home-Based Program on Mobility in Patients With Total Knee Arthroplasty: The HIHO Randomized Clinical Trial. JAMA J Am Med Assoc 2017;317:1037–46. doi:10.1001/jama.2017.1224
23. Chekerov R, Harter P, Fuxius S, et al. Preference of elderly patients' to oral or intravenous chemotherapy in heavily pre-treated recurrent ovarian cancer: final results of a prospective multicenter trial. Gynecol Oncol Res Pract 2017;4:6. doi:10.1186/s40661-017-0040-2
24. Creutzig U, Semmler J, Kaspers GL, et al. Re-induction with L-DNR/FLAG improves response after AML relapse, but not long-term survival. Klin Padiatr 2014;226:323–31. doi:10.1055/s-0034-1385918
25. Crowther CA, Dodd JM, Hiller JE, et al. Planned Vaginal Birth or Elective Repeat Caesarean: Patient Preference Restricted Cohort with Nested Randomised Trial. PLoS Med 2012;9:e1001192. doi:10.1371/journal.pmed.1001192
26. Dalal HM, Evans PH, Campbell JL, et al. Home-based versus hospital-based rehabilitation after myocardial infarction: A randomized trial with preference arms--Cornwall Heart Attack Rehabilitation Management Study (CHARMS). Int J Cardiol 2007;119:202–11. doi:10.1016/j.ijcard.2006.11.018
27. Ejlertsen B, Jensen M-B, Mouridsen HT, et al. DBCG trial 89B comparing adjuvant CMF and ovarian ablation: similar outcome for eligible but non-enrolled and randomized breast cancer patients. Acta Oncol 2008;47:709–17. doi:10.1080/02841860802001475
28. Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007;56:2382–91.http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=105979335&lang=nl&site=ehost-live&scope=site
29. Fong DYT, Cheung KMC, Wong YW, et al. An alternative to a randomised control design for assessing the efficacy and effectiveness of bracing in adolescent idiopathic scoliosis. Bone Joint J 2015;97–B:973–81. doi:10.1302/0301-620X.97B7.35147
30. Gall CA, Weller D, Esterman A, et al. Patient satisfaction and health-related quality of life after treatment for colon cancer. Dis Colon Rectum 2007;50:801–9. doi:10.1007/s10350-006-0815-8
31. Glazener C, Breeman S, Elders A, et al. Clinical effectiveness and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a comprehensive cohort study – results from the PROSPECT Study. Health Technol Assess (Rockv) 2016;20:1–452. doi:10.3310/hta20950
32. Grant A, Boachie C, Cotton S, et al. Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial). Heal Technol Assess 2013;17:1–167. doi:10.3310/hta17220
33. Hartley S, Haddock G. Self-help therapy and recovery in psychosis: methodological considerations and service user involvement in a partially randomised preference trial. Trials 2011;12:A84. doi:10.1186/1745-6215-12-S1-A84
34. Hatcher S, Sharon C, Parag V, et al. Problem-solving therapy for people who present to hospital with self-harm: Zelen randomised controlled trial. Br J Psychiatry 2011;199:310–6. doi:10.1192/bjp.bp.110.090126
35. Howard L, Flach C, Leese M, et al. Effectiveness and cost-effectiveness of admissions to women's crisis houses compared with traditional psychiatric wards: pilot patient-preference randomised controlled trial. Br J Psychiatry Suppl 2010;53:s32-40. doi:10.1192/bjp.bp.110.081083
36. Hubacher D, Spector H, Monteith C, et al. Long-acting reversible contraceptive acceptability and unintended pregnancy among women presenting for short-acting methods: a randomized patient preference trial. Am J Obstet Gynecol 2017;216:101–9. doi:10.1016/j.ajog.2016.08.033
37. Jones L, Harrington J, Barlow CA, et al. Advance care planning in advanced cancer: can it be achieved? An exploratory randomized patient preference trial of a care planning discussion. Palliat Support Care 2011;9:3–13. doi:10.1017/S1478951510000490
38. Karidakis GK, Karachalios T. Oxidized Zirconium Head on Crosslinked Polyethylene Liner in Total Hip Arthroplasty: A 7- to 12-year In Vivo Comparative Wear Study. Clin Orthop Relat Res 2015;473:3836–45. doi:10.1007/s11999-015-4503-7
39. Karlsen SJ, Renkel J, Tahir AR, et al. Extracorporeal shockwave lithotripsy versus ureteroscopy for 5- to 10-mm stones in the proximal ureter: Prospective effectiveness patient-preference trial. J Endourol 2007;21:28–33. doi:10.1089/end.2006.0153
40. Kearney RS, Achten J, Parsons NR, et al. The comprehensive cohort model in a pilot trial in orthopaedic trauma. BMC Med Res Methodol 2011;11:39. doi:10.1186/1471-2288-11-39

41. Kröz M, Reif M, Glinz A, et al. Impact of a combined multimodal-aerobic and multimodal intervention compared to standard aerobic treatment in breast cancer survivors with chronic cancer-related fatigue - results of a three-armed pragmatic trial in a comprehensive cohort design. BMC Cancer 2017;17:166. doi:10.1186/s12885-017-3142-7
42. Lock C, Wilson, J, Steen N, et al. Comparison of case note review methods for evaluating quality and safety in health care. Health Technol Assess (Rockv) 2010;14:1–164, iii–iv. doi:10.3310/hta14130
43. Majumdar A, Latthe P, Toozs-Hobson P. Urodynamics prior to treatment as an intervention: A pilot study. Neurourol Urodyn 2009;:n/a-n/a. doi:10.1002/nau.20810
44. Mills N, Metcalfe C, Ronsmans C, et al. A comparison of socio-demographic and psychological factors between patients consenting to randomisation and those selecting treatment (the ProtecT study). Contemp Clin Trials 2006;27:413–9. doi:10.1016/j.cct.2006.04.008
45. Mitchell-Jones N, Farren JA, Tobias A, et al. Ambulatory versus inpatient management of severe nausea and vomiting of pregnancy: a randomised control trial with patient preference arm. BMJ Open 2017;7:e017566. doi:10.1136/bmjopen-2017-017566
46. Mittal R, Harris IA, Adie S, et al. Surgery for Type B Ankle Fracture Treatment: a Combined Randomised and Observational Study (CROSSBAT). BMJ Open 2017;7:e013298. doi:10.1136/bmjopen-2016-013298
47. Narasimmaraj P, Stover Fiscalini A, Kaplan C, et al. Abstract P3-10-01: A pilot feasibility study of the WISDOM study, a preference-tolerant randomized controlled trial evaluating a risk-based breast cancer screening strategy. Cancer Res 2016;76:P3-10-01-P3-10-01. doi:10.1158/1538-7445.SABCS15-P3-10-01
48. Nozaki I, Kato K, Igaki H, et al. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc 2015;29:3519–26. doi:10.1007/s00464-015-4102-4
49. Prescott RJ, Kunkler IH, Williams LJ, et al. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess 2007;11:1–149, iii–iv.http://www.ncbi.nlm.nih.gov/pubmed/17669280 (accessed 8 May 2018).
50. Purepong N, Channak S, Boonyong S, et al. The effect of an acupressure backrest on pain and disability in office workers with chronic low back pain: A randomized, controlled study and patients' preferences. Complement Ther Med 2015;23:347–55. doi:10.1016/j.ctim.2015.03.005
51. Ramanathan K, Ioannou K, Keshmiri H, et al. 326 Disparity Between Clinical Trials and Registry Outcomes: Reflections From the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) Trial. Can J Cardiol 2012;28:S218–9. doi:10.1016/j.cjca.2012.07.307
52. Raue W, Langelotz C, Paolucci V, et al. Problems of randomization to open or laparoscopic sigmoidectomy for diverticular disease. Int J Colorectal Dis 2011;26:369–75. doi:10.1007/s00384-010-1074-7
53. Robson S, Kelly T, Howel, D, et al. Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation (TOPS). Health Technol Assess (Rockv) 2009;13. doi:10.3310/hta13530
54. Ryan M, Nitsun M, Gilbert L, et al. A prospective study of the effectiveness of group and individual psychotherapy for women CSA survivors. Psychol Psychother 2005;78:465–79. doi:10.1348/147608305X42226
55. Schweikert B, Hahmann H, Steinacker JM, et al. Intervention study shows outpatient cardiac rehabilitation to be economically at least as attractive as inpatient rehabilitation. Clin Res Cardiol 2009;98:787–95. doi:10.1007/s00392-009-0081-6
56. Schwieger T, Campo S, Weinstein SL, et al. Body Image and Quality-of-Life in Untreated Versus Brace-Treated Females With Adolescent Idiopathic Scoliosis. Spine (Phila Pa 1976) 2016;41:311–9. doi:10.1097/brs.0000000000001210
57. Shavelle D, Kapasi N, Banerjee S, et al. TCT-127 Prior Coronary Artery Bypass Graft Surgery and Hemodynamically Supported High Risk Percutaneous Coronary Intervention: Observations from The PROTECT II Randomized Trial and The cVAD Registry. J Am Coll Cardiol 2016;68:B51. doi:10.1016/j.jacc.2016.09.033
58. Shi GX, Liu CZ, Guan W, et al. Effects of acupuncture on Chinese medicine syndromes of vascular dementia. Chin J Integr Med 2014;20:661–6. doi:10.1007/s11655-013-1323-4

59. Sinclair C, Auret KA, Evans SF, et al. Advance care planning uptake among patients with severe lung disease: A randomised patient preference trial of a nurse-led, facilitated advance care planning intervention. BMJ Open 2017;7:e013415. doi:10.1136/bmjopen-2016-013415
60. Underwood M, Ashby D, Cross P, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ 2008;336:138–42. doi:10.1136/bmj.39399.656331.25
61. Impact of Vitamin D on Insulin Resistance... (PDF Download Available). https://www.researchgate.net/publication/264216208_Impact_of_Vitamin_D_on_Insulin_Resistance_in_Patients_with_Type_II_Diabetes_A_Comprehensive_Cohort_Design (accessed 8 May 2018).
62. van der Kooij SM, Hehenkamp WJK, Birnie E, et al. The effect of treatment preference and treatment allocation on patients' health-related quality of life in the randomized EMMY trial. Eur J Obstet Gynecol Reprod Biol 2013;169:69–74. doi:10.1016/j.ejogrb.2013.01.019
63. Van Heest AE, Bagley A, Molitor F, et al. Tendon transfer surgery in upper-extremity cerebral palsy is more effective than botulinum toxin injections or regular, ongoing therapy. J Bone Jt Surg Am 2015;97:529–36. doi:10.2106/jbjs.m.01577
64. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus Nonsurgical Therapy for Lumbar Spinal Stenosis. N Engl J Med 2008;358:794–810. doi:10.1056/NEJMoa0707136
65. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. N Engl J Med 2007;356:2257–70. doi:10.1056/NEJMoa070302
66. Wiegel T, Stöckle M, Bartkowiak D. PREFEREnce-based Randomized Evaluation of Treatment Modalities in Low or Early Intermediate-risk Prostate Cancer. Eur Urol 2015;67:1–2. doi:10.1016/j.eururo.2014.09.016
67. Witbrodt J, Bond J, Kaskutas LA, et al. Day hospital and residential addiction treatment: randomized and nonrandomized managed care clients. J Consult Clin Psychol 2007;75:947–59. doi:10.1037/0022-006x.75.6.947
68. Witt CM, Jena S, Selim D, et al. Pragmatic randomized trial evaluating the clinical and economic effectiveness of acupuncture for chronic low back pain. Am J Epidemiol 2006;164:487–96. doi:aje/kwj224
69. Witt CM, Jena S, Brinkhaus B, et al. Acupuncture in patients with osteoarthritis of the knee or hip: a randomized, controlled trial with an additional nonrandomized arm. Arthritis Rheum 2006;54:3485–93. doi:10.1002/art.22154
70. C.G. Wood, P. Srivastava, L. Lacombe, A.I. Gorelov, S. Gorelov, P. Mulders, H. Zielinski, F. Teofilovici, L. Isakov BE. Survival update from a multicenter, randomized, phase III trial of vitespen versus observation as adjuvant therapy for renal cell carcinoma in patients at high risk of recurrence. J Clin Oncol 2009;27:3009–3009. doi:10.1200/jco.2009.27.15s.3009 Journal of Clinical Oncology 27, no. 15S (May 20 2009) 3009-3009.
71. Yoneda T, Shoji K, Takase H, et al. Effectiveness and safety of 1-year ad libitum consumption of a high-catechin beverage under nutritional guidance. Metab Syndr Relat Disord 2009;7:349–56. doi:10.1089/met.2008.0061
72. Woodward J, Kelly SM. A pilot study for a randomised controlled trial of waterbirth versus land birth. BJOG 2004;111:537–45. doi:10.1111/j.1471-0528.2004.00132.x
73. Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet 2005;365:82–93. doi:10.1016/S0140-6736(04)17670-8
74. Bothwell LE, Greene JA, Podolsky SH, et al. Assessing the Gold Standard — Lessons from the History of RCTs. N Engl J Med 2016;374:2175–81. doi:10.1056/NEJMms1604593
75. Chalmers TC, Celano P, Sacks HS, et al. Bias in treatment assignment in controlled clinical trials. N Engl J Med 1983;309:1358–61. doi:10.1056/NEJM198312013092204
76. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. Stat Med 1989;8:441–54.http://www.ncbi.nlm.nih.gov/pubmed/2727468 (accessed 7 Aug 2018).
77. Sackett DL. Evidence-based medicine : how to practice and teach EBM. Churchill Livingstone 2000. https://books.google.nl/books?hl=nl&id=Qh1ntQEACAAJ&focus=searchwithinvolume&q=stop+reading (accessed 7 Aug 2018).
78. Benson K, Hartz AJ. A Comparison of Observational Studies and Randomized, Controlled Trials. N Engl J Med 2000;342:1878–86. doi:10.1056/NEJM200006223422506

79. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92. doi:10.1056/NEJM200006223422507
80. Murthy VH, Krumholz HM, Gross CP. Participation in Cancer Clinical Trials. JAMA 2004;291:2720. doi:10.1001/jama.291.22.2720

Supplementary Table S2.1. Significant sociodemographic findings preference vs. randomised cohorts

Preference cohorts in comparison to randomised cohorts		
Sociodemographic differences		
Age	Older[17,27,41,44,52,60]	6/34 trials tested
	Younger[46,50]	2/34
Gender	Female[35,50]	2/24 trials tested
	Male[67]	1/24
Education	Higher[17,46,51,61]	4/19 trials tested
	Lower	0/19
Employment	Yes[14,18,26]	3/13 trials tested
	No[52]	1/13 trials tested
Race	Caucasian[14,17,54,56]	4/14 trials tested
	Non-Caucasian[23]	1/14
Obese	Yes	0/7 trials tested
	No[13,41,43,46]	4/7
Smoking	Yes	0/5 trials tested
	No[13,46]	2/5
Married	Yes	0/9 trials tested
	No[51]	1/9
Experienced	Yes[27,52,65]	3/9 trials tested
	No[26]	1/9
Clinical differences		
Clinical problems	More severe[13,21,23,26,37,54,60]	7/20 trials tested
	Less severe[14,16,25,32,41,50,51,56,57,61]	10/20
	Not consistent[40,43,67]	3/20


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 3

The predictive value of inflammation at ileocaecal resection margins for postoperative Crohn's recurrence – a cohort study

Karin A Wasmann, Jojanneke van Amesfoort, Maurits L van Montfoort, Lianne Koens, Willem A Bemelman, Christianne J Buskens

IBD. 2019; Dec 27; izz290

Abstract

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

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

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

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

Introduction

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

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

Materials and methods

Patients

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

In all patients, a limited close bowel resection of macroscopically affected bowel was performed as recommended by current guidelines.[2] Patients were operated upon supervision of a dedicated colorectal surgeon specialized in inflammatory bowel disease. Reporting of the data adheres to the STROBE Statement.[8]

Histological features

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

Active inflammation at the margins was scored according to the validated Geboes grading system for ulcerative colitis (UC), as there is currently no validated histological score for CD. The Geboes score (GS) grades on a scale of 0 to 5. A higher score represents more severe histological inflammation (see Supplementary Table S3.1).[9] Results of the GS have demonstrated to reliably distinguish between UC patients in histological remission and activity. Recently, a GS cutoff of > 3 compared with the original cutoff of > 2 seems to be more clinically relevant, as the presence of neutrophils in the epithelium is the main marker of histological activity (also in the context of the Robarts and Nancy score).[10] Therefore, active inflammation at the resection margin was defined as a GS of > 3.

Myenteric plexitis at the proximal or distal resection specimen margin was histologically defined as the presence of inflammatory cells per high power field (HPF), adjacent to or within an enteric ganglion or nerve bundle. It was based on the appearance of the most severely inflamed ganglion or nerve bundle in the resection margin slide. Myenteric plexitis was graded mild (1–3 inflammatory cells/HPF), moderate (4–9 inflammatory cells/HPF), or severe (≥ 10 cells/HFP). Myenteric plexitis was recorded when moderate or severe plexitis was found.[6]

The presence of granulomas at the resection margins was defined as a focal collection of macrophages at the proximal and distal resection margins.[11] The presence of granulomas in the overall resection specimen was retrieved from the pathology report, as this was already part of standard histological evaluation during the study period.

Variables and outcomes

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

Prophylactic therapy was scored if patients started Crohn's medication directly postoperative, before endoscopic or clinical recurrence. It included immunomodulators (azathioprine [AZA], 6-mercaptopurine [6MP], methotrexate [MTX]), or biologicals (antitumor necrosis factor alpha [anti-TNF alpha]). During the study period, a "wait and see" policy regarding prophylactic therapy was conducted in our hospital. The follow-up protocol consisted of a routine surveillance colonoscopy within 6 to 12 months postoperatively, after which prophylactic therapy could be considered.[2] Only during a multidisciplinary meeting could it be decided to start prophylaxis directly postoperatively, dependent on patients' risk profiles. Afterward, colonoscopy was performed on indication, which means either suspicion of recurrent disease or to evaluate a new drug therapy.

The primary endpoint was recurrence, defined as reappearance of symptoms confirmed by endoscopy (modified Rutgeerts score ≥ i2)[12] or other imaging, preferably MRE (MaRIA score ≥ 7), requiring upscaling of anti-inflammatory medical treatment.[13]

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

Statistical analysis

Differences in baseline characteristics between patients with and without certain histological features were assessed using a χ^2 square test for categorical variables, or in case of low counts (< 5), a Fisher exact test. The unpaired *t*-test was used for numerical variables. Mean and standard deviation (SD) were reported in case of normally distributed variables; for non-normally distributed variables, median and interquartile range (IQR) were reported. Pearson correlation was assessed to test the correlation between histological features. Kaplan-Meier analysis with log rank test was used to compare recurrence free survival. Patients were categorized into proximal, distal, or no involved margins. Patient with inflammation at both margins were distributed to the resection margin with the strongest association to recurrence in univariate analysis. Independent factors associated with recurrence were identified using Cox regression. Variables with a *P* value of $P \leq 0.1$ in the univariable analyses were included in the multivariable model after assessing multicollinearity. P values and confidence intervals (CIs) were calculated at a 95% confidence level. For statistical analyses, SPSS Statistics version 24 (SPSS Inc., Chicago, IL) was used.

Ethical considerations

This study was waived from review of the medical ethics board.

Results

Patients and histopathological findings

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

For 66 patients (62%), microscopic disease activity was found in at least 1 of the resection margins: active inflammation in 40 patients, myenteric plexitis in 58 patients, and granulomas in 7 patients (Table 3.1, Figures 3.1 and 3.2). When looking at baseline characteristics, no association between clinical parameters and microscopic disease activity at the resection margins could be demonstrated (Table 3.2). When specifically looking at patients with L3 disease compared with patients with L1 disease, only active inflammation at the distal colonic resection margin was more frequently seen (30% vs. 10%; $P = 0.02$).

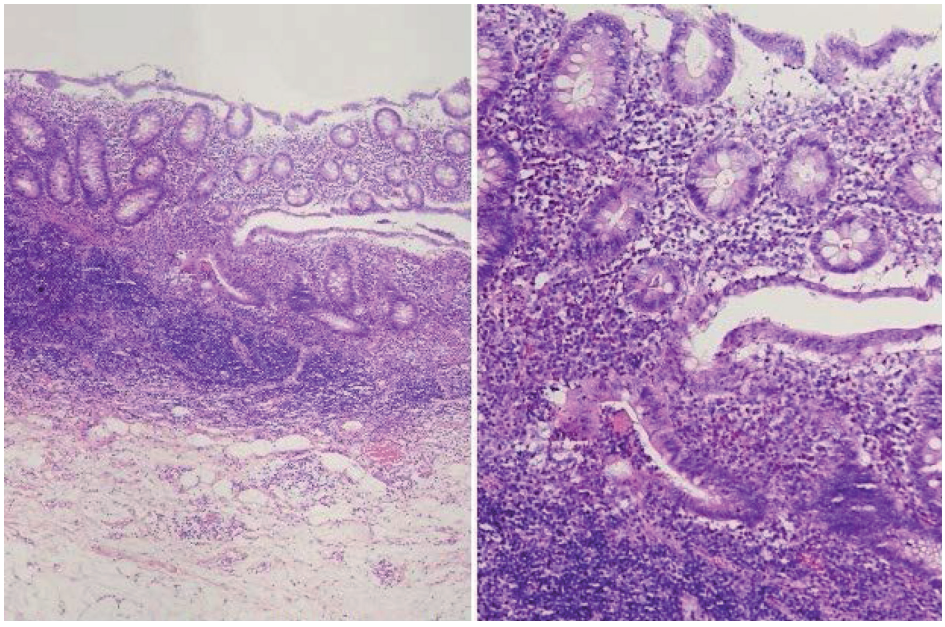
Table 3.1. Histologic features

	Active inflammation at resection margins (n: 40) n (%)	Myenteric plexitis at resection margins (n: 58) n (%)	Granulomas at resection margins (n: 7) n (%)
Proximal	29 (27%)	39 (37%)	4 (4%)
Distal	16 (16%)	34 (32%)	6 (6%)
Both	5 (5%)	15 (14%)	3 (3%)

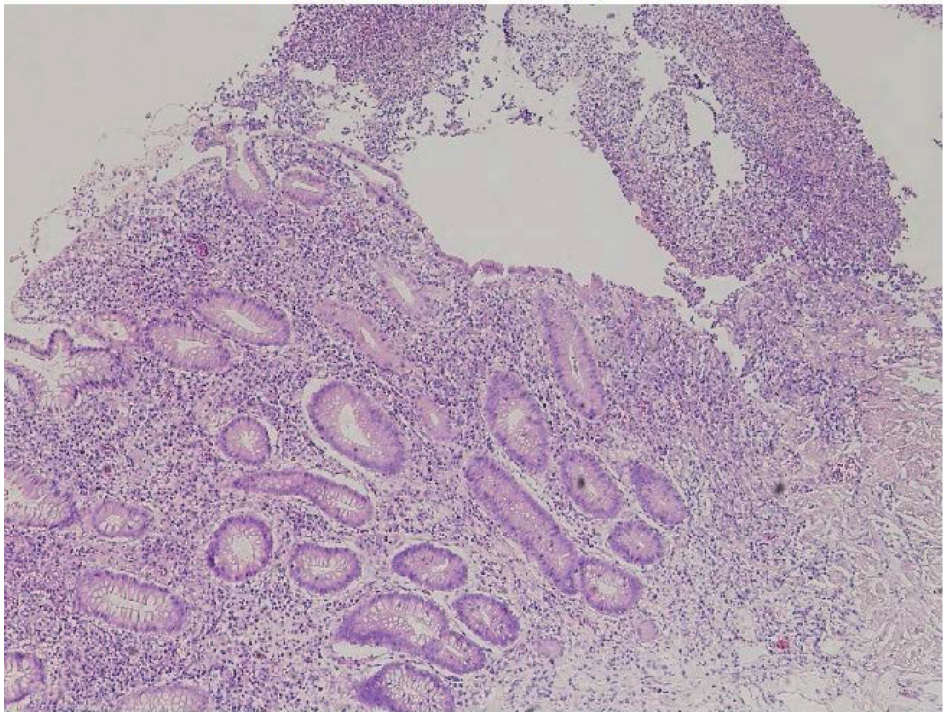
Recurrences

Median follow-up was 8.7 years (IQR, 5.9–11.3). Recurrence after 2, 5, and 10 years was 24%, 38%, and 53%, respectively (Figure 3.3). A minority of patients (38%) received postoperative medical prophylaxis. Local recurrence was higher in patients with microscopic disease activity at resection margins compared with patients without involved margins; however, this was not significant (63% vs. 47%, *Plog* = 0.08, respectively).

The association between recurrence and active inflammation, myenteric plexitis, or granulomas at the distal colonic margin was stronger compared with the occurrence of these features at the proximal ileal margin. Similar results were shown after excluding patients with a histologic features at both resection margins. Only active inflammation at the distal colonic resection margin was significantly associated with local recurrence: 14

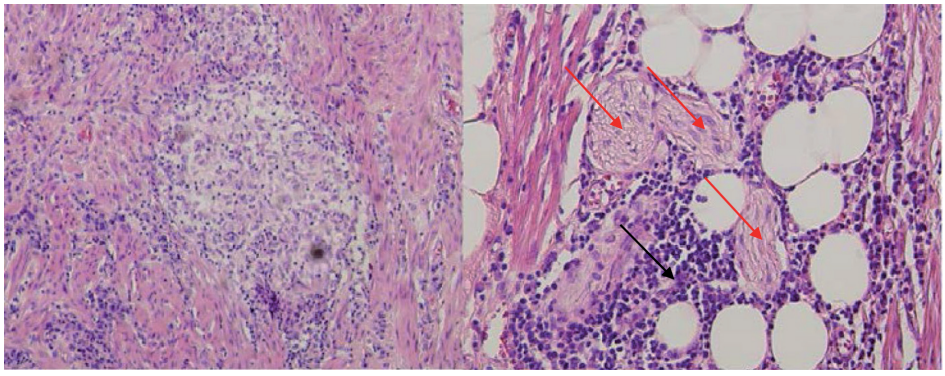


Colonic mucosa with some irregular crypts, cryptitis and pratial destruction of a crypt



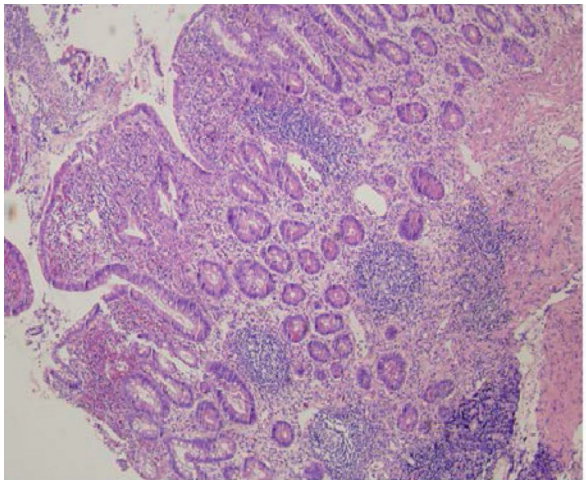
Ileal mucosa showing chronic active inflammation with apparent ulceration

Figure 3.1. Active inflammation at resection margins.



Colonic mucosa with a granuloma

Colonic mucosa with severe myenteric plexitis



Colonic mucosa showing chronic active inflammation with cryptitis, myenteric plexitis and multiple granulomas

Figure 3.2. Chronic inflammation, active inflammation, myenteric plexitis, and granulomas at resection margins.
Red arrow shows structures of the myenteric plexus. Black arrow shows heavy influx of lymfocytes/plasma cells around these structures.

out of 16 patients (88%) with active inflammation at the distal colonic resection margin developed local recurrence after a median of 2 years (IQR, 1.5–6.5). Local recurrence rates were comparable between patients with active inflammation at the proximal ileal resection margin (43%) and patients without active inflammation at resections margins (51%, *Plog* = 0.008, Figure 3.4). Recurrence rates for myenteric plexitis were 67% when present at the distal (colon) margin, 55% at proximal (ileum) margin, and 50% for no involved margins (*Plog* = 0.64). An increased recurrence rate was also observed for granulomas at the distal resection margin. However, the small numbers precluded statistical analyses: the corresponding rates were 83%, 0%, and 57%, respectively.

Table 3.2. Baseline patients and disease characteristics

		Total (n = 106)		Any inflammation at resection margins (n = 66)		No inflammation at resection margins (n = 40)	
Baseline patients and disease characteristics		**n**	**%**	**n**	**%**	**n**	**%**
Gender	Female	70	66	40	61	30	75
Age at surgery	Mean (SD)	32 (13)		33 (14)		31 (12)	
Duration of disease (months)	Mean (SD)	59 (76)		50 (67)		75 (90)	
Smoking		26	25	20	30	6	15
Emergency surgery	Yes	16	15	9	14	7	18
Operation date	2002–2005	52	49	32	49	20	50
	2006–2009	54	51	34	51	20	50
Age at diagnosis	Montreal A1	15	14	8	12	7	18
	Montreal A2	75	71	47	71	28	72
	Montreal A3	15	14	11	17	4	10
Location of disease at surgery	Montreal L1	79	74	50	76	29	73
	Montreal L3	27	26	16	24	11	28
Behaviour of disease at surgery	Montreal B1	29	18	10	15	9	23
	Montreal B2	52	49	33	50	19	47
	Montreal B3	35	33	23	35	12	30
Perianal disease	Yes	27	26	19	29	8	20
Preoperative biologic therapy	Yes	33	31	20	30	13	33
Peri-operative therapy within	None	10	9	8	12	2	7
12 weeks before surgery	Steroids	25	24	17	26	5	20
	Immunomodulators (AZA/6MP/MTX)	45	43	25	38	20	50
	Biologicals (anti-TNF alpha)	26	25	16	24	10	25
Concomitant surgical	Concomitant bowel resection	6	6	2	3	4	10
intervention	Stricturoplasty	2	2	2	3	0	0
	Fistulotomy	12	11	8	12	4	10
Resection length (cm)	Mean (SD)	30 (15)		32 (17)		27 (12)	
Prophylactic therapy	No	66	62	42	64	24	60
	Immunomodulators	33	31	20	30	13	33
	Biologicals	7	7	4	6	3	7

None of the above baseline patients characteristics were significantly differed between the two groups. Any inflammation at resection margins is microscopic disease activity, present when one of the variables, active inflammation, myenteric plexitis, and/or granulomas was detected at one or both resection margins. Smoking was defined as daily smoking, independently of the number of units. Disease location and behaviour were graded according to the Montreal classification.[14] Perianal disease was scored using the fistula drainage assessment.[15] Preoperative biological therapy, included patients ever on biologic drugs (anti-tumour necrosis factor alpha (anti-TNF alpha)). Peri-operative CD medication was scored if patients used steroids, immunomodulators (azathioprine (AZA), 6-mercaptopurine (6MP), methotrexate (MTX)), or biologicals within 12 weeks before surgery. Concomitant surgery included, concomitant bowel resection for entero-enteral or entero-vesical fistula, stricturoplasty for small bowel lesions, or fistulotomy resection.

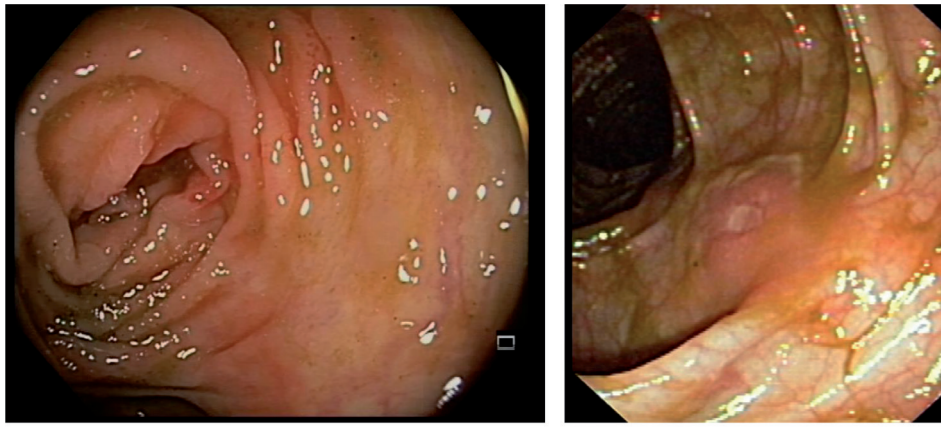
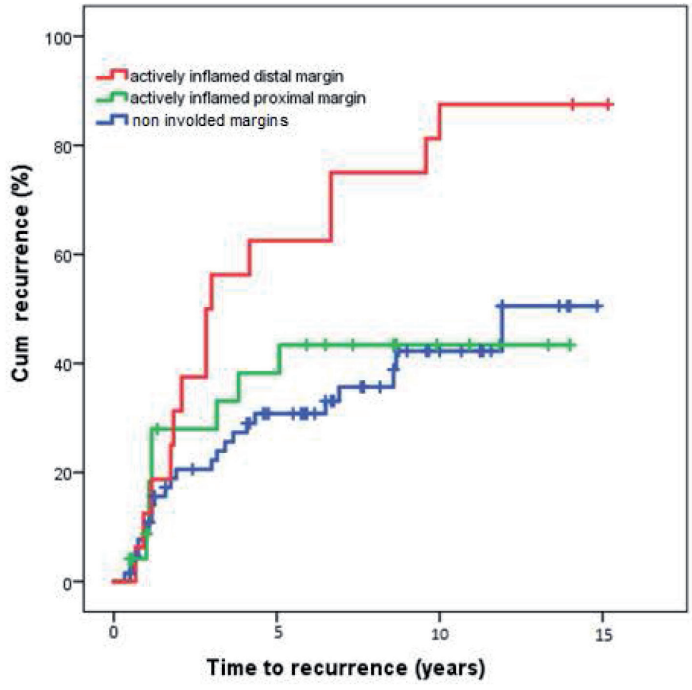


Figure 3.3. Endoscopic pictures of remission and recurrence; left, ileum in remission; right, colon with ulcer.



Number of patients at risk

	T = 0	T = 5	T = 10	T = 15
Distal	16	6	3	1
Proximal	24	12	4	0
No involved	66	36	13	0

Figure 3.4. Kaplan-Meier analysis.

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

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

Table 3.3. Multivariate analysis for local recurrence

Risk factors for recurrence	Univariate (HR and CI)	*P* value	Multivariate (HR and CI)	*P* value
Clinical factors				
Female	1.26 (0.7–2.5)	.3		
Smoking	2.07 (1.1–3.8)	.02	2.60 (1.4–4.9)	.004
Young age at surgery (< 30 years)	1.62 (0.9–3.0)	.1		
Young age at diagnosis (< 20 years)	1.11 (0.6–2.0)	.7		
Short duration of disease (< 5 years)	1.60 (0.8–3.0)	.2		
Ileocolonic disease (Montreal L3), ref: L1	1.0 (0.7–1.4)	1.0		
Penetrating disease (Montreal B3), ref: B1,B2	0.51 (0.3–1.1)	.07	0.60 (0.3–1.3)	.20
Perianal disease	0.94 (0.5–1.8)	.8		
Preoperative medication, ref: none		.3		
Steroids	0.73 (0.2–2.5)			
Immunomodulators	1.40 (0.5–4.1)			
Biologicals: anti-TNF alpha	1.68 (0.6–5.1)			
Extensive small bowel resection (> 50 cm)	1.73 (0.6–4.8)	.3		
No postoperative prophylaxis	1.56 (0.8–2.9)	.2		
Histologic features				
Disease activity resection margin(s)	1.74 (0.9–3.3)	0.09		
No active inflammation at margins (ref)		0.01		
Actively inflamed (GS > 3) proximal resection margin	1.18 (0.5–2.5)	0.67		
Actively inflamed (GS > 3) distal resection margin	2.68 (1.4–5.2)	0.003	2.89 (1.4–5.8)	0.003
No myenteric plexitis at margins (ref)		0.65		
Myenteric plexitis proximal resection margin	1.25 (0.6–2.7)	0.56		
Myenteric plexitis distal resection margin	1.37 (0.7–2.7)	0.36		
No granulomas at margins (ref)		0.13		
Granulomas proximal resection margin	0.00 (0.0–)	0.98		
Granulomas distal resection margin	2.62 (1.0–6.6)	0.04		
Granulomas overall resection specimen	0.97 (0.6–1.5)	0.9		

Young age at surgery was defined as < 30 years, young age at diagnosis as < 20 years, and short duration of disease as < 5 years.[16] Extensive small bowel resection was defined as a resection greater than 50 centimetre.[17]

Due to multicollinearity, granulomas at distal resection margins were not included in the multivariate analyses. After multivariate analysis, active inflammation at the distal resection margin and smoking were the only independent prognostic parameters (hazard ratio [HR], 2.89; 95% CI, 1.4–5.8; $P = 0.003$; and HR, 2.60; 95% CI, 1.4–4.9; $P = 0.004$) (Table 3.3).

In addition, results indicated that patients with active inflammation at the distal resection margin more frequently developed postoperative colonic recurrence compared with patients with active inflammation at the proximal resection margin or no actively inflamed resection margins (56% vs. 9% vs. 7%; $P < 0.001$, respectively). The incidence of surgical recurrence was 2% after 5 years, which was too low to perform statistical analyses.

Finally, excluding the 27 patients who were preoperatively known with colonic Crohn's disease did not change the results. Active inflammation at the distal resection margin remained significantly associated with postoperative recurrence compared with patients with active inflammation at the proximal resection margin or no actively inflamed resection margins (88% vs. 49% vs. 56%; $P < 0.035$, respectively, Supplementary Figure S3.1).

Discussion

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

The local recurrence rate in the patient group with active inflammation at the distal resection margin was 88%. This is much higher than currently known predictive parameters, whereas the HRs for most established clinical risk factors for CD recurrence were comparable to previous series.[2,5] The relatively low HRs for ileocolonic L3 disease and penetrating B3 disease in this study are explained, as these patients were considered for prophylactic therapy according to protocol.

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

Prior studies used controversial definitions of inflammation, causing conflicting results. Both studies demonstrating a prognostic value of inflammation at the resection margins[5,18–23] and studies showing no effect[24–30] did not distinguish between proximal and distal resection margins—or analyzed the proximal margin only. The studies revealing an association consisted of remarkably larger cohorts (± 300 patients vs. ± 100 patients), suggesting that the smaller studies were underpowered. In the absence of a validated score, most studies did not distinguish between histological chronic and active inflammation. This probably decreases validity of prior studies results, as the relevance of scoring chronic inflammation is not acknowledged. With regard to the proximal margin, current findings corroborate the results of the only randomised controlled trial (RCT) where no reduced recurrence rates were reported after more extensive ileum resection during ileocecal resection.[3] Furthermore, a microscopically actively inflamed proximal resection margin having no prognostic value is intuitively supported by studies demonstrating good clinical results after stricturoplasty, leaving the affected bowel in situ.[31] The RCT did not evaluate the distal margin.

Most studies describe myenteric plexitis at the proximal margin as an independent predictor for endoscopic,[6] clinical,[23] and surgical recurrence,[32] which is in contrast to our findings. The difference can be understood because prior studies did not include other histological features as active inflammation and granulomas in the multivariate model, while the correlation between active inflammation and myenteric plexitis seems high. The role of granulomas in CD is not yet clarified.[2,33] In the current series, granulomas in the overall resection specimen did not show any predictive value. In contrast, in these study results the presence of granulomas at the distal margin was suggested to have clinical relevance in univariate analyses; however, the numbers were small. In addition, granulomas and active inflammation distally had a strong correlation. Decreased lymphatic vessel density[34] and increased Paneth cells[35] are once described as potential associated features with recurrence. However, as these histological features are not easily implementable in daily clinical histological practice, the current value is debatable.

Because it is not common practice to assess the distal resection margins, results of presumed L1 ileocolic disease are confounded by L3 ileocolic disease.[14,36] In general, the prognosis after ileocecal resection for terminal ileitis only (L1 disease) is good, with less than 20% recurrent surgery after 10 years.[5] This contrasts the surgical outcome for colonic disease (L3 disease). A meta-analysis demonstrated that at least one third of these patients will need a re-resection within a few years, and a substantial proportion of patients will end with a permanent ileostomy due to refractory disease.[37] Whether this hypothesis of a different prognostic colonic CD profile could be extrapolated to patients with histological inflammation at the colon resection margin remains speculative, but the data clearly suggest a different risk profile for both local and colonic recurrence when the colon is involved.

One of the drawbacks of this study is the relatively small number of patients with active inflammation. Although the results come from a large consecutive series, there are only 16 patients with active inflammation at the distal resection margin. Nevertheless, the observation that 14 of these patients developed local recurrence is striking and should not be considered coincidence. Whether the results could be influenced by a relatively high percentage of patients with a history of ileocolonic L3 disease in this series (26%) is difficult to assess. However, overall recurrence rates are comparable to existing literature, and active inflammation at the distal resection margin was not confined to patients with a history of L3 disease. Excluding L3 patients from the analysis did not change results (Supplementary Figure S3.1). Nonetheless, including these patients increases extrapolation of the results to daily clinically practice, particularly as it has been demonstrated that the preoperative differentiation between L1 and L3 disease is difficult with an interobserver variation of up to 50%.[38] The results of this study are strengthened as a prospective database was used, in which the majority of patients did not start postoperative prophylaxis. Therefore, the results accurately reflect the natural postoperative course. Due to the strict endoscopic surveillance program (colonoscopy after 6–12 months) and because only 1 patient was lost to follow-up, it is unlikely that recurrences would have been missed.

Currently, systematic evaluation of disease activity at resection margins is not routine practice, as there is no advice in guidelines on standard pathology reporting. This is also reflected by the fact that there is only 1 (nonvalidated) pathological activity score for CD,[39] whereas there are over 20 different histological scoring systems for UC.[40] The use of the validated Geboes score known for scoring UC was chosen, as this score is most frequently used in literature and daily practice.

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

Acknowledgements
The authors wish the thank F. Wasmann for linguistics editing.

References

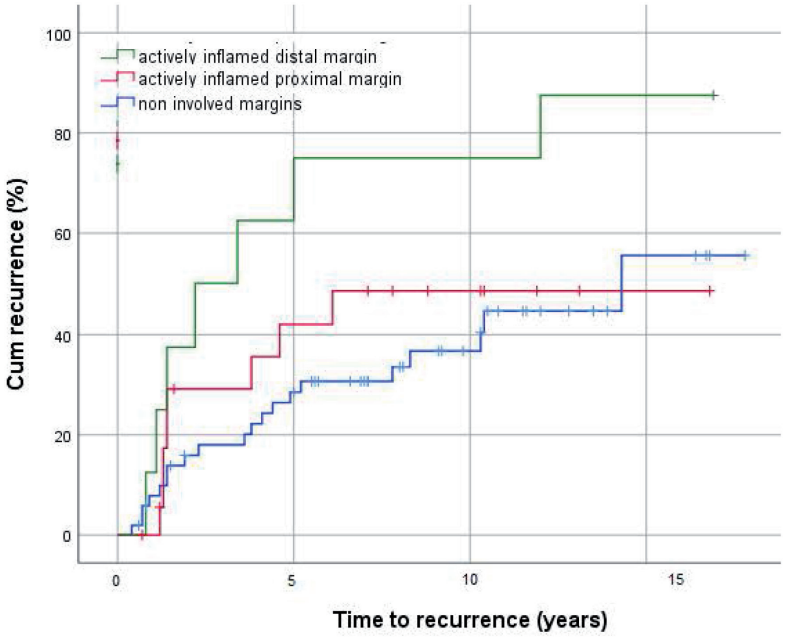
1. Peyrin-Biroulet L, Loftus E V, Colombel J-F, et al. The natural history of adult Crohn's disease in population-based cohorts. Am. J. Gastroenterol. 2010;105:289–97. Available at: http://www.nature.com/doifinder/10.1038/ajg.2009.579
2. Gionchetti P, Dignass A, Danese S, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. J. Crohn's Colitis. 2017;11:135–149. Available at: https://academic.oup.com/ecco-jcc/article-lookup/doi/10.1093/ecco-jcc/jjw169
3. Fazio VW, Marchetti F, Church M, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Ann. Surg. 1996;224:563-71; discussion 571–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8857860
4. Botti F, Carrara A, Antonelli B, et al. [The minimal bowel resection in Crohn's disease: analysis of prognostic factors on the surgical recurrence]. Ann. Ital. Chir. 74:627–33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15206803
5. Buck van Overstraeten A de, Eshuis EJ, Vermeire S, et al. Short- and medium-term outcomes following primary ileocaecal resection for Crohn's disease in two specialist centres. Br. J. Surg. 2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28745410
6. Ferrante M, Hertogh G de, Hlavaty T, et al. The Value of Myenteric Plexitis to Predict Early Postoperative Crohn's Disease Recurrence. Gastroenterology. 2006;130:1595–1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16697723
7. Bressenot A, Peyrin-Biroulet L. Histologic Features Predicting Postoperative Crohn's Disease Recurrence. Inflamm. Bowel Dis. 2015;21:468–475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25437814
8. Elm E von, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–1457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18064739
9. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47:404–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10940279
10. Magro F, Lopes J, Borralho P, et al. Comparison of different histological indexes in the assessment of UC activity and their accuracy regarding endoscopic outcomes and faecal calprotectin levels. Gut. 2018:gutjnl-2017-315545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29437913
11. Mitchell RN, Kumar V, Abbas AK, et al. Pocket companion to Robbins and Cotran pathologic basis of disease. Available at: https://www.ncbi.nlm.nih.gov/nlmcatalog/101677190
12. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2394349
13. Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: Joint ECCO and ESGAR evidence-based consensus guidelines. J. Crohn's Colitis. 2013;7:556–585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23583097
14. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55:749–753. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16698746.
15. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease. N. Engl. J. Med. 1999;340:1398–1405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10228190
16. Yamamoto T, Umegae S, Kitagawa T, et al. Postoperative change of mucosal inflammation at strictureplasty segment in Crohn's disease: cytokine production and endoscopic and histologic findings. Dis. Colon Rectum. 2005;48:749–57. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003453-200548040-00008
17. Poggioli G, Laureti S, Selleri S, et al. Factors affecting recurrence in Crohn's disease. Results of a prospective audit. Int. J. Colorectal Dis. 1996;11:294–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9007626
18. Kåresen R, Serch-Hanssen A, Thoresen BO, et al. Crohn's disease: long-term results of surgical treatment. Scand. J. Gastroenterol. 1981;16:57–64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7233081

19. Heimann TM, Greenstein AJ, Lewis B, et al. Prediction of early symptomatic recurrence after intestinal resection in Crohn's disease. Ann. Surg. 1993;218:294-8; discussion 298-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8373272
20. Kinchen J, Rajaratnam K, Kingston G, et al. 1068 The Presence of Microscopic Disease at the Resection Margins Predicts Post-Surgical Relapse in Crohn's Disease. Gastroenterology. 2012;142:S-189-S-190. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0016508512607112
21. Lindhagen T, Ekelund G, Leandoer L, et al. Recurrence rate after surgical treatment of Crohn's disease. Scand. J. Gastroenterol. 1983;18:1037–44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6673073
22. Simillis C, Purkayastha S, Yamamoto T, et al. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. Dis. Colon Rectum. 2007;50:1674–87. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003453-200750100-00024
23. Sokol H, Polin V, Lavergne-Slove A, et al. Plexitis as a predictive factor of early postoperative clinical recurrence in Crohn's disease. Gut. 2009;58:1218–1225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19625280
24. Pennington L, Hamilton SR, Bayless TM, et al. Surgical management of Crohn's disease. Influence of disease at margin of resection. Ann Surg. 1980;192:311–318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6998388
25. Heuman R, Boeryd B, Bolin T, et al. The influence of disease at the margin of resection on the outcome of Crohn's disease. Br. J. Surg. 1983;70:519–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6616154
26. Cooper JC, Williams NS. The influence of microscopic disease at the margin of resection on recurrence rates in Crohn's disease. Ann. R. Coll. Surg. Engl. 1986;68:23–6. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2498195/pdf/annrcse01536-0028.pdf
27. Adloff M, Arnaud JP, Ollier JC. Does the histologic appearance at the margin of resection affect the postoperative recurrence rate in Crohn's disease? Am. Surg. 1987;53:543–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3674595
28. Kotanagi H, Kramer K, Fazio VW, et al. Do microscopic abnormalities at resection margins correlate with increased anastomotic recurrence in Crohn's disease? Retrospective analysis of 100 cases. Dis. Colon Rectum. 1991;34:909–16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1914726
29. Kurer MA, Stamou KM, Wilson TR, et al. Early symptomatic recurrence after intestinal resection in Crohn's disease is unpredictable. Colorectal Dis. 2007;9:567–71. Available at: http://doi.wiley.com/10.1111/j.1463-1318.2006.01202.x
30. Hamilton SR, Reese J, Pennington L, et al. The role of resection margin frozen section in the surgical management of Crohn's disease. Surg. Gynecol. Obstet. 1985;160:57–62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3964965
31. Stebbing JF, Jewell DP, Kettlewell MG, et al. Recurrence and reoperation after strictureplasty for obstructive Crohn's disease: long-term results [corrected]. Br. J. Surg. 1995;82:1471–4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8535795
32. Bressenot A, Chevaux J-B, Williet N, et al. Submucosal plexitis as a predictor of postoperative surgical recurrence in Crohn's disease. Inflamm. Bowel Dis. 2013;19:1654–61. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00054725-201307000-00011
33. Simillis C, Jacovides M, Reese GE, et al. Meta-analysis of the role of granulomas in the recurrence of Crohn disease. Dis. Colon Rectum. 2010;53:177–85. Available at: https://insights.ovid.com/crossref?an=00003453-201002000-00011
34. Rahier J-F, Beauce S De, Dubuquoy L, et al. Increased lymphatic vessel density and lymphangiogenesis in inflammatory bowel disease. Aliment. Pharmacol. Ther. 2011;34:533–43. Available at: http://doi.wiley.com/10.1111/j.1365-2036.2011.04759.x
35. VanDussen KL, Liu T-C, Li D, et al. Genetic Variants Synthesize to Produce Paneth Cell Phenotypes That Define Subtypes of Crohn's Disease. Gastroenterology. 2014;146:200–209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24076061
36. Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. Lancet (London, England). 2016;387:156–67. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0140673615004651

37. Tekkis PP, Purkayastha S, Lanitis S, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. Colorectal Dis. 2006;8:82–90. Available at: http://doi.wiley.com/10.1111/j.1463-1318.2005.00903.x
38. Peyrin-Biroulet L. Is ileocaecal Crohn's disease L1 or L3 according to the Montreal classification? Gut. 2008;57:427–427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18268062
39. D'Haens GR, Geboes K, Peeters M, et al. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998;114:262–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9453485
40. Bryant RV, Winer S, SPL T, et al. Systematic review: Histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. J. Crohn's Colitis. 2014;8:1582–1597. Available at: https://academic.oup.com/ecco-jcc/article-lookup/doi/10.1016/j.crohns.2014.08.011

Supplementary Table S3.1. Validated Geboes score, myenteric plexitis, and typical lesions

Grade 0: Architectural changes	0.0 No abnormality
	0.1 Mild abnormality
	0.2 Mild/moderate diffuse or multifocal abnormalities
	0.3 Severe diffuse or multifocal abnormalities
Grade 1: Chronic inflammatory infiltrate	1.0 No increase
	1.1 Mild but unequivocal increase
	1.2 Moderate increase
	1.3 Marked increase
Grade 2A: Eosinophils in lamina propria	2A.0 No increase
	2A.1 Mild but unequivocal increase
	2A.2 Moderate increase
	2A.3 Marked increase
Grade 2B: Neutrophils in lamina propria	2B.0 No increase
	2B.1 Mild but unequivocal increase
	2B.2 Moderate increase
	2B.3 Marked increase
	Percentage circumferention
Grade 3: Neutrophils in epithelium	3.0 None
	3.1 < 5% crypts involved
	3.2 < 50% crypts involved
	3.3 > 50% crypts involved
	Percentage circumferention
Grade 4: Crypt destruction	4.0 None
	4.1 Probable: local excess of neutrophils in part of the crypts
	4.2 Probable: marked attenuation
	4.3 Unequivocal crypt destruction
Grade 5: Erosions and ulcerations	5.0 No erosion, ulceration or granulation tissue
	5.1 Recovering epithelium + adjacent inflammation
	5.2 Probable erosion: focally stripped
	5.3 Unequivocal erosion
	5.4 Ulcer or granulation tissue
	Percentage circumferentie
Meyenteric plexitis	0.0 no cells/HPF
	0.1 1–4 cells/HPF, mild
	0.2 5–9 cells/HPF, moderate
	0.3 > 9 cells/HPF, severe
Granulomas	0.0 no
	0.1 yes
Fissures	0.0 no
	0.1 yes
Transmural	0.0 no
	0.1 yes



Number of patients at risk

	T = 0	T = 5	T = 10	T = 15
Distal	8	2	2	0
Proximal	19	9	2	0
No involved	52	29	10	0

Supplementary Figure S3.1. Kaplan-Meier analysis, excluding Montreal L3 patients.
Also when excluding patients preoperatively known with Montreal L3 disease, active inflammation at the distal resection margin was significantly associated with postoperative recurrence compared to patients with active inflammation at the proximal resection margin or no actively inflamed resection margins (88% vs. 49% vs. 56%; $P < .035$, resp.).


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 4

Anatomical variation in mesenteric macrophage phenotypes in Crohn's disease

Jonathan H M van der Meer, Karin A Wasmann, Jarmila D W van der Bilt, Marte A J Becker, Marja A Boermeester, Willem A Bemelman, Manon E Wildenberg, Christianne J Buskens

Clin Transl Gastroenterol. 2020; 11(8): e00198

Abstract

Introduction: Clinical trials are currently investigating whether an extended mesenteric resection for ileocecal resections could reduce postoperative recurrence in Crohn's disease. Resection of the mesorectum, which contains pro-inflammatory macrophages, during proct(ocol)ectomy, is associated with reduced recurrent inflammation and improved wound healing. We aimed to characterize the macrophages in the ileocecal mesentery, which were compared with those in the mesorectum, to provide a biological rationale for the ongoing trials.

Methods: In 13 patients with Crohn's disease and 4 control patients undergoing a proctectomy, tissue specimens were sampled at 3 locations from the mesorectum: distal (rectum), middle, and proximal (sigmoid). In 38 patients with Crohn's disease and 7 control patients undergoing ileocecal resections, tissue specimens also obtained from 3 locations: adjacent to the inflamed terminal ileum, adjacent to the noninflamed ileal resection margin, and centrally along the ileocolic artery. Immune cells from these tissue specimens were analyzed by flow cytometry for expression of CD206 to determine their inflammatory status.

Results: In the mesorectum, a gradient from pro-inflammatory to regulatory macrophages from distal to proximal was observed, corresponding to the adjacent inflammation of the intestine. By contrast, the ileocecal mesentery did not contain high amounts of pro-inflammatory macrophages adjacent to the inflamed tissue, and a gradient toward a more pro-inflammatory phenotype was seen in the central mesenteric area.

Discussion: Although the mesentery is a continuous structure, the mesorectum and the ileocecal mesentery show different immunological characteristics. Therefore, currently, there is no basis to perform an extended ileocecal resection in patients with Crohn's disease.

Introduction

Alterations of the mesentery such as "creeping fat" were already mentioned in the first description of Crohn's disease in 1932.[1] Nonetheless, it was not until recent years that a more prominent role was suggested for the mesentery in Crohn's disease, although the question remains whether this tissue is pathological or regulatory.[2–6] Characterization of immune and mesenchymal cells of the mesentery has shown varying results with the presence of both pro- and anti-inflammatory factors and cell types.[7–16] Because, currently, there is no consensus on the biological function of the mesentery in inflammatory bowel disease and the mesentery is important for the vascularization of the intestine, surgical guidelines advise mesentery-sparing resections for these benign diseases.[17,18] By contrast, in patients who undergo proct(ocol)ectomy, recent findings have shown that resection of the rectal mesentery is beneficial to reduce postoperative complication rates (pelvic/perianal abscesses, perineal wound infections, wound dehiscence, persisting fistulas) and promote healing.[19] This effect is seen specifically in patients with Crohn's disease but not in patients with ulcerative colitis. In addition, resection of remaining rectal mesentery in patients with Crohn's disease with a persistent presacral sinus that had already undergone a mesentery-sparing proct(ocol) ectomy, helped overcome chronic nonhealing perineal wounds.[19] These findings were associated with the presence of considerable numbers of macrophages in the rectal mesentery. Macrophages exist in a spectrum of sub-phenotypes, ranging from highly inflammatory (CD206-low) to immunosuppressive and wound healing (CD206-high). These immunosuppressive macrophages play an important role in dampening disease activity, and are the cells that mediate the therapeutic effect of anti-TNF ([20-23]). A low ratio of $CD206^+$ vs. $CD206^-$ cells indicates a relatively pro-inflammatory phenotype of macrophages,[20,21] which was indeed seen in the mesorectal tissue in Crohn's disease.[19] In line with the findings in the mesorectum, it has been suggested that a more extended resection including the mesentery in ileocecal resections would lead to fewer surgical recurrences.[22] To further investigate this, 2 randomized controlled trials have been initiated in which more extended resections of the mesentery are compared with standard close bowel ileocecal resections in patients with Crohn's disease (NCT02542904 and NCT03172143).

We aimed to determine the distribution of pro-inflammatory macrophages in the mesentery of the rectum and ileocecal region to guide surgical resection margins. We hypothesized that macrophages reside in the mesentery in a gradient from a pro-inflammatory to a wound-healing phenotype depending on the proximity to the inflamed intestinal tissue.

Methods

Tissue collection and analysis

Specimen collection and culturing was approved by the biobank review committee of the Academic Medical Center Amsterdam (number 178#A201470). Rectal mesentery from 13 patients with Crohn's disease and 4 control patients (3 suffering from ulcerative colitis and 1 from refractory constipation) was sampled at 3 locations: distal (adjacent to the inflamed intestine), middle, and proximal (adjacent to least inflamed sigmoid, Figure 4.1a). Ileocecal mesentery from 38 patients with Crohn's disease and 7 control patients (3 suffering from ulcerative colitis, 2 from refractory constipation, and 2 from a cecal adenoma/carcinoma) was also sampled at 3 locations: adjacent to the inflamed ileum, near the noninflamed ileum (at the ileal resection margin), and centrally (near the base of the ileocecal artery, Figure 4.1d).

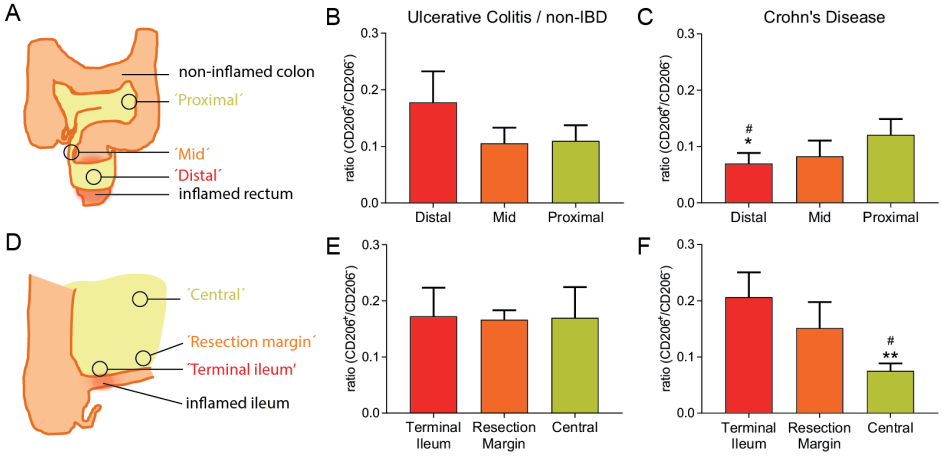


Figure 4.1. Mesenteric macrophages show a pro-inflammatory to regulatory gradient at the rectum, but this is inverted in the ileocecal region.
(a) Schematic overview of mesorectal tissue sampling. **(b)** Mesorectal $CD206^+/CD206^-$ ratios in control patients (n = 4: 3 suffering from ulcerative colitis and 1 from refractory constipation). **(c)** Mesorectal $CD206^+/CD206^-$ ratios in patients with Crohn's disease (n = 13). $^*P < 0.05$ compared with proximal, $\#P < 0.05$ compared with distal ulcerative colitis (UC)/noninflammatory bowel disease (IBD) as calculated by *t*-test. **(d)** Schematic overview of mesenteric tissue sampling in the ileocecal region. **(e)** $CD206^+/CD206^-$ ratios in the ileocecal region of patients with UC or without IBD (n = 7: 3 suffering from ulcerative colitis, 2 from refractory constipation, and 2 from a cecal adenoma/carcinoma). **(f)** $CD206^+/CD206^-$ ratios in the ileocecal region of patients with Crohn's disease with terminal ileitis (n = 38). $^{**}P < 0.01$, compared with terminal ileum; $\#P < 0.05$, compared with central UC/non-IBD as calculated by *t*-test.

Tissue sections were then cultured on a nontissue culture–treated petri dish using RPMI 1640 medium containing 10% fetal calf serum (Lonza, Verviers, Belgium), 2 mM l-glutamine (Invitrogen, Carlsbad, CA), 100 U/mL penicillin–streptomycin (Invitrogen), 50 µg/mL gentamicin (Lonza), and 50 µg/mL amphotericin B (Thermo Fisher, Landsmeer, the Netherlands). After 48 hours of culture, tissue sections were removed, and cells

were harvested by means of 5 mM ethylenediaminetetraacetic acid. Adherent and nonadherent cells were collected separately and both were used for analysis. Cells were then stained using the following antibodies: anti-CD45-AF700 (clone HI30; Biolegend, Uithoorn, the Netherlands), anti-CD3-AF488 (clone OKT3; Biolegend), anti-CD14-PE/Cy7 (clone 61D3; eBioscience, Vienna, Austria), and anti-CD206-APC (Clone 19.2; BD Bioscience, Breda, the Netherlands). Expression was analyzed by flow cytometry using a FACS Fortessa (BD Bioscience) with FlowJo software (Treestar, Ashland, OR).

Statistical analysis

Data are presented as mean and standard error of the mean. Statistical tests used are indicated in figure legends. For statistical analysis, GraphPad Prism (version 8.3.0; GraphPad Software, La Jolla, CA) was used. A P value < 0.05 was considered statistically significant. No data imputation was performed.

Results

Samples were collected from the indicated anatomical locations as described in the Methods section and Figure 4.1a and d. Patient characteristics are summarized in Table 4.1.

In control patients, $CD206^+/CD206^-$ ratios did not alter along the length of the colon and rectum (Figure 4.1b). In patients with Crohn's disease, these ratios revealed a gradient from pro-inflammatory to regulatory macrophages from distal to proximal mesorectum (Figure 4.1c). The samples collected from the "distal" part of the rectum in patients with Crohn's disease showed a significantly decreased $CD206^+/CD206^-$, and thus more pro-inflammatory, ratio compared with that of the "proximal" samples from the same patients and with that of the samples from the control patients. This was in line with previous findings.[19] Confirming our hypothesis, these results indicate that the macrophages in the mesorectum gradually become less pro-inflammatory further away from the inflamed intestinal tissue.

Subsequently, we investigated whether a similar gradient was present in the mesentery of the terminal ileum toward the central part of the mesentery. Again, in control patients, the $CD206^+/CD206^-$ ratios were consistent throughout the sampled locations (Figure 4.1e) with a predominantly regulatory phenotype. However, in the patients with Crohn's disease, the opposite was observed of what was found in the mesorectum (Figure 4.1e): adjacent to the inflamed ileum and the noninflamed resection margin, macrophages displayed a regulatory phenotype comparable with the level of controls (Figure 4.1e and f). By contrast, the "central" tissue had a low $CD206^+/CD206^-$ ratio, indicative of a pro-inflammatory phenotype (Figure 4.1f). This "central" ratio decreased significantly compared with that of the "terminal ileum" samples from the same patients and with

Table 4.1. Patient characteristics

	Rectal resections		Ileocecal resections	
Baseline characteristics	**CD**	**UC / non-IBD**	**CD**	**UC / non-IBD**
n	13	4	38	7
Male (n, %)	2 (15.4)	0 (0)	10 (26.3)	0 (0.0)
Age at surgery in years (mean, SD)	42.0 (13.9)	43.3 (18.7)	35.9 (16.0)	51.3 (18.7)
Disease duration in years (mean, SD)	17.2 (10.4)	N/A	8.0 (10.1)	N/A
BMI (mean, SD)	24.4 (3.8)	28.7 (11.5)	23.5 (4.6)	27.6 (6.9)
Smoking (n, %)				
Yes	3 (23.1)	0 (0.0)	9 (23.7)	3 (42.9)
No	9 (69.2)	2 (50.0)	26 (68.4)	1 (14.3)
Stopped	1 (7.7)	2 (50.0)	3 (7.9)	3 (42.9)
Diabetes (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diversion prior surgery (n, %)	11 (84.6)	2 (50.0)	N/A	N/A
Duration of diversion in years (median, IQR)	4.6 (6.8)	0.75 (4.2)	N/A	N/A
Previous Ileocecal resection (n, %)	N/A	N/A	6 (15.8)	0 (0.0)
Indication for surgery (n, %)				
Therapy refractory	3 (23.1)	N/A	N/A	N/A
Perianal fistulas	7 (53.8)	N/A	N/A	N/A
Diversion colitis	3 (23.1)	N/A	N/A	N/A
Ulcerative colitis	N/A	3 (75.0)	N/A	3 (42.9)
Constipation	N/A	1 (25.0)	N/A	2 (28.6)
Adenoma/carcinoma	N/A	0 (0.0)	N/A	2 (28.6)
Anti-TNFα therapy (n, %)*				
Ever prior to surgery	13 (100.0)	2 (50.0)	19 (50.0)	N/A
< 6 months before surgery	6 (46.2)	0 (0.0)	11 (28.9)	N/A
Never	0 (0.0)	2 (50.0)	19 (50.0)	N/A
Disease extent (Montreal) (n, %)				
L				
L1	0 (0.0)	N/A	28 (73.7)	N/A
L2	6 (46.2)	N/A	0 (0.0)	N/A
L3	7 (53.8)	N/A	10 (26.3)	N/A
Disease behavior (Montreal) (n, %)				
B1	2 (15.4)	N/A	4 (10.5)	N/A
B2	5 (38.5)	N/A	20 (52.6)	N/A
B3	9 (69.2)	N/A	14 (36.8)	N/A

CD, Crohn's disease; UC, Ulcerative colitis; IBD, inflammatory bowel disease.

that of the samples from the "central" tissue of the control patients. In brief, although both the rectal and ileal mesentery in patients with Crohn's disease show a gradient in macrophage subphenotype, the direction of the gradient is completely opposite in the 2 different locations of Crohn's disease.

Within the samples acquired from the ileocecal region, we observed variance between the $CD206^{+}/CD206^{-}$ ratios of the patients. Because the patients who underwent

ileocecal resections form a heterogeneous patient population, we performed subgroup analysis to investigate patient characteristics that influence mesenteric macrophage phenotypes. This subgroup analysis revealed that the mesentery of patients with L3 disease contained more unfavorable pro-inflammatory macrophages at the "central" and "resection margin" sites (Figure 4.2a). This suggests that patients with L3 disease have widespread localization of pro-inflammatory macrophages in the mesentery,

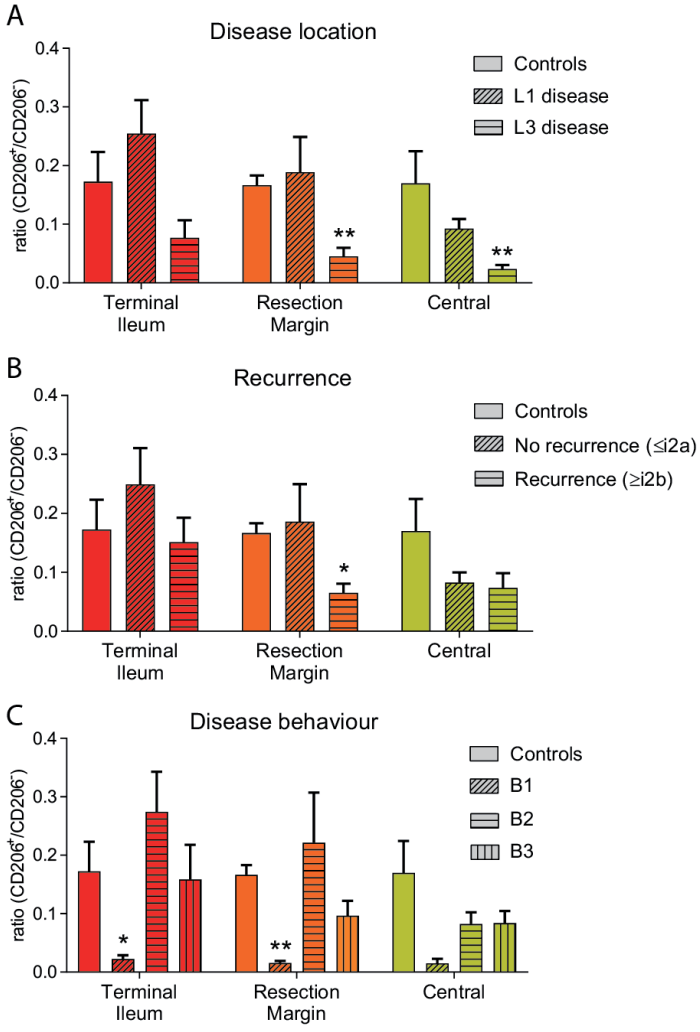


Figure 4.2. B1 and L3 disease are associated with low CD206⁺/CD206⁻ ratios throughout the ileocecal mesentery.

(a) CD206 ratios in patients with L1 (n = 28) and L3 (n = 10) disease, compared with ulcerative colitis (UC)/non-inflammatory bowel disease (IBD) controls (n = 7). **(b)** CD206⁺/CD206⁻ ratios in patients with recurrence, defined as a Rutgeerts score ≥ i2b (n = 9), vs. patients without recurrence, defined as a Rutgeerts score ≤ i2a (n = 26), compared with UC/non-IBD controls (n = 7). **(c)** CD206⁺/CD206⁻ ratios in patients with B1 (n = 4), B2 (n = 20), and B3 (n = 14) disease, compared with UC/non-IBD controls (n = 7). *P < 0.05; **P < 0.01, compared with UC/non-IBD controls as calculated by t-test.

in line with the previous finding that these patients have higher recurrence rates.[23] Interestingly, in our cohort, recurrence (defined as a Rutgeerts score ≥ i2b, 6 months after surgery) was associated with the presence of pro-inflammatory macrophages in the mesentery at the resection margin (Figure 4.2b). Penetrating disease behavior might be expected to result in a pro-inflammatory environment and, thus, influence the mesenteric macrophage subtypes. However, in our cohort, patients suffering from stricturing and penetrating disease (B2/3) tended to show a more favorable regulatory macrophage profile rather than pro-inflammatory (Figure 4.2c).

Discussion

In Crohn's disease patients, while in the mesorectum, macrophages are less pro-inflammatory, the further they are located from the inflamed tissue, this phenomenon was not observed in the ileocecal region. The mesentery adjacent to the inflamed ileum resembled a healthy regulatory phenotype, suggesting an attempt of the immune system to dampen the intestinal inflammatory processes. By contrast, the central area of the mesentery contained fewer regulatory macrophages. Whether this area contributes to disease activity remains to be investigated. Thus, although the mesentery is anatomically a continuous structure, the mesorectum and the mesentery at the ileocecal region show distinctly different immunological characteristics in Crohn's disease. It is well known that, in cases of intestinal perforation, omental fat tissue can migrate over the intestinal tissue to limit the perforation.[24] Possibly, the mesenteric fat tissue has a similar function at the ileocecal region in patients with Crohn's disease. The mesorectum is anatomically different from the ileocecal region in the sense that the mesorectum is wrapped around the rectal tissue, whereas the creeping fat at the terminal ileum has to migrate to wrap itself around the intestine. Thus, this tissue might behave differently from the mesentery in the ileocecal region, explaining the differences we find in macrophage phenotypes. On the other hand, this could also be due to the differences between the patient populations. The patients who require a proct(ocol)ectomy often have longstanding therapy-refractory disease, whereas the patients who underwent an ileocecal resection have relatively short disease duration and the disease location is less extensive. Recently, it has been shown that there are differences in adipocyte size, fibrosis, and the T-cell compartment between the ileocecal and colonic mesentery.[25] Higher levels of tumor necrosis factor-α and interleukin-1β were measured in the mesocolon, which corresponds to our findings that the mesorectum contains pro-inflammatory macrophages. However, the ileal mesentery contained higher amounts of infiltrating T-cells, without a significant change in the composition of T-cell subpopulations between the rectal and ileocecal mesentery.[25] How this corresponds to our findings remains to be elucidated. In the above-mentioned study and by other studies, it has been suggested that ileal and ileocolonic (L1/L3) and isolated

colonic (L2) Crohn's disease are different entities.[26,27] In our cohort of patients who underwent proct(ocol)ectomies, we did not observe differences in the mesenteric macrophages of patients with L2 and L3 disease. From our subgroup analyses, we did find that patients with L3 disease shows more pro-inflammatory macrophages in the ileocecal region compared with patients with L1 disease, which suggests that disease type might influence the mesenteric macrophages. However, numbers are low in our subgroup analyses, so further research is warranted to characterize the mesentery more extensively in various Crohn's disease patient groups, especially considering disease behavior. Additional analysis might also elucidate the role of other cell types that can interact with the macrophages, e.g., adipocytes secreting adipokines, which could influence macrophage polarization.[9,10,14–16] A limitation of our study is that we did not investigate other markers than CD206. However, CD206-positive macrophages have been shown to mediate wound healing,[21] and previously we observed that the macrophages with low $CD206^{+}/CD206^{-}$ ratios express high levels of TNFα, which shows that CD206 ratios correspond to functional inflammatory activity.[19]

When aiming to provide a biological rationale for altered surgical approaches in which more mesentery is resected, the differences between the mesorectum and the ileocecal mesentery should be taken into account. The current findings undermine the reasoning to resect more mesentery in ileocecal resections because the regulatory macrophages adjacent to the inflamed ileum are likely to mediate a wound-healing response.

Financial support
The International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) Operating grant. European Crohn's and Colitis Organisation (ECCO) grant.

References

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: A pathologic and clinical entity. Journal of the American Medical Association 1932;99:1323-9.
2. Schaffler A, Herfarth H. Creeping fat in Crohn's disease: travelling in a creeper lane of research? Gut 2005;54:742-4.
3. Peyrin-Biroulet L, Chamaillard M, Gonzalez F, et al. Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? Gut 2007;56:577-83.
4. Behr MA. The path to Crohn's disease: is mucosal pathology a secondary event? Inflamm Bowel Dis 2010;16:896-902.
5. Siegmund B. Mesenteric fat in Crohn's disease: the hot spot of inflammation? Gut 2012;61:3-5
6. Coffey JC, O'Leary DP. The mesentery: structure, function, and role in disease. The Lancet Gastroenterology & Hepatology 2016;1:238-47.
7. Desreumaux P, Ernst O, Geboes K, et al. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. Gastroenterology 1999;117:73-81.
8. Barbier M, Vidal H, Desreumaux P, et al. Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. Gastroenterol Clin Biol 2003;27:987-91.
9. Yamamoto K, Kiyohara T, Murayama Y, et al. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. Gut 2005;54:789-96.
10. Paul G, Schaffler A, Neumeier M, et al. Profiling adipocytokine secretion from creeping fat in Crohn's disease. Inflamm Bowel Dis 2006;12:471-7.
11. Schaffler A, Furst A, Buchler C, et al. Vascular endothelial growth factor secretion from mesenteric adipose tissue and from creeping fat in Crohn's disease. J Gastroenterol Hepatol 2006;21:1419-23.
12. Schaffler A, Furst A, Buchler C, et al. Secretion of RANTES (CCL5) and interleukin-10 from mesenteric adipose tissue and from creeping fat in Crohn's disease: regulation by steroid treatment. J Gastroenterol Hepatol 2006;21:1412-8.
13. Peyrin-Biroulet L, Gonzalez F, Dubuquoy L, et al. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. Gut 2012;61:78-85.
14. Kredel LI, Batra A, Stroh T, et al. Adipokines from local fat cells shape the macrophage compartment of the creeping fat in Crohn's disease. Gut 2013;62:852-62.
15. Sideri A, Bakirtzi K, Shih DQ, et al. Substance P mediates pro-inflammatory cytokine release form mesenteric adipocytes in Inflammatory Bowel Disease patients. Cell Mol Gastroenterol Hepatol 2015;1:420-32.
16. Coope A, Pascoal LB, da Silva FAR, et al. Transcriptional and Molecular Pathways Activated in Mesenteric Adipose Tissue and Intestinal Mucosa of Crohn's Disease Patients. Int J Inflam 2017;2017:7646859.
17. Lee EC, Dowling BL. Perimuscular excision of the rectum for Crohn's disease and ulcerative colitis. A conservation technique. Br J Surg 1972;59:29-32.
18. Strong S, Steele SR, Boutrous M, et al. Clinical Practice Guideline for the Surgical Management of Crohn's Disease. Dis Colon Rectum 2015;58:1021-36.
19. de Groof EJ, van der Meer JHM, Tanis PJ, et al. Persistent mesorectal inflammatory activity is associated with complications after proctectomy in Crohn's Disease. J Crohns Colitis 2019;13:285-93.
20. Vos AC, Wildenberg ME, Duijvestein M, et al. Anti-tumor necrosis factor-alpha antibodies induce regulatory macrophages in an Fc region-dependent manner. Gastroenterology 2011;140:221-30.
21. Vos AC, Wildenberg ME, Arijs I, et al. Regulatory macrophages induced by infliximab are involved in healing in vivo and in vitro. Inflamm Bowel Dis 2012;18:401-8.
22. Coffey JC, Kiernan MG, Sahebally SM, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. J Crohns Colitis 2018;12:1139-50.
23. Wasmann KATGM, van Amesfoort J, van Montfoort ML, et al. The Predictive Value of Inflammation at Ileocecal Resection Margins for Postoperative Crohn's Recurrence: A Cohort Study. Inflamm Bowel Dis 2020;26:1691-9.
24. Liebermann-Meffert D. The greater omentum. Anatomy, embryology, and surgical applications. Surg Clin North Am 2000;80:275-93, xii.
25. Kredel LI, Jodicke LJ, Scheffold A, et al. T-cell Composition in Ileal and Colonic Creeping Fat - Separating Ileal from Colonic Crohn's Disease. J Crohns Colitis 2019;13:79-91.
26. Subramanian S, Ekbom A, Rhodes JM. Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease: the third IBD? Gut 2017;66:362-81.

27. Dulai PS, Singh S, Vande Casteele N, et al. Should We Divide Crohn's Disease Into Ileum-Dominant and Isolated Colonic Diseases? Clin Gastroenterol Hepatol 2019;17:2634-43.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 5

Complications while waiting for IBD surgery – short report

Karin A Wasmann, on behalf of the IBD study group Amsterdam UMC, location AMC

JCC. 2020; 14(2): 277-80

Abstract

Background and aims: While striving to meet the quality standards for oncological care, hospitals frequently prioritize oncological procedures, resulting in longer waiting times to surgery for benign diseases like inflammatory bowel disease (IBD). The aim of this Short Report is to highlight the potential consequences of a longer interval to surgery for IBD patients.

Methods: The mean waiting times to elective surgery for IBD patients with active and inactive disease (e.g., pouch surgery after subtotal colectomy) at the Amsterdam UMC, location AMC, between 2013 and 2015 were compared with those for colorectal cancer surgery. Correlations between IBD waiting times and disease complications (e.g., > 5% weight loss, abscess formation) and additional health-care consumption (e.g., telephone/outpatient clinic appointment, hospital admission) during these waiting times were assessed.

Results: The mean waiting was 10 weeks (SD 8) for patients with active disease (n = 173) and 15 weeks (SD 16) for those with inactive disease (n = 97), remarkably higher than that for colorectal cancer patients (5 weeks). While awaiting surgery, 1 out of 8 patients had to undergo surgery in an acute or semi-acute setting. Additionally, 19% of patients with active disease had disease complications, and 44% needed additional health care. The rates were comparable for patients with inactive disease.

Conclusions: The current waiting time to surgery is not medically justified and creates a burden for health-care resources. This issue should be brought to the attention of policy makers, as it requires a structural solution. It is time to also set a maximally acceptable waiting time to surgery for IBD patients.

Introduction

In 2015, gastroenterologist Dr A. van Bodegraven and colleagues wrote an alarming manifest: 'Oncology first, other care compromised.'[1] He stated that 'because hospitals want to adhere to the newly implemented oncology quality- and volume standards, oncological surgeries are given priority'.[1] These days, oncological treatment should be started within the 6 weeks following diagnosis, and this is enforced by the Dutch Health Care Inspectorate, insurance companies and patient's organisations.[2] Additionally, since the introduction of the national bowel cancer screening program in the Netherlands, the demand for oncological surgical resections has risen worldwide.[3–6] The subsequent longer waiting time for 'benign' diseases is not only inconvenient, but for inflammatory bowel disease (IBD) patients it may lead to severe complications.

Inflammatory bowel disease patients requiring surgery are mainly therapy refractory and have longstanding disease after failing a series of immunosuppressive drugs, weakening the patient. In addition, as IBD is a progressive inflammatory disease, complications such as strictures and fistulas with or without abscess formation develop in 50% of patients during their disease course.[7,8] When surgery is postponed and the disease progresses, surgery may become more complex, resulting in worse outcomes.[9,10] A stenosis leads to decreased oral intake, followed by weight loss and ultimately a patient being in poor pre-operative condition. A preoperative abscess increases the risk of anastomotic leakage and therefore the chance of a (temporary) stoma postoperatively.[11,12] Additionally, patients with a fistula or inflammatory mass are at increased risk of more extensive surgery, including resection of the otherwise unaffected healthy tissue.

These complicated cases should preferably be operated on in specialized high-volume centres by a laparoscopic approach to improve short- and long-term postoperative outcomes.[13–16] Considering the complexity of IBD management, subspecialized gastroenterologists and surgeons should ideally provide IBD care within multidisciplinary and specialized IBD units, optimizing the integration of medical management and surgery. However, especially in tertiary referral centres, where the most complex cases are treated, increasing waiting times have become problematic.[1]

Case report

We performed a retrospective study analysing the waiting times, complications and additional health-care consumption during these waiting times of all consecutive adult IBD patients who underwent elective surgery at the tertiary Amsterdam UMC IBD centre, location AMC, between January 2013 and December 2015. This time period spans the waiting times before and after the implementation of the national bowel

cancer screening program in the Netherlands.[17] In 2014, more than 80% of the target population was invited to participate in the national bowel cancer screening program.[17] Patients with planned acute or urgent (within one week) surgery, day care surgery, surgery for IBD-related (pre)malignancy, or surgery in study settings (appendectomy or ileocaecal resection) were excluded.

In the analyses, patients with active disease were distinguished from patients with inactive disease scheduled for a second-stage surgery (e.g., stoma reversal, completion of proctectomy with pouch procedure).

In this period, 270 patients with Crohn's disease and 144 patients with ulcerative colitis were operated upon. In total, 270 patients were included, of whom 173 were electively operated for active disease and 97 underwent an elective procedure for inactive disease (Table 5.1). The number of patients treated for active disease was 68 in 2013, 64 in 2014, and 41 in 2015. For inactive disease, these numbers were 34, 34, and 29 patients, respectively.

The mean waiting time for the whole study period was 10 weeks (SD 8) for patients with active disease and 15 weeks (SD 16) for patients with inactive disease. The mean waiting time increased over the years in both groups. For active disease, the mean waiting time was 8 weeks (SD 6) in 2013, 11 weeks (SD 10) in 2014, and 14 weeks (SD 8) in 2015. For inactive disease, the waiting time was 11 weeks (SD 12) in 2013, 16 weeks (SD 10) in 2014, and 20 weeks (SD 23) in 2015. The mean waiting time for colorectal cancer patients in the Amsterdam UMC, location AMC, remained stable at 5 weeks in the study period. The number of colorectal cancer patients treated in the AMC was 49 patients in 2013, 58 in 2014, and 54 in 2015.

For 1 out of 8 patients, the waiting time proved too long, as they required surgery in an acute or semi-acute setting while waiting for surgery. Additionally, 19% of the patients with active disease had disease complications during the waiting time (i.e., > 5% weight loss, fistula or abscess formations requiring radiological intervention, and dehydration or hypokalaemia requiring intravenous supplementation). One patient required admission to the intensive care unit with abdominal sepsis following a rectal stump perforation as a result of a progressing stenosis. The disease complication rate was 15% for patients on the waiting list with inactive disease (e.g., dehydration following a high-output stoma).

In addition, to analyse whether disease complications were related to a longer waiting time, the mean waiting times of patients with and without disease complications were compared. For these analyses, patients converted to acute or semi-acute surgery were excluded. The mean waiting time of patients with active disease and a disease complication was 13 weeks (SD 7), compared with 10 weeks (SD 8) for patients without any disease complication during the waiting time, $P = 0.173$. In patients on the waiting

Table 5.1. Patient characteristics

	Active disease (n = 173)	Inactive disease (n = 97)
Gender (F:M)	102:71	44:53
Age, mean SD	41 (SD 14)	39 (SD 13)
Diagnoses (UC:CD)	44:129	57:40
Disease complications		
Proctitis	0	4
Dehydration (following high output stoma) requiring supplementation	1	6
Stoma prolapse	0	1
Bowel obstruction	6	0
Stricture formation	1	0
Abscess formation requiring radiological drainage	3	1
Fistula formation	4	0
> 5% weight loss	16	3[1]
Hypokalemia requiring supplementation	2	0
Rectal stump stenosis	1[2]	0
Surgery		
(Neo)terminal ileocaecal resection	62	-
Stricturoplasty	5	-
(Reversal) stoma surgery	21	25
Pouch surgery after subtotal colectomy	-	56
Redopouch	15	5
Subtotal colectomy	33	-
Proctocolectomy with pouch	7	-
Completion proctocolectomy after subtotal colectomy	17	2
Pouch excision for Crohn's disease	1	-
Mesorectal excision	1	-
Other	11	9

[1] One patient required total parenteral nutrition [2] One patient required intensive care unit admission because of sepsis due to rectal stump perforation following progressing stenosis.

list for inactive disease, this difference was significantly higher: the mean waiting time of patients with a disease complication was 24 weeks (SD 27), compared with 14 weeks (SD 12) for patients without disease complications, $P = 0.027$ (Figure 5.1).

The proportion of patients using additional health care during the waiting time was 44% for patients with active disease and 43% for patients with inactive disease. Additional health-care consumption was defined as extra appointments at the out-patient clinic (including telephone consultations), visits to the emergency department, or hospital admission. To assess whether additional health-care consumption was also associated with a longer waiting time, the waiting times of the patients who did and did not use additional health care were compared. After excluding patients converted to acute or semi-acute surgery, for patients with active disease consuming additional health care

the mean waiting time was 13 weeks (SD 8), compared with 9 weeks (SD 8) for patients not using additional health care, $P = 0.002$. Equally, for patients with inactive disease using additional heath care the mean waiting time was 23 weeks (SD 21), compared with 11 weeks (SD 7) for patients not consuming additional health care, $P < 0.001$ (Figure 5.1).

A longer waiting time was also associated with postoperative complications in patients with active disease (Clavien Dindo > I, Figure 5.1). The mean waiting time for patients with anastomotic leakage was 17 weeks (SD 10), compared with 10 weeks (SD 8) for patients who did not develop anastomotic leakage after surgery, $P = 0.011$.

In patients electively operated upon within 6 weeks, less preoperative and postoperative complications were observed compared with patients who had to wait longer.

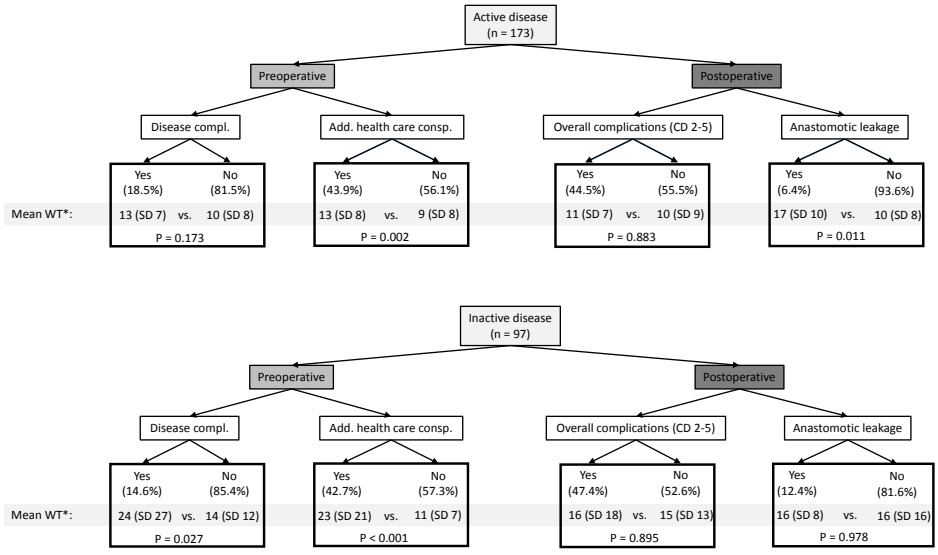


Figure 5.1. The association of mean waiting time and pre- and postoperative complications and additional health-care consumption.

* WT; waiting time in weeks assessed with unpaired *t*-test; patients converted to surgery in a (semi-) acute setting were excluded from these analyses. Disease Comp.: disease complications. Add. health care consp.: additional health-care consumption. Overall complications (CD 2–5): defined as any postoperative complication within 30 days or in hospital with Clavien–Dindo score ≥ 2.[25] Anastomotic leakage: was either confirmed by radiological imaging or during surgical exploration.

Discussion

Based on these results, we conclude that for a large number of IBD patients the current waiting time is unacceptable. This is not only because of the medically unjustifiable increased complication rate, but also because of the general dissatisfaction, logistic

difficulties, and hospital costs associated with the extra interventions and hospital visits.[18] In addition, for the 'non-ill' patients group a mean waiting time of 15 weeks for a stoma reversal should be avoided.[19] The social lives of these, mainly young, patients are often on hold during the waiting time.[20] Moreover, in this era where prehabilitation and pre-operative optimization is promoted,[21,22] complications due to a waiting list are not tolerable.

Due to the current trend towards auditing, quality checks and volume norms, there are many incentives for hospitals to specialize. Nevertheless, the incentive to do so in the direction of oncology care seems greater than for benign disease, reflecting the higher level of support and emotion surrounding colorectal cancer in our society. However, the appropriateness of prioritizing oncology patients at the expense of timely care for IBD patients should be questioned.

Physicians and surgeons have an obligation to provide the most optimal care for every patient. In oncology, quality criteria, like regular multidisciplinary team meetings, centralization of care, and health-care regulatory bodies setting the norm for time to treatment, are well established.[23] For IBD centres, however, quality criteria are heterogeneous and suboptimal.[24]

Following an interview program carried out across 48 Dutch hospitals in 2014, the average waiting time to IBD surgery in peripheral hospitals was 3.5 weeks, compared with 9 weeks in university hospitals.[1] While awaiting guidelines for a maximal acceptable waiting time, the IBD centre of the Amsterdam UMC has made an alliance with a non-academic teaching hospital nearby. Currently, one academic and one peripheral IBD surgeon run a joint outpatient clinic. Patients in good condition requiring standard care (e.g., ileocecal resection for terminal ileitis) are being operated upon in the allied hospital with a considerably shorter waiting time. However, this local initiative will not be a structural solution for the magnitude of this problem.

Public awareness of the situation of IBD patients must be raised to a similar level to that of oncology patients to fuel the development of norms for maximum waiting times for surgery, while enforcing the volume norms.

Acknowledgments

Collaborators in the IBD Study Group: Christianne J. Buskens (c.j.buskens@amsterdamumc.nl), Willem A. Bemelman (w.a.bemelman@amsterdamumc.nl), Roel Hompes (r.hompes@amsterdamumc.nl), Pieter J. Tanis (p.j.tanis@amsterdamumc.nl), Geert R.A.M. D'Haens (g.dhaens@amsterdamumc.nl), Onur B. Dolmaci (o.b.dolmaci@amsterdamumc.nl), Jip Groen (jip.groen@gmail.com), Jarmila van der Bilt (j.vanderbilt@amsterdamumc.nl), Cyriel I.J. Ponsioen (c.y.ponsioen@amsterdamumc.nl), Marjolijn Duijvestein (m.duijvestein@

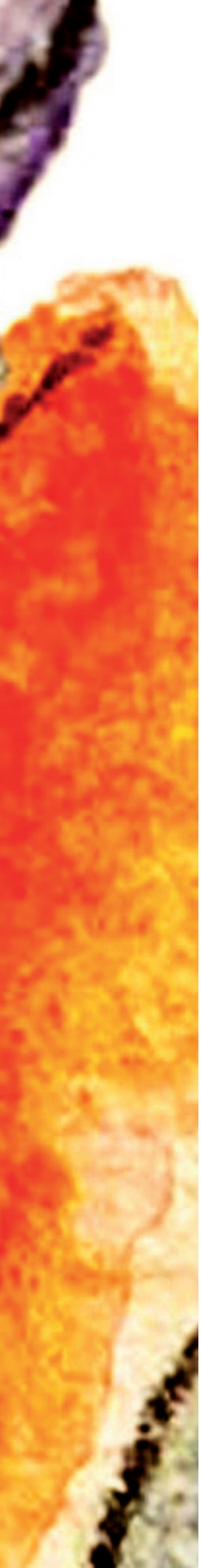
amsterdamumc.nl), Mark Lowenberg (m.lowenberg@amsterdamumc.nl), Manon E. Wildenberg (m.e.wildenberg@amsterdamumc.nl), and Krisztina B. Gecse (k.b.gecse@amsterdamucm.nl).

References

1. Oncologie gaat voor, andere zorg in de verdrukking | medischcontact. Available at: https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/oncologie-gaat-voor-andere-zorg-in-de-verdrukking.htm#. Accessed April 17, 2019.
2. IKNL. Landelijke werkgroep Gastro Intestinal Tumoren. Colorectaal carcinoom. Landelijke richtlijn, versie 3.0, 2014. OncolineNl 2014.
3. Wolf AMD., Fontham ETH., Church TR., Flowers CR., Guerra CE., LaMonte SJ., et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68(4):250–81. Doi: 10.3322/caac.21457.
4. Zorzi M., Fedeli U., Schievano E., Bovo E., Guzzinati S., Baracco S., et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2015;64(5):784–90. Doi: 10.1136/gutjnl-2014-307508.
5. Brenner H., Stock C., Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348(apr09 1):g2467. Doi: 10.1136/bmj.g2467.
6. Schreuders EH., Ruco A., Rabeneck L., Schoen RE., Sung JJY., Young GP., et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64(10):1637–49. Doi: 10.1136/gutjnl-2014-309086.
7. Peyrin-Biroulet L., Loftus E V., Colombel J-F., Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010;105(2):289–97. Doi: 10.1038/ajg.2009.579.
8. Cosnes J., Gowerrousseau C., Seksik P., Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011;140(6):1785–94. Doi: 10.1053/j.gastro.2011.01.055.
9. Sahami S., Bartels SAL., D'Hoore A., Fadok TY., Tanis PJ., Lindeboom R., et al. A Multicentre Evaluation of Risk Factors for Anastomotic Leakage After Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease. J Crohns Colitis 2016;10(7):773–8. Doi: 10.1093/ecco-jcc/jjv170.
10. 2015 European Society of Coloproctology collaborating group. Risk factors for unfavourable postoperative outcome in patients with Crohn's disease undergoing right hemicolectomy or ileocaecal resection An international audit by ESCP and S-ECCO. Colorectal Dis 2017;20(3):219–27. Doi: 10.1111/codi.13889.
11. Morar PS., Hodgkinson JD., Thalayasingam S., Koysombat K., Purcell M., Hart AL., et al. Determining predictors for intra-abdominal septic complications following ileocolonic resection for Crohn's disease-considerations in pre-operative and peri-operative optimisation techniques to improve outcome. J Crohn's Colitis 2015;9(6):483–91. Doi: 10.1093/ecco-jcc/jjv051.
12. Aratari A., Papi C., Leandro G., Viscido A., Capurso L., Caprilli R. Early versus late surgery for ileo-caecal Crohn's disease. Aliment Pharmacol Ther 2007:1303–12. Doi: 10.1111/j.1365-2036.2007.03515.x.
13. Dasari BV., McKay D., Gardiner K. Laparoscopic versus Open surgery for small bowel Crohn's disease. In: Dasari BV, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2011. p. CD006956.
14. de Groof EJ., Buskens CJ., Bemelman WA. Single-Port Surgery in Inflammatory Bowel Disease: A Review of Current Evidence. World J Surg 2016;40(9):2276–82. Doi: 10.1007/s00268-016-3509-y.
15. Gardenbroek TJ., Verlaan T., Tanis PJ., Ponsioen CY., D'Haens GRAMAM., Buskens CJ., et al. Single-port versus multiport laparoscopic ileocecal resection for Crohn's disease. J Crohn's Colitis 2013;7(10):e443–8. Doi: 10.1016/j.crohns.2013.02.015.
16. Bartels SAL., Gardenbroek TJ., Ubbink DT., Buskens CJ., Tanis PJ., Bemelman WA. Systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis. Br J Surg 2013;100(6):726–33. Doi: 10.1002/bjs.9061.
17. CRC screening in the Netherlands from pilot to national programme. | RIVM. Available at: https://www.rivm.nl/documenten/crc-screening-in-netherlands-from-pilot-to-national-programme. Accessed June 13, 2019.
18. Reducing Wait Times for Health Care: What Canada Can Learn from Theory and International Experience | Fraser Institute. Available at: https://www.fraserinstitute.org/studies/reducing-wait-times-for-health-care. Accessed April 30, 2019.

19. Oudhoff JP., Timmermans DR., Rietberg M., Knol DL., van der Wal G. The acceptability of waiting times for elective general surgery and the appropriateness of prioritising patients. BMC Health Serv Res 2007;7(1):32. Doi: 10.1186/1472-6963-7-32.
20. Oudhoff J., Timmermans D., Knol D., Bijnen A., van der Wal G. Waiting for elective general surgery: impact on health related quality of life and psychosocial consequences. BMC Public Health 2007;7(1):164. Doi: 10.1186/1471-2458-7-164.
21. Carli F., Scheede-Bergdahl C. Prehabilitation to Enhance Perioperative Care. Anesthesiol Clin 2015;33(1):17–33. Doi: 10.1016/j.anclin.2014.11.002.
22. Bruns ERJ., van Rooijen SJ., Argillander TE., van der Zaag ES., van Grevenstein WMU., van Duijvendijk P., et al. Improving Outcomes in Oncological Colorectal Surgery by Prehabilitation. Am J Phys Med Rehabil 2019;98(3):231–8. Doi: 10.1097/PHM.0000000000001025.
23. Luzietti E., Pellino G., Nikolaou S., Qiu S., Mills S., Warren O., et al. Comparison of guidelines for the management of rectal cancer. BJS Open 2018;2(6):433–51. Doi: 10.1002/bjs5.88.
24. Panés J., O'Connor M., Peyrin-Biroulet L., Irving P., Petersson J., Colombel J-F. Improving quality of care in inflammatory bowel disease: What changes can be made today? J Crohn's Colitis 2014;8(9):919–26. Doi: 10.1016/j.crohns.2014.02.022.
25. Clavien PA., Barkun J., de Oliveira ML., Vauthey JN., Dindo D., Schulick RD., et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(2):187–96. Doi: 10.1097/SLA.0b013e3181b13ca2.


RETHINKING
DOGMAS



PART 2

Ulcerative colitis – Innovative surgical strategies for pouch surgery


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 6

Transanal versus transabdominal minimally invasive (completion) proctectomy with ileal pouch-anal anastomosis in ulcerative colitis: a comparative study

Anthony de Buck van Overstraeten, Anders Mark-Christensen, Karin A Wasmann, Vivian P Bastiaenen, Christianne J Buskens, Albert M Wolthuis, Koen Vanbrabant, André D'Hoore, Willem A Bemelman, Anders Tottrup, Pieter J Tan

Ann Surg. 2017; 266(5): 878-83

Abstract

Objective: This study aims to compare surgical outcome of transanal ileal pouch-anal anastomosis (ta-IPAA) with transabdominal minimal invasive approach in ulcerative colitis (UC), using the comprehensive complication index (CCI).

Background: Recent evolutions in rectal cancer surgery led to transanal dissection of the rectum resulting in a better exposure of the distal rectum and presumed better outcome. The same approach was introduced for patients with UC, resulting in decreased invasiveness.

Methods: All patients, undergoing minimally invasive restorative proctocolectomy in 1, 2, or 3 stages between January 2011 and September 2016 in 3 referral centers were included. Only patients who underwent either multiport, single port, single port with 1 additional port, hand-assisted, or robotic (R) laparoscopy were included in the analysis. CCI, registered during 90 days after pouch construction, was compared between the transanal and the transabdominal approach.

Results: Ninety-seven patients (male: 52%) with ta-IPAA were compared to 119 (male: 53%) with transabdominal IPAA. Ninety-nine (46%) patients had a defunctioning ileostomy at time of pouch construction. A 2-step model showed that the odds for postoperative morbidity were 0.52 times lower in the ta-IPAA group (95% confidence interval [0.29; 0.92] $P = 0.026$). In patients with morbidity, mean CCI of the transanal approach was 2.23 points lower than the transabdominal approach (95% confidence interval: [-6.64; 3.36] $P = 0.13$), which was not significant.

Conclusions: Ta-IPAA for UC is a safe procedure, resulting in fewer patients with morbidity, but comparable CCI when morbidity is present. Overall, ta-IPAA led to lower CCI scores.

Introduction

Laparoscopic surgery for the treatment of ulcerative colitis (UC) has shown an improved short-term outcome, a reduction of peritoneal adhesions, a better-preserved female fecundity and a reduced incidence of incisional hernias.[1-5] Even for emergency colectomy, laparoscopic surgery is the approach of choice in centers of expertise.[6]

To overcome the technical hurdles occurring during laparoscopic pelvic dissection and distal rectal transection, created by the bony confinement of the pelvis, modern technologies have arisen to assist the surgeon.[7] Robotic technology probably facilitates pelvic accessibility by the presence of wrists and improved vision.[8] More recently, transanal surgical techniques have been explored in the total mesorectal excision (TME) surgery, and has shown encouraging low conversion rates in a recent registry analysis.[9]

In analogy to transanal TME, transanal ileal pouch-anal anastomosis (ta-IPAA) has been proposed to patients with UC, resulting in the same technical improvements.[10,11] In addition to a better pelvic accessibility, transanal access gives the opportunity to the surgeon to appreciate more appropriately the level of the anastomosis at the top of the transition zone. In a pilot study, the authors demonstrated the feasibility of ta-IPAA with single stapled anastomosis.[12] Leo et al.[13] published a series reporting short-term outcome in 16 patients. However, no comparative data have ever been published reporting the short-term surgical outcome of ta-IPAA compared to minimally invasive transabdominal IPAA (tabd-IPAA).

This study aims to compare outcome of ta-IPAA compared to laparoscopic/robotic IPAA in terms of early surgical outcome.

Patients and methods

Consecutive patients undergoing primary IPAA for UC or inflammatory bowel disease unclassified in 1, 2, modified 2, or 3 stages between 2011 and 2016, were included. All data were registered prospectively in dedicated pouch surgery databases. Patients with tabd-IPAA, including multiport (MP), single port (SP), SP with 1 additional port (SP+1), hand-assisted (HA), or robotic (R) were compared to patients with ta-IPAA, combined with an MP, SP, SP+1, HA, or R laparoscopic approach. Only the operation during which the (colo-)proctectomy with pouch creation with or without diverting ileostomy was considered for analysis. In other words, transabdominal minimal invasive rectal dissection was compared to transanal proctectomy. Patients with an open proctectomy through a Pfannenstiel were excluded.

Data were retrieved from dedicated pouch surgery databases. In Leuven, the Dendrite database (Dendrite clinical systems, Henley-on-Thames, UK) is used for all pouch

patients since 2011. Both in Aarhus and Amsterdam institutional databases are in use. Eventual missing data were retrieved in patients' medical charts. The comprehensive complication index (CCI), reflecting the short-term postoperative morbidity, was used as primary outcome.[14] This index is based on the Clavien-Dindo classification for postoperative morbidity.[15] The CCI was calculated using a predefined formula, reflecting complication's severity, and resulting in a number between 0 and 100. The index represents the sum of all occurring complications, weighted for their severity, resulting in a continuous scale to rank the severity of any combination of complications in a single patient. A Clavien-Dindo I complication would for example result in a score of 8.7 on the CCI scale, whereas a Clavien-Dindo IIIa complication is represented by 26.2 on the same scale. CCI was calculated by using the online CCI calculator (www.assessurgery.com). All postoperative complications within 90 days after construction of the pouch were taken into consideration. Secondary outcomes were conversion rate, anastomotic leak rate (both clinical and radiological), anastomotic stenosis, resumption to oral intake (defined as a delay of 5 days or more), duration of surgery, and postoperative hospital length of stay. Conversion was defined as any change in strategy to a more invasive technique. Transanal dissection converted to transabdominal dissection was also considered as conversion.

Surgical technique

Ta-IPAA with close rectal dissection and single stapled anastomosis has extensively been described by some of the authors.[12] Basically, dissection of the rectum is performed through a transanal port device, enabling the introduction of laparoscopic instruments and an (angled) scope. The use of an appropriate insufflation device with high smoke evacuation is mandatory to obtain a stable operating field and satisfying visibility. Dissection is performed both by monopolar cautery and by an energy device. The surgeon can choose to perform either a close rectal dissection or use the TME plane. The complete proctectomy can be performed transanally or the surgeon can dissect the proximal part of the rectum from the abdomen. A conversion can be caused by insufficient visualization, especially in patients with obesity or when a bleeding occurs.

In any case, even in patients operated by a transanal approach, an abdominal approach is complementary to eventually perform the colectomy or mobilize the mesenteric root of the small bowel to gain length. The ileal pouch can then be created through a utility incision (stomasite, umbilical, or Pfannenstiel). In SP cases, the ileal pouch is always created through the stoma site, avoiding any other unnecessary incisions. Both hand-sewn and single stapled anastomoses are used.

During the transabdominal approach, the proctectomy is performed through the abdomen, using MP, SP, or robotic techniques. The surgical technique for proctectomy is basically the same (close rectal dissection or TME), using monopolar cautery or energy

devices for dissection. A double stapled technique or hand-sewn anastomosis is used. The type of abdominal approach (SP, MP, R, SP+1, HA) was upon surgeon's discretion.

There is no specific difference in indication to perform either one or the other technique. Basically, in all centers, there was a shift from the transabdominal approach toward the transanal approach.

Statistical analysis

Continuous data were summarized by median and interquartile range (IQR) or mean and standard deviation. Categorical data were presented by their observed frequencies and percentages. Treatment-selection bias, caused by the retrospective design of the study, was dealt with by propensity scores. These were defined as the probability of being assigned to either transabdominal or transanal proctectomy, conditional on observed baseline variables. These propensity scores were obtained from a logistic regression model (with treatment status as an outcome) using the following variables as predictor: preoperative use of steroids, azathioprine, or biologicals (within 8 weeks before surgery), anastomotic technique (stapled or hand-sewn), number of operative stages, age at time of pouch construction, sex, and type of rectal dissection (TME or close rectal dissection). The variables were selected on a theoretical basis before the weighing analysis was carried out. In this study, the propensity scores were used as inverse probability weights in all models that were used to compare the primary and secondary outcomes between both treatment options.[16,17] The descriptive statistics are based on the observed data. The results from inferential analyses are based on statistical models that made use of the inverse-probability weights.

Because of its zero inflation, CCI was considered to contain 2 types of information: the probability of developing complications (i.e., a zero vs. a non-zero CCI score) and complication severity (i.e., a CCI score between 1 and 100). The probability of complications was evaluated via a logistic regression, whereas the difference, expressed in means between both pouch approaches for the subset of patients with a positive CCI score, was evaluated via a gamma generalized linear model with a log link. This gamma generalized linear model was used because the CCI (i.e., non-zero) scores were positively skewed. A difference of 5 or less of the CCI was considered as clinically negligible.

A logistic regression model was used to evaluate the difference in proportion in conversion, anastomotic leak, and prolonged postoperative ileus. A linear regression was used to estimate the difference in mean between both pouch methods for the duration of the operation and the logarithm of postoperative admission length.

All analyses were performed using R version 3.3.1 (2016) in RStudio (Boston, MA).

Results

Between January 2011 and September 2016 a total of 216 patients with UC or inflammatory bowel disease unclassified underwent a minimally invasive restorative proctectomy, either by transabdominal or transanal approach. Ninety-seven patients (44.9%; men 51.6%) with a median age of 35 years (IQR: 26–50) underwent ta-IPAA. Tabd-IPAA was performed in 119 patients (55.1%; men: 52.9%) with a median age of 39 years (IQR: 30–48). Observed patients' and surgical characteristics are summarized in Tables 6.1 and 6.2.

Median number of complications per patient was 1 (range: 0–6). After inverse probability weighted *t*-test, mean CCI score for ta-IPAA was 13.1 compared to 18.25 for the transabdominal approach group, with a mean difference of -5.15 (95% confidence interval [CI; -9.79; -0.51], $P = 0.03$). The odds for postoperative morbidity were 0.52 times lower in

Table 6.1. Patients' demographics

	Total N = 216	Transanal N = 97 (44.9%)	Transabdominal N = 119 (55.1%)
Gender n (%)			
Male	113 (52.3%)	50 (51.6%)	63 (52.9%)
Female	103 (47.7%)	47 (48.5%)	56 (47.0%)
Median age (IQR)	37 (27.8–49.3)	35 (26–50)	39 (30–48)
ASA n (%)			
1	35 (16.2%)	11 (11.3%)	24 (20.2%)
2	154 (71.3%)	73 (75.3%)	81 (68.1%)
3	27 (12.5%)	13 (13.4%)	14 (11.8%)
Median BMI (IQR)	23.3 (21.0–25.9)	23.4 (21.3–25.8)	23.3 (20.8–26.5)
Diagnosis n (%)			
UC	213 (98.6%)	95 (97.9%)	118 (99.2%)
IBDU	3 (1.4%)	2 (2.1%)	1 (0.8%)
Concommittant cancer n (%)			
Yes	9 (4.2%)	2 (2.1%)	7 (5.9%)
No	207 (95.8%)	95 (97.9%)	112 (94.1%)
Preop medication n (%)			
Steroids			
Yes	21 (9.7%)	9 (9.3%)	12 (10.1%)
No	195 (90.3%)	88 (90.7%)	107 (89.9%)
Unspecified	-	-	-
Azathioprine			
Yes	21 (10.2%)	6 (6.9%)	15 (12.6%)
No	185 (89.8%)	59 (90.8%)	104 (87.4%)
Unspecified	10 (4.6%)	10 (10.3%)	-
Biologicals			
Yes	29 (13.4%)	17 (17.5%)	12 (10.1%)
No	187 (86.6%)	80 (82.5%)	107 (89.9%)
Unspecified	-	-	-

ASA, American Society of Anesthesiology; BMI, Body Mass Index). These are observed data without using the inverse probability weights.

Table 6.2. Study population surgical characteristics

	Total N = 216	Transanal N = 97	Transabdominal N = 119
Hospital n (%)			
UHL	99 (45.8%)	31 (32.0%)	68 (57.1%)
AUH	91 (42.1%)	42 (43.3%)	49 (41.2%)
AMC	26 (12.0%)	24 (24.7%)	2 (1.7%)
Number of stages			
1	13 (6.0%)	3 (3.1%)	10 (8.4%)
2	12 (5.6%)	4 (4.1%)	8 (6.7%)
Modified 2	104 (48.1%)	51 (52.6%)	53 (44.5%%)
3	87 (40.3%)	39 (40.2%)	48 (40.3%)
Type of abdominal access n (%)			
MP	109 (50.5%)	47 (48.5%)	62 (52.1%)
SP	52 (24.1%)	46 (47.4%)	6 (5.0%)
SP + 1	5 (2.3%)	3 (3.1%)	2 (1.7%)
HA	1 (0.5%)	1 (1.0%)	-
R	49 (22.7%)	-	49 (41.2%)
Type of rectal dissection n (%)			
TME	151 (69.9%)	44 (45.4%)	107 (89.9%)
CRD	65 (30.1)	53 (54.6%)	12 (10.1%)
Conversion n (%)	33 (15.3%)	5 (5.2%)	28 (23.5%)
To laparotomy	19 (8.8%)	3 (3.1%)	16 (13.5%)
To pfannenstiel	13 (6.0%)	1 (1.0%)	12 (10.1%)
Type of pouch-anal anastomosis n (%)			
Single stapled	100 (46.3%)	95 (97.9%)	5 (4.2%)
Double stapled	112 (51.9%)	-	112 (94.1%)
Hand-sewn	4 (1.9%)	2 (2.1%)	2 (1.7%)
Site of specimen delivery n (%)			
Umbilical	12 (5.6%)	1 (1.0%)	11 (9.2%)
Pfannenstiel	88 (40.7%)	20 (20.6%)	68 (57.1%)
Stoma site	26 (12.2%)	7 (7.2%)	19 (16.4%)
Laparotomy	18 (8.3%)	2 (2.1%)	16 (13.4%)
Transanal	45 (20.8%)	41 (42.3%)	4 (3.4%)
Unspecified	27 (12.5%)	26 (26.8%)	1 (0.8%)
Pouch design n (%)			
J-pouch	216 (100%)	97 (100%)	119 (100%)
Defunctioning ileostoma n (%)			
Yes	99 (45.8%)	43 (44.3%)	56 (47.1%)
No	117 (54.2%)	54 (55.6%)	63 (52.9%)
Mean duration of surgery mean (STD)	218.2 (63.2)	211.3 (54.4)	223.8 (69.3)

UHL, University Hospital of Leuven; AUH, Aarhus University Hospital; AMC, Amsterdam Medical Center; TME, total mesorectal excision; CRD, Close rectal dissection. These are the observed data without using the inverse probability weights.

the ta-IPAA group (95% CI [0.29; 0.92] $P = 0.026$). When complications were present, patients in the transabdominal group had a mean CCI score of 25.7 compared to 23.5 in the transanal group, with a difference of -2.23 (95% CI [-6.64; 3.36]). Thus, the difference in observed CCI scores was due to a lower probability of complications for patients in the transanal group. When postoperative morbidity was present, both approaches

did not differ on complication severity. The obtained result implied noninferiority of the transanal procedure within the group of patients with morbidity. Moreover, both complication rate and complication severity were not significantly different in patients with or without a defunctioning ileostomy ($P = 0.518$). CCI is represented in Figure 6.1. The outcome according to the Clavien-Dindo classification is summarized in Table 6.3. Odds ratio for grade III complication or more was 1.1 (95% CI: 0.53–2.22; $P = 0.789$).

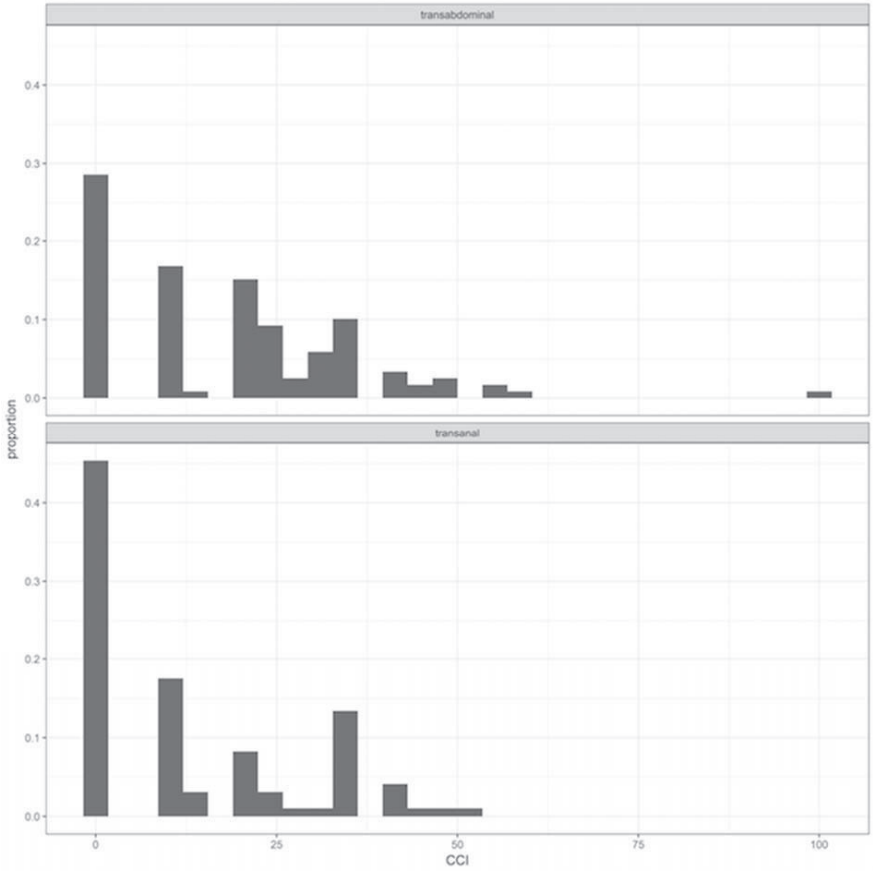


Figure 6.1. Histogram representing the comprehensive complication index for both pouch approaches.
Histogram displaying the probability of receiving a transanal pouch, obtained from a logistic regression model with surgical technique as an outcome and the following variables as predictors: use of steroids, use of azathioprine, use of biologicals, anastomotic type, number of surgical stages, age at surgery, gender and type of rectal dissection.

Sixteen patients (7.4%) developed an anastomotic leak. The odds of having a leak were 1.09 times higher for patients in the transanal approach compared to patients in the transabdominal approach (95% CI of [0.36; 3.07]). Patients of both treatment conditions did not differ in the odds of having a leak ($P = 0.869$).

Table 6.3. 90-day morbidity classified according to the Clavien-Dindo classification

	Total N = 216	Transanal N = 97	Transabdominal N = 119
Grade of complication n (%)			
Grade I	56 (25.9%)	25 (25.8%)	31 (26.1%)
Grade II	43 (19.9%)	11 (11.3%)	32 (26.9%)
Grade IIIa	6 (2.8%)	3 (3.1%)	3 (2.5%)
Grade IIIb	27 (12.5%)	14 (14.4%)	13 (10.9%)
Grade IVa	5 (2.4%)	-	5 (4.2%)

Twenty-eight (23.5%) patients with tabd-IPAA were converted compared with 5 (5.2%) in the transanal group. Sixteen (13.5%) patients in the transabdominal group were converted to laparotomy and 12 (10.1%) to a Pfannenstiel incision compared to 3 (3.1%) and 1 (1.0%) patients in the transanal group, respectively. None of ta-IPAA patients was converted to a transabdominal laparoscopic approach. The odds after inversed probability weighted *t*-test, for undergoing a conversion were 0.16 times lower for patients undergoing a ta-IPAA (95% CI of [0.05; 0.42], $P < .001$).

Duration of surgery for ta-IPAA was 13.2 minutes shorter after controlling for diverting ileostomy (95% CI of [-28.4; 1.99], $P = 0.088$).

The average postoperative admission length was 9.08 days for the transabdominal approach and significantly differed from the 7.34 days for the transanal approach ($P = 0.001$). Mean difference between both approaches was 1.74 days (95% CI of [0.74; 2.63]).

The odds of having delayed resumption of oral intake were 0.46 times lower for patients in the transanal approach compared to patients in the transabdominal approach (95% CI of [0.24; 0.84]). Tabd-IPAA had a probability of ileus of 0.41, whereas ta-IPAA had a probability of 0.25 ($P = 0.014$).

Discussion

This is the first study comparing surgical outcome between ta-IPAA and tabd-IPAA. It shows that ta-IPAA is safe in patients with UC, with decreasing rates of postoperative morbidity. Moreover, it had a favorable impact on the occurrence of delayed resumption of oral intake and postoperative length of hospital stay, without any significant impact on the duration of surgery. Surgeons using the transanal approach had a significantly lower conversion rate. Anastomotic leakage was, however, not impacted by the surgical approach.

CCI was used in this study to report surgical outcome. This instrument, published in 2013, has several significant advantages.[14] First, it includes any occurring postoperative

morbidity, even in patients with multiple postoperative complications. This is obviously not the case with the traditional Clavien-Dindo classification, which indeed, only considers the heaviest complication, omitting all associated morbidity. This often leads to an underestimation of postoperative morbidity. Moreover, CCI is expressed by a number between 0 and 100, facilitating comparison between different groups of patients. Finally, it is easy to use with a freely accessible online calculator.

Many studies have reported the importance of minimal invasive techniques in patients with IBD. Laparoscopic surgery indeed enhances postoperative recovery, fastens restoration of intestinal continuity, improves female fecundity, and improves body image and cosmesis.[1,2,4,5,18] Some series have also described some advantages of SP surgery in terms of incision length, hospital stay, and postoperative pain.[19] However, distal dissection of the rectum is still difficult and can be overcome either by robotic dissection, transanal techniques, or a combination of both.[20] This was introduced earlier for the treatment of rectal cancer, and appeared to ease the accessibility of the distal rectum with presumed oncological advantages, better preserving the TME specimen.[21] In analogy to rectal cancer treatment, patients with UC have been proposed the transanal approach to ease distal dissection and eventually promoting the transabdominal SP dissection, decreasing invasiveness even further.[10,13] Moreover, the significantly lower conversion rate during transanal proctectomy may be explained by easier access to the rectum.

Concurrently to the introduction of transanal proctectomy, the appearance of the single stapled, or double purse string anastomosis, which is typically used during ta-IPAA, was thought to have a possible beneficial impact on anastomotic leakage. However, this appeared not to be the case in this study. The single stapled technique has, however, 2 hypothetic advantages. First, the surgeon can better appreciate mucosal quality at the distal rectum that is to be used for anastomosis. He/she has the possibility to decide at what level he wants to place the anastomosis to increase the chance of uncomplicated healing. This is typically not the case in a double-stapled anastomosis, where the circular stapler is put blindly through the anus to perform an anastomosis. Moreover, by using the single stapled anastomosis, he can precisely judge the length of rectal cuff, avoiding any retained rectum, very short cuff or more often an irregular cuff due to inaccurate laparoscopic transverse stapling. However, the supposed benefit of the single stapled anastomosis was not reflected in the results of this study, which was obviously not powered for anastomotic leakage. More research is therefore necessary to investigate the effect of single stapling on anastomotic outcome.

Long-term functional outcome is of utmost importance for pouch patients. They expect to recover a normal professional and social life, which has been the case in the majority of patients in the large series, reporting functional outcome.[22,23] Therefore, the quest to less invasive techniques should not harm functional outcome but improve it. A

transient decrease in anal pressure after transanal surgery, with a complete recovery after 12 months, has been described.[24] The impact of ta-IPAA on anal function should therefore be investigated.

This study also has some limitations. First of all, it is a retrospective study reporting surgical outcome in terms of morbidity. Registration bias is probably present; however, this is minimized by the presence of predefined follow-up protocols in each center with prearranged follow-up visits and the use of prospective databases. Standardized follow-up arrangements across the 3 centers were, however, not made. It is also limited by its multicenter design, which may induce heterogeneity amongst included patients and postoperative protocols. A thorough patient selection, including only patients who were operated on using strictly minimally invasive techniques, excluding any other open or hybrid technique was done to aim for a homogenous cohort making comparison reliable. Moreover, it gave the opportunity to have a large cohort, reporting surgical outcome of this very recent technique, setting a beacon for surgeons wanting to introduce this technique. Of course, future research should focus on both prospective, comparative trials and functional outcome.

References

1. Bartels SA, Gardenbroek TJ, Ubbink DT, et al. Systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis. Br J Surg 2013; 100(6):726-33.
2. Fajardo AD, Dharmarajan S, George V, et al. Laparoscopic versus open 2-stage ileal pouch: laparoscopic approach allows for faster restoration of intestinal continuity. J Am Coll Surg 2010; 211(3):377-83.
3. Eshuis EJ, Slors JF, Stokkers PC, et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. Br J Surg 2010; 97(4):563-8.
4. Bartels SA, D'Hoore A, Cuesta MA, et al. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. Ann Surg 2012; 256(6):1045-8.
5. Bartels SA, Vlug MS, Henneman D, et al. Less adhesiolysis and hernia repair during completion proctocolectomy after laparoscopic emergency colectomy for ulcerative colitis. Surg Endosc 2012; 26(2):368-73.
6. Oresland T, Bemelman WA, Sampietro GM, et al. European evidence based consensus on surgery for ulcerative colitis. J Crohns Colitis 2015; 9(1):4-25.
7. Brannigan AE, De Buck S, Suetens P, et al. Intracorporeal rectal stapling following laparoscopic total mesorectal excision: overcoming a challenge. Surg Endosc 2006; 20(6):952-5.
8. Baek SJ, Kim CH, Cho MS, et al. Robotic surgery for rectal cancer can overcome difficulties associated with pelvic anatomy. Surg Endosc 2015; 29(6):1419-24.
9. Penna M, Hompes R, Arnold S, et al. Transanal Total Mesorectal Excision: International Registry Results of the First 720 Cases. Ann Surg 2017; 266(1): 111-7.
10. Tasende MM, Delgado S, Jimenez M, et al. Minimal invasive surgery: NOSE and NOTES in ulcerative colitis. Surg Endosc 2015; 29(11): 3318-8.
11. Liyanage C, Ramwell A, Harris GJ, et al. Transanal endoscopic microsurgery: a new technique for completion proctectomy. Colorectal Dis 2013; 15(9):e542-7.
12. de Buck van Overstraeten A, Wolthuis AM, D'Hoore A. Transanal completion proctectomy after total colectomy and ileal pouch-anal anastomosis for ulcerative colitis: a modified single stapled technique. Colorectal Dis 2016; 18(4):O141-4.
13. Leo CA, Samaranayake S, Perry-Woodford ZL, et al. Initial experience of restorative proctocolectomy for ulcerative colitis by transanal total mesorectal rectal excision and single-incision abdominal laparoscopic surgery. Colorectal Dis 2016; 18(12):1162-1166.
14. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013; 258(1):1-7.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-13.
16. Curtis LH, Hammill BG, Eisenstein EL, et al. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. Med Care 2007; 45(10 Supl 2):S103-7.
17. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015; 34(28):3661-79.
18. Dunker MS, Stiggelbout AM, van Hogezand RA, et al. Cosmesis and body image after laparoscopic-assisted and open ileocolic resection for Crohn's disease. Surg Endosc 1998; 12(11):1334-40.
19. Maggiori L, Gaujoux S, Tribillon E, et al. Single-incision laparoscopy for colorectal resection: a systematic review and meta-analysis of more than a thousand procedures. Colorectal Dis 2012; 14(10):e643-54.
20. Sammour T, Malakorn S, Bednarski BK, et al. Oncological Outcomes After Robotic Proctectomy for Rectal Cancer: Analysis of a Prospective Database. Ann Surg 2018; 267(3):521-6.
21. Penna M, Buchs NC, Bloemendaal AL, et al. Transanal total mesorectal excision for rectal cancer: The journey towards a new technique and its current status. Expert Rev Anticancer Ther 2016; 16(11):1145-53.
22. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg 2013; 257(4):679-85.
23. Hahnloser D, Pemberton JH, Wolff BG, et al. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg 2007; 94(3):333-40.

24. Allaix ME, Rebecchi F, Giaccone C, et al. Long-term functional results and quality of life after transanal endoscopic microsurgery. Br J Surg 2011; 98(11):1635-43.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 7

Transanal ileal pouch-anal anastomosis for ulcerative colitis has comparable long-term functional outcomes to transabdominal approach: a multicentre comparative study

Pramodh Chandrasinghe*, Michele Carvello*, Karin A Wasmann, Caterina Foppa, Pieter J Tanis, Zarah Perry-Woodford, Janindra Warusavitarne, Antonino Spinelli, Willem A Bemelman

* Shared first authors

JCC. 2020; 14(6): 726-33

Abstract

Background: The transanal approach to ileal pouch-anal anastomosis (Ta-IPAA) provides better access to the lower pelvis with lower short-term morbidity in ulcerative colitis (UC). The aim of this study was to assess the long-term functional outcomes after Ta-IPAA vs. transabdominal IPAA (Abd-IPAA) in UC.

Methods: A multicentre cohort analysis was performed between March 2002 and September 2017. Patient characteristics, surgical details and postoperative outcomes were compared. CGQL (Cleveland global quality of life) score at 12 months with a functioning pouch was considered the primary end point.

Results: A total of 374 patients (100 Ta-IPAA vs. 274 Abd-IPAA) were included. Ta-IPAA demonstrated a comparable overall quality of life (CGQL score) to Abd-IPAA (0.75 ± 0.11 vs. 0.71 ± 0.14; respectively, $P = 0.1$). Quality of life (7.71 ± 1.17 vs. 7.30 ± 1.46; $P = 0.04$) and energy-level items (7.16 ± 1.52 vs. 6.66 ± 1.68; $P = 0.03$) were significantly better after Ta-IPAA, while the quality of health item was comparable (7.68 ± 1.26 vs. 7.64 ± 1.44; $P = 0.96$). Analysis excluding anastomotic leaks did not change the overall CGQL scores. Stool frequencies (> 10/24 h: 22% vs. 21%; $P = 1.0$) and the rate of a single episode of major incontinence during the following 12-month period (27% vs. 26%; $P = 0.89$) were similar. The differences in 30-day morbidity rates (33% vs. 41%; $P = 0.2$) and anastomotic leak rates were not significant (6% vs. 13%; $P = 0.09$).

Conclusions: This study provides evidence of comparable long-term functional outcome and quality of life after Ta-IPAA and Abd-IPAA for UC.

Introduction

Despite the improvements in medical therapy for ulcerative colitis (UC), a colectomy is required in up to 15% of patients.[1] For these patients a proctocolectomy with ileal pouch anal anastomosis (IPAA) is the standard procedure. This procedure is preferably performed using a staged approach, starting with a subtotal colectomy with closed rectal stump and end ileostomy.[2–4] To restore the continuity, the rectal stump is resected and an ileal reservoir (the J pouch) is connected to the anus. Conventionally, rectal dissection and creation of a double stapled IPAA was performed transabdominally using either a laparoscopic or an open (e.g., midline or Pfannenstiel incision) approach. However, this can be technically challenging due to restricted space in the pelvis and technical difficulties with cross stapling of the distal rectum.

The transanal approach has been recently introduced to overcome the most cumbersome phase of a laparoscopic approach to the distal mesorectum and is gaining popularity around the world.[5] This technique was an advancement of the transanal minimally invasive surgery (TAMIS) platform.[6] The transanal approach for IPAA (Ta-IPAA) has three major advantages over the transabdominal approach (Abd-IPAA). First, it provides easier access especially to the deep, narrow male pelvis allowing more precise dissection in either the close rectal or the mesorectal plane. Second, it enables controlled rectotomy with precise determination of the length of the rectal cuff and overcomes the difficulty of rectal transection using rigid stapling devices in the deep pelvis. An optimal rectal cuff reduces the risk and burden of cuffitis while preserving the anal transitional zone. Third, the double purse-string, single stapler technique of IPAA prevents the intersection of stapler lines and formation of 'dog ears' in the rectal stump, both of which are potential contributors to anastomotic failure.[7] Transanal access also allows for a reverse air leak test of the anastomosis and reinforcement sutures when necessary. All the above factors may contribute to fewer anastomotic leaks[7,8] and can be hypothesized to result in better functional outcomes. Furthermore, a safer anastomosis could potentially provide justification for not using a diverting stoma.

Some studies have also suggested that better nerve preservation and close rectal dissection may contribute to better genitourinary function, less pelvic sepsis and greater awareness of pouch filling.[9,10] The combined laparoscopic and transanal approach also allows the surgeon to complete the proctectomy without an additional incision for extraction.

Since the introduction of the transanal approach for total mesorectal excision for rectal cancer, its safety and functional outcome following surgery for rectal cancer has been reported.[11–15] The safety of Ta-IPAA in UC patients was compared with transabdominal surgery in a recent report by de Buck van Overstraeten and colleagues, in which a lower complication rate and a comparable comprehensive complication index (CCI) following

the transanal approach was observed.[16] In a quality of life operation such as IPAA, the functional outcomes are of paramount importance. However, long-term functional outcome data after the transanal approach to pouch surgery have not been reported previously. There has been some concern regarding the consequences of prolonged stretching of the anus on sphincter function. We undertook a multicentre prospective cohort study aiming to assess quality of life and function following Ta-IPAA compared to Abd-IPAA (conventional laparoscopic or open) in UC patients.

Methods

Design and patients

A multicentre cohort study was undertaken in which consecutive UC patients undergoing IPAA performed between 2002 and 2017 at three tertiary care referral centres (Amsterdam UMC – Amsterdam; Humanitas Research Hospital – Milan; St. Mark's Hospital – London) were prospectively followed up. Ta-IPAA has been routinely performed at the Amsterdam UMC, St. Mark's Hospital London and at the Humanitas Hospital since 2015. Patients were followed up at 6 weeks, 3 months, 6 months and 1 year time for pouch function and quality of life assessments at the outpatient clinic. The primary end point was pouch function-related quality of life as assessed by the previously validated CGQL (Cleveland global quality of life) score.[17,18] The CGQL assesses three main functions: the quality of health, quality of life and energy level reported by patients. The score for each subsection is given out of 10 and the total is divided by 30 to get a final score ranging between 1 and 0. The score has been validated in large cohorts of patients with pouches and has shown consistency and reproducibility.[17–20]

All patients with a functional pouch at 12 months (i.e., 12 months from closure of the ileostomy or 12 months from the time of surgery in modified two-stage or single-stage procedures) completed a self-administered questionnaire. The questionnaire included quality of life, quality of health and energy score assessment along with the assessment of individual components of bowel function.

One-year postoperative mean CGQL scores of the Ta-IPAA and Abd-IPAA groups were compared. In addition, the three separate components of the CGQL, incontinence rates and stool frequencies were compared among the two groups. Reporting of data adheres to the principles of reporting cohort studies as stated in the STROBE statement.[21] The study was registered as an audit (not requiring formal approval of an Ethics Committee).

Variables

All postoperative complications were reported by means of the Clavien–Dindo classification.[22] Complications requiring surgical, endoscopic or radiological reintervention or

intensive care management (i.e., Clavien–Dindo III–IV) and complications causing death (Clavien–Dindo V) were considered a severe complication. A pouch leak was defined as computed tomographic (CT) or magnetic resonance imaging (MRI) evidence of a pelvic collection or visualization of an anastomotic defect during endoscopy or surgical re-exploration. Major incontinence was defined as at least one self-reported episode of incontinence during the 12-month follow-up period affecting normal daily routine. Pouch failure was defined by either excision of the pouch of creation of a permeant ileostomy for pouch dysfunction. A subgroup analysis was performed to compare the functional outcome between those who had a total mesorectal excision and those with a close rectal dissection. Genitourinary and sexual function were also assessed in a smaller subgroup using the International Erectile Function Score (IEFS-5)[23] for males and Female Sexual Function Index (FSFI) for females.[24]

Surgical techniques

A restorative proctocolectomy with IPAA (RPC-IPAA) can be performed either as a single or a multistage procedure. Proctocolectomy followed by creation of the ileal pouch in a single procedure, without a diverting ileostomy, defines a single-stage RPC-IPAA. In a two-stage procedure, an end ileostomy was performed at the initial operation. A subtotal colectomy with an end ileostomy followed by a proctectomy with an IPAA and diverting ileostomy, closed at the third stage, comprises a three-stage procedure. A modified two-stage procedure omits the diverting ileostomy. All procedures were performed by experienced colorectal surgeons using the techniques described below.

Ta-IPAA

Patients were placed in the modified lithotomy position. Abdominal access was gained through a single port at the right iliac fossa either by detaching and closing the existing ileostomy (if a previous subtotal colectomy was performed) or through an incision at a site marked for the proposed stoma in a single-stage procedure. Transabdominally, the proximal part of the remaining rectum was dissected up to the peritoneal reflexion. In selected cases an additional 5-mm port was used at the left iliac fossa for retraction of the sigmoid colon. A second surgeon commenced the transanal part of the operation concurrently. First, exposure of the anus was achieved with a Lone Star retractor (Cooper Surgical). Thereafter, the Gelpoint Path Transanal Access Platform (Applied Medical)[16] was inserted into the anus and a pneumorectum was created. A purse string was inserted to close the rectum 1 cm proximal to the proposed site of rectotomy. The distal rectum was then transected approximately 3 cm above the dentate line and the rectal dissection was continued cephalad until rendezvous. Both hook diathermy and ultrasonic energy devices were used depending on operator preference. The rectum was extracted either transanally or transabdominally through the single port at the stoma site.

In the next phase, the J pouch was fashioned by delivering the ileum through the abdominal wound using linear staplers. A purse string suture was placed at the base of the pouch and tied around the central rod of the anvil of the circular stapler. A second purse string suture was placed and tied at the edge of the rectal cuff. The pouch was then approximated towards the rectal cuff, so that the anvil could be connected to the shaft of the stapler to create a single-stapled double purse string IPAA. Occasionally, stiches were placed transanally to reinforce the anastomosis.

Abd-IPAA

As previously described,[25–27] for staged procedures a midline (or a Pfannenstiel incision in the case of proctectomy alone) was performed in open cases, while a standardized port insertion was used in laparoscopic procedures. After rectal dissection, a linear stapler was used to close the anorectal stump. The specimen was removed through the abdominal incision (Pfannenstiel in laparoscopic) and the pouch was created. After approximation of the pouch towards the rectal cuff, the circular stapler was fired to complete the double-stapled IPAA.

In laparoscopic restorative proctocolectomy, rectal dissection down to the pelvic floor was carried out laparoscopically. A Pfannenstiel incision was used for distal stapling of the rectum stump, specimen delivery and creation of the pouch. After re-establishing the pneumoperitoneum, a double-stapled IPAA was created laparoscopically.

Statistical analyses

Continuous non-parametric data are presented as median and standard deviation, whereas nominal data are presented as percentage frequency of occurrence. The Mann–Whitney U-test was used to compare non-parametric data. To compare proportions, Pearson's chi-squared test or Fisher's exact test was used, as appropriate. A P value of < 0.05 was considered statistically significant.

Results

A total of 374 patients underwent IPAA for UC at the three centres in the study period. One hundred patients (mean age: 39.94 ± 12.75 years; range 16–67; male: 55%) had Ta-IPAA and 274 patients (mean age: 38.23 ± 13.24 years; range 9–71; male: 55%) had Abd-IPAA (Table 7.1). A defunctioning stoma was created at the time of pouch construction in 46 (46%) patients undergoing Ta-IPAA and in 130 (47%) patients undergoing Abd-IPAA ($P = 0.90$). Most of the Ta-IPAA procedures were performed as modified two-stage procedures (53%). Stoma closure was performed on average between 5 and 6 months from the time of surgery in both groups.

Table 7.1. Patient characteristics, surgical technique, short term and long-term outcome following IPAA

Characteristics	Abd-IPAA (n = 274)	TaIPAA (n = 100)	*P* value
Age, year, mean ± SD (Range)	39.23 ± 13.24 (9–71)	38.73 ± 12.78 (16–67)	0.74
Female, % (n)	45% (122)	45% (45)	1.00
Surgical details			
Surgery technique, % (n)			< 0.0001
1 stage	21% (57)	1% (1)	
2 stage	18% (49)	11% (11)	
Modified 2 stage	32% (87)	54% (54)	
3 stage	30% (81)	34% (34)	
Post-operative complication, % (n)	41% (111)	33% (33)	0.22
None	59% (163)	67% (67)	
Clavien Dindo I	9% (25)	7% (7)	
Clavien Dindo II	7% (19)	11% (11)	
Clavien Dindo III	23% (62)	15% (15)	
Clavien Dindo IV	2% (5)	-	
Anastomotic leakage	13% (35)	6% (6)	0.09
Pouch failure at 12 months, % (n)	3% (7)	1% (1)	0.85
Pouch complication at 4 years follow-up, % (n)	35% (95)	25% (25)	0.10
Time to stoma closure, months, mean ± SD	5.83 ± 6.93	5.35 ± 3.51	0.64
Stool frequency	Abd-IPAA (n = 239)	TaIPAA (n = 96)	
Stool frequency at 12 months, % (n)			1.00
< 10/24 h	79% (188)	78% (75)	
> 10/24 h	21% (51)	22% (21)	
Major incontinence	Abd-IPAA (n = 264)	TaIPAA (n = 100)	
Major Incontinence at 12 months, % (n)	26% (69)	27% (27)	0.89
Functional questionnaires	Abd-IPAA (n = 232)	TaIPAA (n = 98)	
CGQoL 12 months	0.71 ± 0.14	0.75 ± 0.11	0.11

Short-term postoperative complications

Postoperative complication rates were comparable among the two groups ($P = 0.22$), and overall immediate postoperative complication rates were comparable for both cohorts (Ta-IPAA: 33% vs. Abd-IPAA: 41%; $P = 0.2$). In the Ta-IPAA cohort none had experienced a Clavien–Dindo IV complication compared with 2% in the Abd-IPAA cohort ($P = 0.07$). Although the anastomotic leak rate was higher in the Abd-IPAA group, this was not statistically significant (Ta-IPAA: 6% vs. Abd-IPAA: 13%; $P = 0.09$).

Long-term functional outcomes

CGQL scores for those with a functioning pouch for at least 12 months were available for 98 (98%) patients in the Ta-IPAA and 232 (85%) in the Abd-IPAA group. The mean CGQL (Fazio) scores for the two groups were similar (Abd-IPAA: 0.71 ± 0.14 vs. Ta-IPAA: 0.75 ± 0.12; $P = 0.11$) (Figure 7.1). Analysis of the scores for separate items in the CGQL

revealed a significantly better quality of health and energy level in the transanal group (quality of health: 7.30 ± 1.53 vs. 7.73 ± 1.19, $P = 0.04$; energy level: 6.68 ± 1.74 vs. 7.17 ± 1.54, $P = 0.03$) (Figure 7.2). After excluding IPAAs with leaks, the CGQL did not differ between the two groups (Ta-IPAA:0.75 ± 0.11 vs. Abd-IPAA: 0.72 ± 0.15; $P = 0.21$) and all three individual components were also comparable (Figures 7.1 and 7.2). The 24-h stool frequency values among the two groups were also comparable with 78% and 79% having a stool frequency of less than 10 in Ta-IPAA and Abd-IPAA, respectively ($P = 0.77$) (Figure 7.3). Patients reporting at least one episode of major incontinence during the 12-month period were also comparable between the two groups (Ta-IPAA: 27% vs. Abd-IPAA: 26%; $P = 0.8$) (Figure 7.4). Pouch failure rates at 12 months were comparable for the two groups (1% vs. 3%; $P = 0.85$) (Figure 7.5).

Total mesorectal excision vs. close rectal dissection

The overall CGQL score was comparable in the total mesorectal excision (TME) and close rectal dissection (CRD) subgroups ($P = 0.14$). Stool frequency rates and major incontinence rates also did not show a significant difference (Table 7.2). However, a higher stool frequency rate (> 10/24 h) was reported in the CRD group (15% vs. 27%).

Postoperative sexual function

Subgroup analysis included 13 males from each cohort, 16 females from the transabdominal group and five patients from the transanal group. The median IEFS-5 for Abd-IPAA was 20.84 (SD 3) and for Ta-IPAA was 19.69 (SD 6.7). Women in the Abd-IPAA group reported a median FSFI of 17.12 (SD 10) compared with 18.86 (SD 8.7) for the Ta-IPAA group (Figure 7.6).

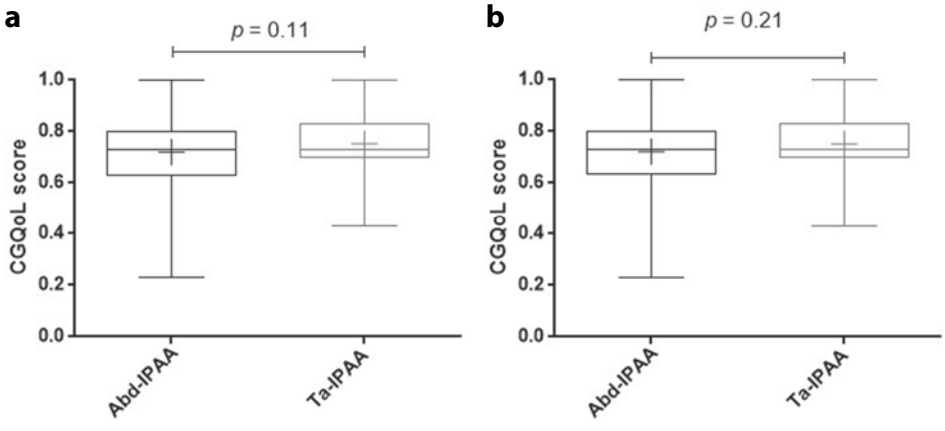


Figure 7.1. Comparison of overall CGQL [a] including anastomotic leaks and [b] excluding anastomotic leaks.

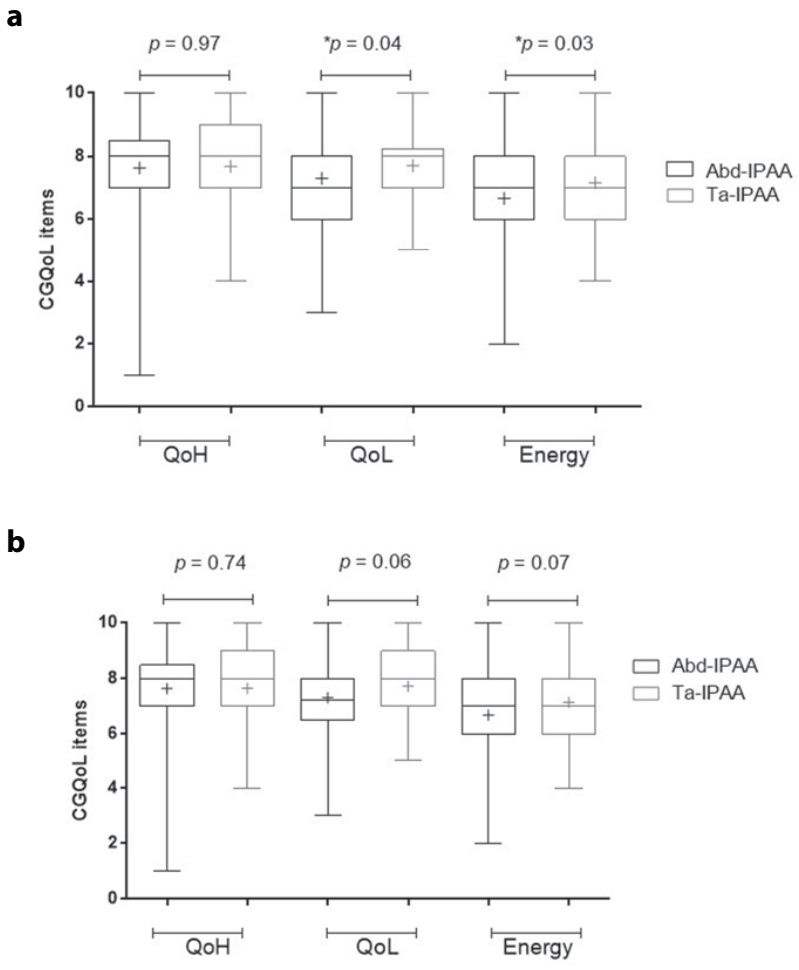


Figure 7.2. Comparison of individual components of the CGQL [a] including anastomotic leaks and [b] excluding anastomotic leaks.

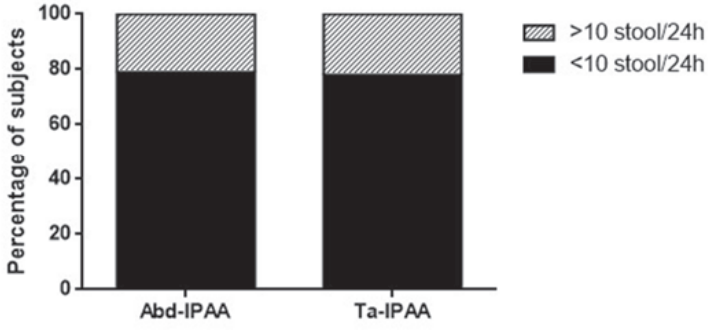


Figure 7.3. Comparison of 24-h stool frequency rates.

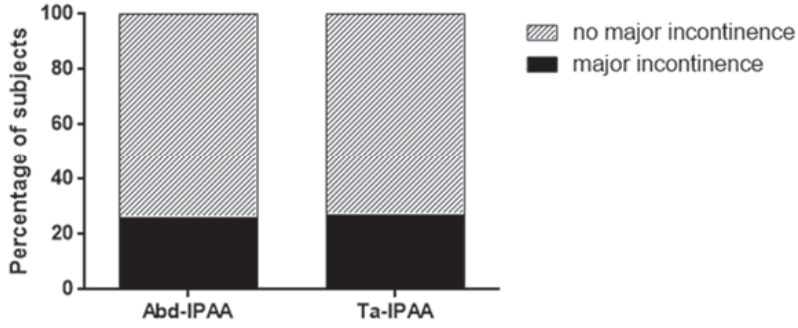


Figure 7.4. Comparison of major incontinence rates.

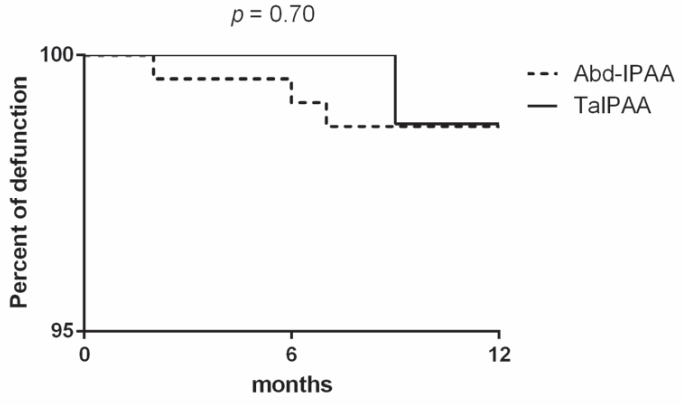


Figure 7.5. Comparison of pouch survival rates between Ta-IPAA and Abd-IPAA.

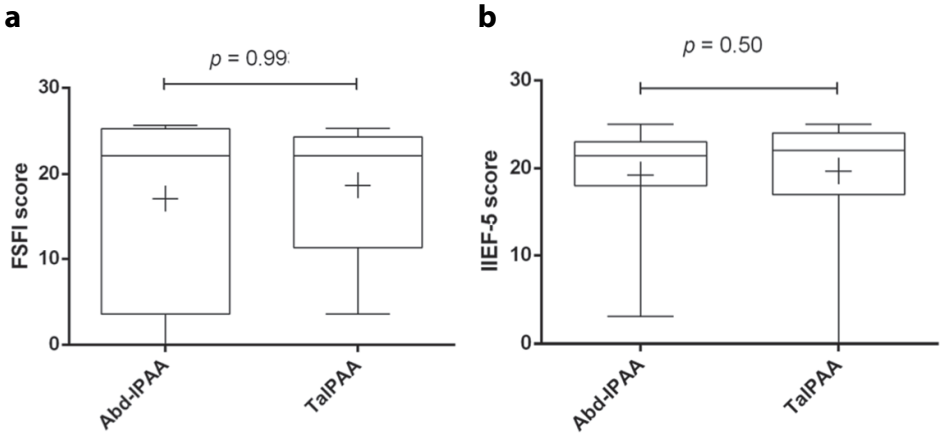


Figure 7.6. Compariosn of [a] International Erectile Function Score-5 (IEFS-5) and [b] Female Sexual Function Index (FSFI).

Table 7.2. Comparison of quality of life function between close rectal dissection and total mesorectal excision in Ta-IPAA

	TME	CRD	*P* value
Stool frequency at 12 months, % (n)	N = 40	N = 56	
< 10 stools/ 24 hours	85% (34)	73% (41)	
> 10 stools/ 24 hours	15% (6)	27% (15)	0.21
Major incontinence	N = 41	N = 59	
Episode of major incontinence/ 12 months	5% (2)	8%(5)	0.25
Quality of life	N = 41	N = 57	
CGQL score	0.77 ± 0.12	0.73 ± 0.11	

Discussion

To date, this is the first study evaluating the long-term outcomes of Ta-IPAA vs. Abd-IPAA in restorative proctocolectomy. Our results showed that Ta-IPAA is associated with comparable quality of life and improved quality of health and energy level compared to Abd-IPAA. Furthermore, a significantly lower severe complication rate and a non-significant lower anastomotic leak rate were found with the transanal approach.

De Buck van Overstraeten and colleagues have shown that the odds of a short-term postoperative complication is 0.52 times lower in Ta-IPAA for UC compared to the transabdominal approach.[28] They also reported an insignificant yet favourable difference in anastomotic leak rates with the transanal approach. Anastomotic leaks are known to result in poor functional outcome. Therefore, an additional analysis was carried out comparing CGQL scores excluding confirmed anastomotic leaks in the two cohorts. In the comparison of quality of life excluding leaks, mean CGQL scores remained comparable. The quality of life and quality of energy scores, which were significantly different in the original cohort (leaks included), were also comparable after correction for leaks.

An argument against use of the transanal approach is presumed sphincter damage due to insertion of the transanal port. The rates of reported incontinence in both cohorts are comparable in the current study, indicating that there is no increased risk of incontinence. The apparently high rates of 26% and 27% relate to those who have experienced at least one major episode of major incontinence during the period of 12 months. However, individual figures need to be interpreted with care because these are patient-reported data and are subjective assessments.

The CGQL score has been validated against previously used quality of life scores such as SF36.[17] Fazio and colleagues validated the questionnaire amongst a cohort of patients who underwent IPAA for colitis with conventional laparoscopic and open surgery, and reported a strong correlation with existing tools.[29] The CGQL score has

the advantage of being simple and easy to administer while assessing quality of life comprehensively.[19,30] Although less sensitive than more complex questionnaires, the authors felt it was appropriate for the assessment of a large population with a longer follow-up. The CGQL scores reported by Fazio and colleagues in a larger cohort are comparable to those reported by the cohorts in the current study.[19] Although Fazio and colleagues observed that CGQL scores improved after the first 2 years from surgery, there is evidence to suggest that pouch function at 1 year accurately represents long-term outcome.[31] By comparing transanal and transabdominal IPAA performed at the same centres we aimed to eliminate any biases due to postoperative management and social demographics. Both laparoscopic and open IPAA were grouped as Abd-IPAA as there is compelling evidence to suggest that the long-term and short-term outcomes from open, hand-assisted and total laparoscopic procedures are comparable.[26,32] This is probably because an abdominal incision is required for specimen retrieval.

Stool frequency has been shown to be a significant contributor to quality of life after pouch surgery. A frequency of 10 or more bowel movements per 24 h is considered to have a significant influence on quality of life.[33] In this cohort both groups showed similar percentages of patients having a stool frequency of more than 10, in line with the comparable CGQL scores.

In subgroup analysis, no difference in quality of life outcome was noted between the TME and CRD groups. The non-significant increased stool frequency in the CRD group is of interest because reduced pelvic space for the pouch in CRD has been a concern. However, a cohort with a larger number of patients is required to draw a conclusion in this regard. Data on postoperative sexual function were available for only a small subgroup. The comparison did not show a difference between the abdominal or transanal approach. Although the numbers are not adequate to draw a conclusion, the absence of a significant difference suggests that the transanal approach does not more seriously affect the pelvic nerves. Similar comparable results have been reported by authors comparing transanal with transabdomoinal surgery for rectal cancer.[34,35]

Transanal surgery has gained in popularity since the latter part of the last decade for both rectal cancer and benign disease. Transanal resection of the rectum has now been established as a successful procedure and in some situations has been shown to have better outcomes to its comparators.[7,16,36] The application of this technique in inflammatory bowel disease was limited to enthusiasts and thus robust long-term functional and outcome data are limited. Unlike in cancer surgery specimen quality is not a performance indicator in proctectomy for colitis allowing for close rectal dissection or intra-mesorectal dissection. This reduces the risk of pelvic nerve and urethral injury that is highlighted by opponents of the transanal technique in cancer surgery.

A major limitation of this study is the difference in time periods of the two cohorts. Assessment of the Abd-IPAA cohort started before the Ta-IPAA cohort for obvious yet inevitable reasons. The surgical approach with regard to diversion of the IPAA, preoperative medication and techniques may have undergone change during the period along with other unmeasured or unknown confounding factors. However, because all patients selected for Ta-IPAA after it became the standard procedure were included in the assessment a possible selection bias is avoided. We have also compared pouch function and failure rates at 12 months for both cohorts to eliminate a bias from longer follow-up times. These results may not be able to be generalized because all procedures were performed at tertiary care centres by experts in the transanal approach. Conversely, this fact eliminates the learning curve effect on the transanal procedure during the initial phase and evidence is emerging to suggest that the safety and short-term outcomes are not affected by technical variation amongst experts.[37]

This study has shown that the transanal approach to pouch surgery provides equivalent quality of life and functional results to the abdominal approach for ileoanal pouch surgery.

Acknowledgments
We thank all participating patients and supporting operating room staff from the three institutions: Amsterdam UMC, St. Mark's Hospital London and Humanitas Hospital Milan.

References

1. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol. 2012;107(8):1228-1235.
2. Bartels SA, Gardenbroek TJ, Ubbink DT, Buskens CJ, Tanis PJ, Bemelman WA. Systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis. Br J Surg. 2013;100(6):726-733.
3. Sahami S, Bartels SA, D'Hoore A, et al. A Multicentre Evaluation of Risk Factors for Anastomotic Leakage After Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(7):773-778.
4. Sahami S, Buskens CJ, Fadok TY, et al. Defunctioning Ileostomy is not Associated with Reduced Leakage in Proctocolectomy and Ileal Pouch Anastomosis Surgeries for IBD. J Crohns Colitis. 2016;10(7):779-785.
5. Vignali A, Elmore U, Milone M, Rosati R. Transanal total mesorectal excision (TaTME): current status and future perspectives. Updates in Surgery. 2019;71(1):29-37.
6. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc. 2010;24(9):2200-2205.
7. Pellino G, Sahnan K, Penna M, et al. Transanal minimally invasive proctectomy with ileal pouch anal anastomosis (Ta-IPAA) in patients with ulcerative colitis: a cohort study from the TaTME international database. J Crohns Colitis. 2018;12:S12-S13.
8. Levic Souzani K, Nielsen CB, Bulut O. Transanal completion proctectomy with close rectal dissection and ileal pouch-anal anastomosis for ulcerative colitis. Asian J Endosc Surg. 2018.
9. Bartels SAL, Gardenbroek TJ, Aarts M, et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. The British journal of surgery. 2015;102(3):281-287.
10. Rink AD, Radinski I, Vestweber KH. Does mesorectal preservation protect the ileoanal anastomosis after restorative proctocolectomy? J Gastrointest Surg. 2009;13(1):120-128.
11. Marks JH, Myers EA, Zeger EL, Denittis AS, Gummadi M, Marks GJ. Long-term outcomes by a transanal approach to total mesorectal excision for rectal cancer. Surg Endosc. 2017;31(12):5248-5257.
12. Deijen CL, Tsai A, Koedam TW, et al. Clinical outcomes and case volume effect of transanal total mesorectal excision for rectal cancer: a systematic review. Tech Coloproctol. 2016;20(12):811-824.
13. Koedam TW, van Ramshorst GH, Deijen CL, et al. Transanal total mesorectal excision (TaTME) for rectal cancer: effects on patient-reported quality of life and functional outcome. Tech Coloproctol. 2017;21(1):25-33.
14. Burke JP, Martin-Perez B, Khan A, et al. Transanal total mesorectal excision for rectal cancer: early outcomes in 50 consecutive patients. Colorectal Dis. 2016;18(6):570-577.
15. Keller DS, Reali C, Spinelli A, et al. Patient-reported functional and quality-of-life outcomes after transanal total mesorectal excision. Br J Surg. 2019;106(4):364-366.
16. de Buck van Overstraeten A, Wolthuis AM, D'Hoore A. Transanal completion proctectomy after total colectomy and ileal pouch-anal anastomosis for ulcerative colitis: a modified single stapled technique. Colorectal Dis. 2016;18(4):O141-144.
17. Fazio VW, O'Riordain MG, Lavery IC, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Annals of surgery. 1999;230(4):575-584; discussion 584-576.
18. Coffey JC, Winter DC, Neary P, Murphy A, Redmond HP, Kirwan WO. Quality of life after ileal pouch-anal anastomosis: an evaluation of diet and other factors using the Cleveland Global Quality of Life instrument. Diseases of the colon and rectum. 2002;45(1):30-38.
19. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg. 2013;257(4):679-685.
20. Fazio VW, Zutshi M, Remzi FH, et al. A Randomized Multicenter Trial to Compare Long-Term Functional Outcome, Quality of Life, and Complications of Surgical Procedures for Low Rectal Cancers. Annals of Surgery. 2007;246(3):481-490.
21. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Prev Med. 2007;45(4):247-251.

22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications - A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery. 2004;240(2):205-213.
23. Rhoden EL, Telöken C, Sogari PR, Vargas Souto CA. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. International Journal of Impotence Research. 2002;14(4):245-250.
24. Carpenter JS, Jones SMW, Studts CR, et al. Female Sexual Function Index Short Version: A MsFLASH Item Response Analysis. Arch Sex Behav. 2016;45(8):1897-1905.
25. Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. Dis Colon Rectum. 2001;44(12):1800-1807.
26. Polle SW, van Berge Henegouwen MI, Slors JF, Cuesta MA, Gouma DJ, Bemelman WA. Total laparoscopic restorative proctocolectomy: are there advantages compared with the open and hand-assisted approaches? Dis Colon Rectum. 2008;51(5):541-548.
27. Maartense S, Bemelman WA, Gerritsen van der Hoop A, Meijer DW, Gouma DJ. Hand-assisted laparoscopic surgery (HALS): a report of 150 procedures. Surg Endosc. 2004;18(3):397-401.
28. de Buck van Overstraeten A, Mark-Christensen A, Wasmann KA, et al. Transanal Versus Transabdominal Minimally Invasive (Completion) Proctectomy With Ileal Pouch-anal Anastomosis in Ulcerative Colitis. Annals of Surgery. 2017;266(5):878-883.
29. Delaney CP, Remzi FH, Gramlich T, Dadvand B, Fazio VW. Equivalent function, quality of life and pouch survival rates after ileal pouch-anal anastomosis for indeterminate and ulcerative colitis. Ann Surg. 2002;236(1):43-48.
30. Fazio VW, O'Riordain MG, Lavery IC, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg. 1999;230(4):575-584; discussion 584-576.
31. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg. 2007;94(3):333-340.
32. Gu J, Stocchi L, Geisler DP, Kiran RP. Staged restorative proctocolectomy: laparoscopic or open completion proctectomy after laparoscopic subtotal colectomy? Surg Endosc. 2011;25(10):3294-3299.
33. Brandsborg S, Nicholls RJ, Mortensen LS, Laurberg S. Restorative proctocolectomy for ulcerative colitis: development and validation of a new scoring system for pouch dysfunction and quality of life. Colorectal Dis. 2013;15(12):e719-725.
34. Pontallier A, Denost Q, Van Geluwe B, Adam J-P, Celerier B, Rullier E. Potential sexual function improvement by using transanal mesorectal approach for laparoscopic low rectal cancer excision. Surgical Endoscopy. 2016;30(11):4924-4933.
35. Veltcamp Helbach M, Koedam TWA, Knol JJ, et al. Quality of life after rectal cancer surgery: differences between laparoscopic and transanal total mesorectal excision. Surgical Endoscopy. 2019;33(1):79-87.
36. Penna M, Hompes R, Arnold S, et al. Transanal Total Mesorectal Excision International Registry Results of the First 720 Cases. Annals of Surgery. 2017;266(1):111-117.
37. Zaghiyan K, Warusavitarne J, Spinelli A, Chandrasinghe P, Di Candido F, Fleshner P. Technical variations and feasibility of transanal ileal pouch-anal anastomosis for ulcerative colitis and inflammatory bowel disease unclassified across continents. Tech Coloproctol. 2018;22(11):867-873.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 8

Endo-sponge assisted early surgical closure of ileal pouch-anal anastomotic leakage preserves long-term function: a cohort study

Karin A Wasmann, Maud A Reijntjes, Merel E Stellingwerf, Cyriel Y Ponsioen, Christianne J Buskens, Roel Hompes, Pieter J Tanis, Willem A Bemelman

JCC. 2019; 13(12): 1537-45

Abstract

Background and aims: Endo-sponge (Braun Medical) assisted early surgical closure (ESC) is an effective treatment to control pelvic sepsis after ileal pouch-anal anastomosis (IPAA) leakage, and became standard treatment in our centre from 2010 onwards. The aim of this cohort study was to assess the long-term pouch function of ulcerative colitis (UC) patients treated with ESC or conventional management (CM) for anastomotic leakage after IPAA.

Methods: Consecutive patients who underwent an IPAA for UC between 2002 and 2017 were included. Patients treated with ESC (2010–2017) or CM (2002–2009) for anastomotic leakage were compared with control patients without anastomotic leakage of the corresponding time period. Main endpoints were long-term pouch function on a 3-point scale and pouch failure, as measured with the validated pouch dysfunction score questionnaire.

Results: Some 280 of 334 patients (84%) returned the pouch dysfunction questionnaire, of whom 18 were treated with ESC and 22 with CM for anastomotic leakage. Control cohorts included 133 (2010–2017) and 107 patients (2002–2009). Between ESC-treated patients and control patients, pouch function ($P = 0.647$) and pouch failure rates (0/18 versus 5/133, $P > 0.99$) were similar. CM resulted in worse pouch function ($P = 0.016$) and a higher pouch failure rate (5/22 versus 5/107, $P = 0.013$) compared with control patients.

Conclusions: ESC, in contrast to CM, for IPAA leakage in UC patients is associated with preservation of pouch function and preclusion of pouch failure, probably due to early and effective treatment of pelvic sepsis.

Introduction

Despite improvements of medical treatment strategies, a colectomy is still required in up to 20% of ulcerative colitis (UC) patients.[1,2] For these patients, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the treatment of choice. Anastomotic leakage occurs in up to 15% of these patients.[3–5] Inadequately managed pelvic sepsis considerably affects long-term pouch function, due to postponement of stoma reversal, pouch fistulas, and pouch fibrosis, all of which are associated with pouch failure. Consequently, anastomotic leakage is the main cause of pouch failure (31%).[5–7]

The conventional management (CM) of anastomotic leakage entails a passive approach by diversion with ileostomy and occasional drainage of the presacral abscess cavity. Subsequently, a wait-and-see approach is adopted. However, the healing process can take up to months, possibly affecting functional outcomes.[8] Aiming at a quick and efficient control of pelvic sepsis, active management of anastomotic leakage by Endo-sponge (Braun Medical, Melsungen, Germany) assisted early surgical closure (ESC) was implemented in our centre in 2010. ESC entails a short course of transanally inserted Endo-sponge (Braun Medical) therapy to clean the presacral cavity and to facilitate early surgical closure of the anastomotic defect.[9] The short-term results of this approach were very promising, revealing a 100% successful closure rate after a median of 7 weeks compared with 52% at 6 months after CM without significant differences in direct medical costs.[10]

Thus far, long-term results of ESC have not been reported. It is expected that the active ESC strategy, in contrast to the passive CM approach, preserves long-term pouch function due to effective control of pelvic sepsis. The aim of this study was to compare the long-term pouch function and pouch failure rate after ESC versus CM in UC patients with anastomotic leakage after IPAA.

Material and methods

Design and patients

Consecutive patients who underwent IPAA in the Amsterdam UMC between January 2002 and October 2017 were prospectively maintained in the institutional IPAA database. Anastomotic leakage was confirmed either by radiological imaging or during surgical exploration within 90 days following IPAA surgery.[11] From January 2010 onwards, patients with an anastomotic leakage after IPAA were managed with ESC. Patients treated with CM for anastomotic leakage between January 2002 and December 2009 were retrospectively identified. Adult UC and inflammatory bowel disease unclassified (IBDU) patients who underwent IPAA were screened for eligibility. Exclusion criteria were: patients with an indication for IPAA due to familial adenomatous polyposis (FAP),

Crohn's disease, or colorectal cancer, postoperative diagnosis of Crohn's disease in the pouch, redo-pouch surgery only in the study period, anastomotic leakage detected later than 3 months after IPAA surgery, leakage treatment strategies not in accordance with the ESC or CM principles, a functioning IPAA of less than 1 year, cognitive inability to reply to the questionnaire, deceased during follow-up, and non-responders to the questionnaire. This study was waived from review of the medical ethics boards on March 9, 2016, since the prospective data collection, as well as the questionnaire, did not interfere with the psychological integrity of the patients. Reporting of the data adheres to the STROBE Statement.[12] All participants provided written informed consent.

Procedures

Ileal pouch-anal anastomosis

The IPAA was created during initial proctocolectomy, or at the time of completion proctectomy. The IPAA was not routinely defunctioned. Patients had an intraluminal pouch drain decompressing the pouch, which was removed the sixth day after surgery. Anastomotic leakage was diagnosed with C-reactive protein (CRP) levels at day 4 and 7 after pouch creation and with contrast enhanced CT imaging for any suspicion of a leak (see flowchart, Figure 8.1a and b). Patients who developed anastomotic leakage underwent immediate pouch defunctioning if not done primarily. During the study period, the laparoscopic approach, as the modified two-stage procedure, became standard of care (stage 1: subtotal colectomy with end-ileostomy in order to improve clinical condition before restorative surgery, e.g., by discontinuing medication and optimising nutrition status, and stage 2: completion proctectomy with IPAA without diverting ileostomy).

Endo-sponge (Braun Medical) assisted early surgical closure

ESC has been described previously.[9,10] In short; in addition to the diversion, an Endo-sponge (Braun Medical) was inserted endoscopically and exchanged under light sedation every 3 to 4 days at the endoscopy room. Admission was not required for Endo-sponge (Braun Medical) therapy. After discharge, outpatient appointments were made to change the Endo-sponge (Braun Medical). When the cavity was clean without significant proximal pouch retraction, transanal suture closure was performed under general anaesthesia in a short hospital admittance. Anastomotic integrity was assessed endoscopically 2 weeks after surgical closure. Subsequently, CT with intraluminal contrast was used to exclude presacral fluid collections. If closure failed, ESC was repeated.

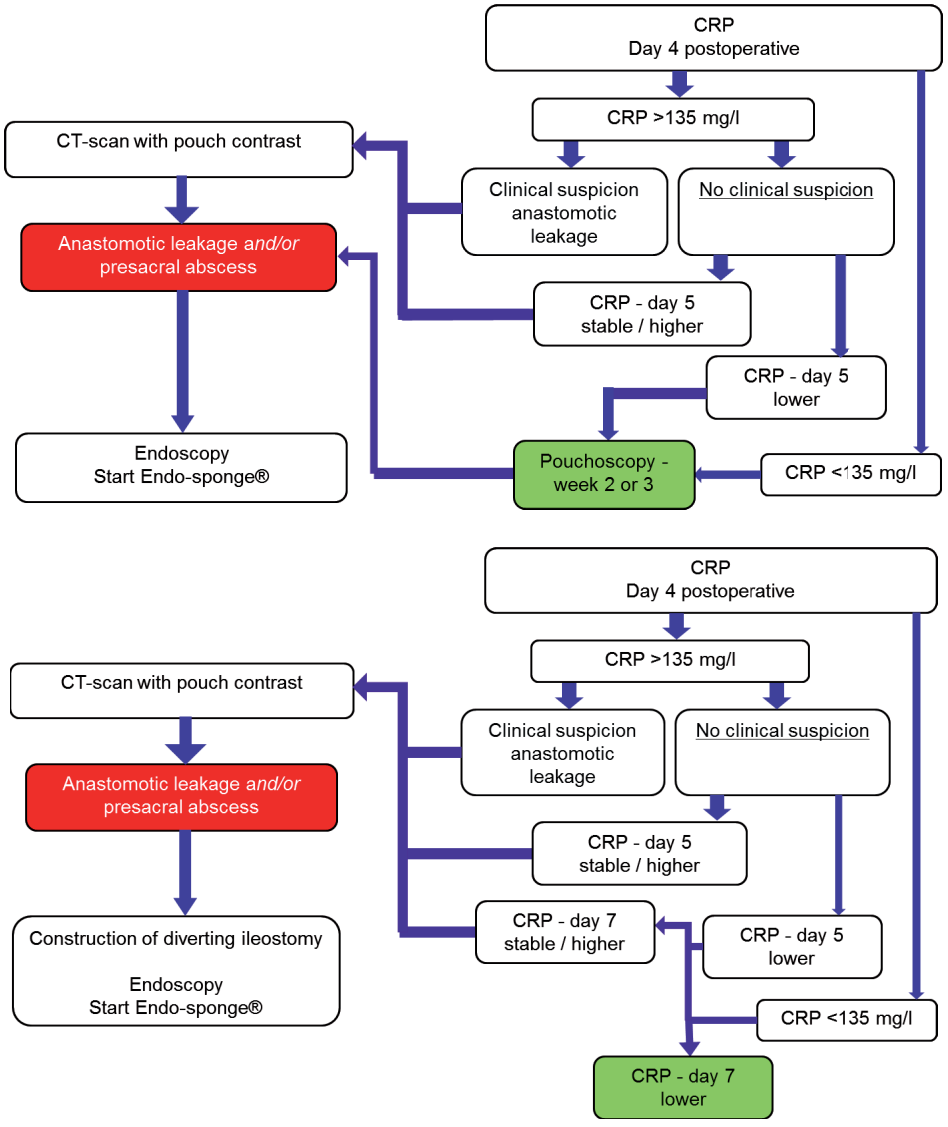


Figure 8.1. a] Postoperative management algorithm of early detection of anastomotic leakage in the diverted pouch. b] Postoperative management algorithm of early detection of anastomotic leakage in the non-diverted pouch.
CRP, C-reactive protein; CT, computed tomography. *Pouch drain is removed at Day 6.

Conventional management

CM of IPAA leakage consisted of diversion combined with transabdominal, transgluteal, or transanal drainage of the presacral abscess cavity. A wait-and-see policy was adopted and progress of anastomotic healing was regularly checked by either contrast enema X-ray or endoscopy. Removal of the drain and reversal of the ileostomy was planned when complete healing was confirmed.

Outcomes

The primary outcome was pouch function which was measured with the validated pouch dysfunction questionnaire (Figure 8.2).[13] Eligible patients were sent an invitation to participate in the study, together with information on the study and the questionnaire. Patients who did not initially respond, were contacted by telephone to encourage return of the questionnaire. Pouch function contained three categories: 'none to minor' dysfunction, 'some to major' dysfunction, and 'pouch failure'. Pouch failure was defined as the requirement of a permanent stoma with or without pouch excision. Patients were asked if they had a stoma. If not, the questionnaire assessed incomplete emptying, number of bowel movement/24 h, major incontinence, use of anti-diarrhoeal medication, and urgency, as these factors have a significant impact on quality of life (QoL) (score of 0 to 7.5 points). Based on the derived scores, patients were categorised into: 'none to minor' dysfunction (0–<2.5 points), 'some to major' dysfunction (≥ 2.5 points), or pouch failure.

Additionally, in supplementary analysis of this study, the reliability of the pouch dysfunction questionnaire was investigated. Therefore, along with the questionnaire, patients were also asked to report the impact of pouch dysfunction on QoL on a 4-point scale (none, minor, some, or major impact on QoL).

Secondary outcomes were pouch failure, treatment-specific details, and short-term results of ESC and CM. Treatment specific details included type of CM drainage, the number of Endo-sponge (Braun Medical) changes (during and after discharge), the

Questions	Score
1. How many times per 24 hours in the last 2 weeks have you had a feeling of incomplete emptying?	
Never or less than 1 per 24 hours	0
1-4 per 24 hours	1
More than 4 times per 24 hours	2
2. Number of bowel-movements per 24 hours in the last 2 weeks	
Less than 10 per 24 hours	0
10 or more per 24 hours	1
3. How many times have you had uncontrolled loss of stools in the last 2 weeks?	
Never	0
Once or more	1
4. Have you used anti-diarrhoeal medication for pouch problems in the last 2 weeks?	
No	0
Yes	0.5
5. Did you have a sudden and severe urge to defecate in the last 2 weeks?	
No	0
If yes, how long can you defer the urge to defecate?	
More than ½ hour	0
More than 5 minutes up to ½ hour	1
5 minutes or less	3

Figure 8.2. Pouch dysfunction score.

0 points was classified as no symptoms which does not interfere with QoL and was scored as pouch dysfunction; > 0 & < 2.5 points was classified as mild symptoms which does not interfere with QoL and was scored as minor pouch dysfunction; 2.5 points was classified as moderate to severe symptoms which interfare with QoL and was scored as some to major pouch dysfunction.

number of Endosponges (Braun Medical) used, and duration of Endo-sponge (Braun Medical) treatment. Short-term results were time from IPAA to anastomotic leakage diagnosis, time from diagnosis to starting treatment, anastomotic closure at 6 months (chronic pelvic sepsis), time from diagnosis to observed closure on imaging, complications of anastomotic leakage treatment within 90 days, and time to ileostomy reversal.

Statistical analysis

Descriptive data were reported as mean ± standard deviation (SD) or median with interquartile range (IQR) according to the distribution. Normally distributed numerical data were analysed with unpaired t test for two subgroups or one-way analysis of variance (ANOVA) for three subgroups. Not normally distributed numerical data were analysed with the Mann–Whitney U test for two subgroups or Kruskal-Wallis for three subgroups. Categorical data were analysed with the chi-square or Fisher's exact test, as appropriate. The functional outcomes of the ESC treated patients were compared with control patients without anastomotic leakage within the same study period (2010–2017). CM treated patients were compared with control patients within the same study period (2002–2009). Pouch function was assessed with the chi-square test for trend. Pouch failure over time was analysed using Kaplan-Meier analysis and compared with log-rank test.

To test the relation between the pouch dysfunction score and QoL, derived from the pouch dysfunction score (0–7.5), using one-way ANOVA and unpaired *t*-test as appropriate; $P < 0.05$ was considered statistically significant. For statistical analyses, SPSS Statistics, version 24 (IBM Corp., Armonk, New York, USA) was used.

Results

Patients

Some 334 patients out of 493 patients who underwent IPAA surgery between January 2002 and October 2017 were eligible. The main exclusion criterion was FAP (n = 108, Supplementary Figure S8.1). Of the eligible patients, 280 returned the pouch dysfunction questionnaire (84% response rate). Two of the 54 patients who did not return the questionnaire had anastomotic leakage after IPAA, both treated conventionally before 2010. Baseline characteristics between responders and the non-responders were not significantly different (Supplementary Table S8.1).

The mean age of the 280 included patients was 38 years (SD 13) and 53% were male. Forty patients (14%) had anastomotic leakage after IPAA. Eighteen were treated with ESC (2010–2017) and 22 patients with CM (2002–2009). The corresponding control cohorts included 133 patients (2010–2017) and 107 patients (2002–2009). In 70 IPAA patients

(25%) a primary diverting ileostomy was constructed during IPAA surgery. At baseline, patients treated with ESC compared with CM, were more often operated according to the modified two-stage and less often received immunosuppressive medication within 3 months before surgery (Table 8.1). When comparing baseline characteristics of ESC and CM patients with the corresponding control patients of the same time period, no difference in baseline characteristics or treatment characteristics remained (Table 8.1).

Long-term pouch function and failure

The overall median time of follow-up was 8 years (IQR 4–12). Median follow-up time was significantly shorter after ESC compared with CM (4 years (IQR 3–6) and 13 years (IQR 10–15), $P < 0.001$). When comparing both treatment strategies with the corresponding control groups, the follow-up time was similar (ESC 4 years (IQR 3–6) versus control (2010–2017) 4 years (IQR 2–6, $P = 0.664$) and (CM 13 years (IQR 10–15) versus control (2002–2009) 12 years (IQR 10–14), $P = 0.673$). Overall, 175 patients (62.5%) had 'none to minor' pouch dysfunction, 90 patients (32.1%) had 'some to major' pouch dysfunction, and 15 patients (5.4%) had pouch failure. Long-term pouch function is shown in Figure 3. When comparing the 18 ESC-treated patients with 133 controls, no difference in pouch function could be observed ($P = 0.647$). In contrast, the 22 CM-treated patients had significantly worse pouch function compared with the 107 controls ($P = 0.016$). Regarding pouch failure, no difference was observed between ESC-treated patients and control patients (0/18, 0.0% versus 5/133, 3.8%, $P > 0.99$), whereas CM-treated patients had a significant higher pouch failure rate compared with controls (5/22, 22.7% versus 5/107, 4.7%, $P = 0.013$). This significant association of pouch failure with CM compared with controls remained after Kaplan-Meier analysis (pouch preservation of 81% versus 96%, $P = 0.009$, respectively Figure 8.4).

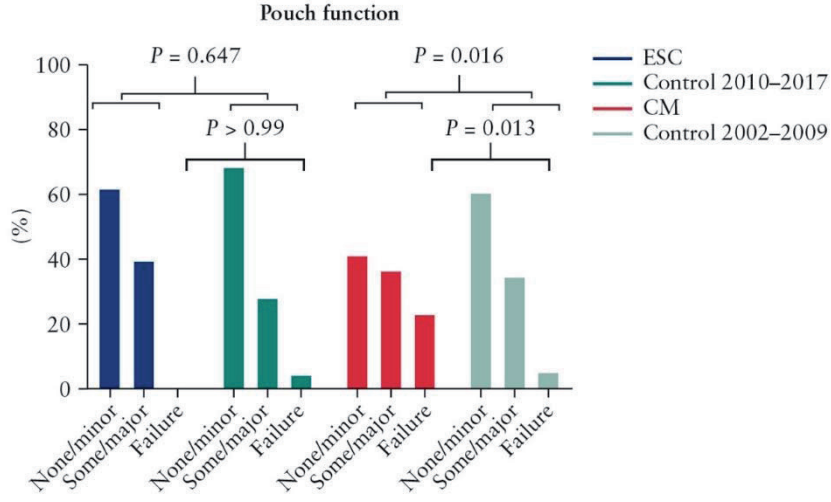


Figure 8.3. Long-term pouch function.

Table 8.1. Baseline characteristics

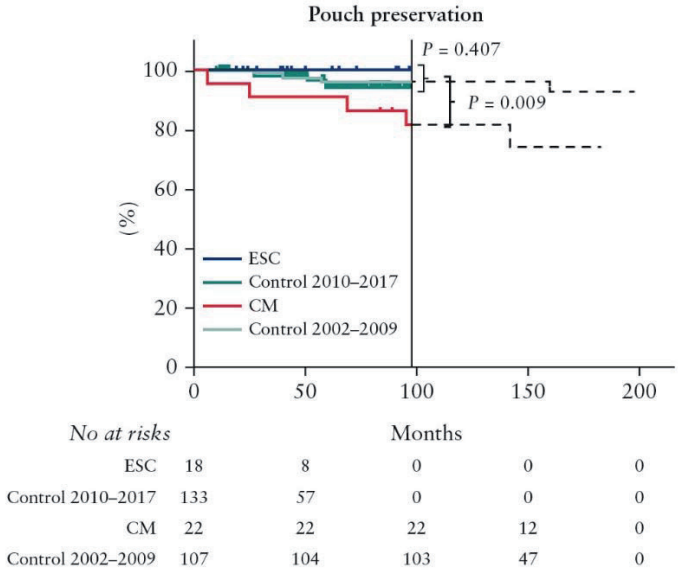
Total n = 280		Anastomotic leakage				*P* value between leakage groups	No leakage Control 2002–2009		*P* value Conv. vs. control	No leakage Control 2010–2017		*P* value ESC vs. control
		Conventional 2002–2009		ESC 2010–2017								
		n = 22	7.9%	n = 18	6.4%		n = 107	38.2%		n = 133	47.5%	
Gender (M)		11	50.0%	12	66.7%	0.35	57	53.3	0.82	68	51.1%	0.32
Age at IPAA surgery Mean (SD)		34.68	(12.98)	40.56	(14.48)	0.19	38.95	10.83	0.16	36.8	(13.55)	0.31
Diagnose[a]	UC	18	81.8%	17	94.4%	0.36	92	86.0	0.74	128	96.2%	0.54
	IBDU	4	18.2%	1	5.6%		15	14.0		5	3.8%	
ASA score	1	7	31.8%	4	22.2%	0.60	31	29.0	0.92	25	19.0%	0.86
	2	14	63.6%	14	77.8%		70	65.4		103	78.0%	
	3	1	4.5%	0	0.0%		6	5.6		4	3.0%	
BMI (kg/m^2)	Mean (SD)	23.95	(3.86)	25.36	(4.58)	0.34	23.64	(3.52)	0.76	23.56	(4.65)	0.16
Smoking	Yes	2	9.1%	5	27.8%	0.37	7	6.5	0.35	18	13.5%	0.27
	No	16	72.7%	11	61.1%		90	84.1		100	75.2%	
	Previously	3	13.6%	2	11.1%		7	6.5		15	11.3%	
	Unknown	1	4.5%	0	0.0%		3	2.8		0	0.0%	
Preoperative	None	7	33.3%	16	88.9%	0.001	41	41.1	0.78	107	81.7%	0.66
medication[b]	Steroids	6	28.6%	1	5.6%		23	23.0		7	5.3%	
	AZA/6MP/MTX	7	33.3%	0	0.0%		33	33.0		11	8.4%	
	Anti-TNF	1	4.8%	1	5.6%		3	3.0		6	4.6%	

Table 8.1 continues on next page

Table 8.1. ***Continued***

Total n = 280		Anastomotic leakage				*P* value between leakage groups	No leakage Control 2002–2009		*P* value Conv. vs. control	No leakage Control 2010–2017		*P* value ESC vs. control
		Conventional 2002–2009		ESC 2010–2017								
		n = 22	7.9%	n = 18	6.4%		n = 107	38.2%		n = 133	47.5%	
IPAA stages	1-stage	14	63.6%	4	22.2%	0.001	38	35.5	0.14	7	5.3%	0.08
	2-stage	3	13.6%	0	0.0%		27	25.2		9	6.8%	
	Mod 2-stage	4	18.2%	13	72.2%		28	26.2		103	77.4%	
	3-stage	1	4.5%	1	5.6%		14	13.1		14	10.5%	
IPAA	Open	9	40.9%	3	16.7%	0.22	52	49.5	0.32	35	26.7%	0.62
Procedure[c]	Laparoscopic	4	18.2%	5	27.8%		5	4.8		41	31.3%	
	Hand-assisted	9	40.9%	10	55.6%		48	45.7		55	42.0%	
J-pouch design		22	100%	18	100%	n/a	103	97.2	> 0.99	127	96.9%	> 0.99
Primary diversion		4	18.2%	1	5.6%	0.36	41	38.3	0.09	24	18.2%	0.31
Abscess size (cm^3) Mean (SD)[d]		177.0	(151.40)	116.0	(106.2)	0.22	n/a			n/a		

[a] Preoperative diagnosis of CU or IBDU was based on results from colonoscopy and pathology reports. [b] Immunosuppressive drug usage was defined as such when patients used steroids, immunomodulators (azathioprine (AZA), 6-mercaptopurine (6MP), and methotrexate (MTX)), or anti-tumour necrosis factor-alpha (anti-TNF) within 12 weeks prior to IPAA, considering the anti-TNF half-life.[14] In case of steroids, patients had to use more than 20 mg/day.[5] [c] The approach of the colectomy was considered laparoscopic in case of a single port, multiport or hand-assisted approach, and open if the colectomy was performed via a median laparotomy or Pfannenstiel incision without the use of any ports. [d] Initial abscess size (cm^3) associated with the anastomotic leakage was measurement at maximum size by an abdominal CT scan; the length was measured on sagittal or axial plane, the height on sagittal or axial plane, the width of the cavity on the coronal or axial plane.



No at risks					
ESC	18	8	0	0	0
Control 2010–2017	133	57	0	0	0
CM	22	22	22	12	0
Control 2002–2009	107	104	103	47	0

Figure 8.4. Pouch failure over time.

Secondary outcomes

Treatment details and short-term results are shown in Table 8.2. Time to diagnosis and time to starting treatment were comparable between ESC- and CM-treated patients. All anastomoses after ESC were successfully closed at 6 months (Figure 8.5). One ESC-treated patient required a second course of ESC due to a failed anastomotic closure, as demonstrated on the 2 week post-ESC endoscopy. In comparison with CM, ESC resulted in significantly more anastomotic closures in a shorter period of time: 100% closure after a median of 30 days versus 67% closure after a median of 76 days. Treatment-related complications occurred in two patients, both treated with CM by transgluteal drainage. In one patient, a recurrent abscess developed 6 months after initial drain placement. The other patient developed a fistula in the former drain tract, which remained symptomatic for 2 years. Median time to stoma reversal was 4 months in both the ESC (IQR 3–6) and the CM group (IQR 3–13). This was for both treatment strategies (significantly) later compared with the corresponding control patients (2010–2017, n = 27 and 2002–2009, n = 38) who received a defunctioning ileostomy at IPAA surgery in the absence of anastomotic leakage (both control groups median 3 months (IQR 2–4), control versus ESC; $P = 0.052$ and control versus CM; $P = 0.018$).

Table 8.2. Treatment details

	CM n = 22	ESC n = 18	*P* value
Treatment specific details			
Transabdominal drain, n	14		
Transgluteal drain, n	4		
Transanal drain, n	4		
No Endo-sponge® changes p.p. mean SD		2.7 (1.4)	
No Endo-sponge® changes after discharge, n %		23 / 48 (47.9%)	
No Endo-sponge® used p.p. mean SD		3.2 (1.7)	
Time Endo-sponge® treatment (days) median IQR		11 (5–15)	
Complications of anastomotic leakage treatment, n %	2 (9.1 %)	0 (0.0%)	n/a
Time to diagnosis (days) median IQR	8 (6–17)	9 (7–13)	0.87
Anastomotic closure at 6 months, n %	14 (66.7 %)[a]	18 (100.0%)	0.01
Time till anastomotic closure (days) median IQR	76 (49–339)[b]	30 (17–40)	< 0.001
Time to stoma reversal (months), median IQR	4 (3-13)[b]	4 (3-6)	0.43

CM, conventional management; ESC, Endo-sponge [Braun Medical] assisted early surgical closure; p.p., per patient; SD, standard deviation; IQR, interquartile range; n/a, not applicable. [a] One patient in the CM group was excluded from this analysis, as leakage follow-up was stopped after 3 months since an end-ileostomy was created due to pouch failure. At last check-up for leakage at 3 months, leakage still persisted. [b] Three patients in the CM group were excluded from this analysis since leakage follow-up was stopped after a persistent stoma was created. The same three patients were excluded from the time to stoma reversal analysis, as the stoma was never reversed due to persistent leakage problems. Time to starting treatment [days] was comparable between CM and ESC, as treatment started in all patients within 24 h after diagnosis.

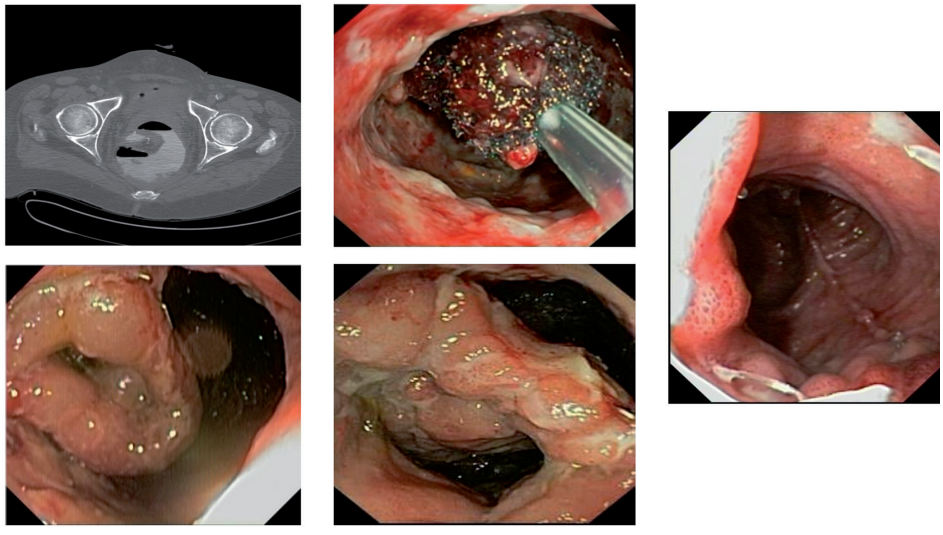


Figure 8.5. Endo-sponge [Braun Medical] assisted early surgical closure.
Day 0: anastomotic leakage. Day 3: after first Endo-sponge change. Day 14: after surgical closure.

Discussion

For the treatment of anastomotic leakage after IPAA surgery in UC patients, ESC is associated with the preservation of pouch function and the pouch, whereas CM is associated with significantly worse pouch function and a higher pouch failure rate compared with controls. Moreover, ESC preserves pouch function despite anastomotic leakage. The present study is the first report on long-term outcomes of ESC treatment for anastomotic leakage after IPAA.

Anastomotic leakage is the main cause of pouch dysfunction and pouch failure (33%).[15–19] The impact is probably even bigger, as silent chronic leaks are responsible for one-third of therapy-refractory chronic pouchitis.[20] A pro-active treatment strategy of anastomotic leakage using ESC, resulted in a quicker restoration of the anastomotic integrity in all patients. In contrast, after the passive CM approach, one-third of the leaks persisted. Time to diagnosis and time to starting treatment were similar between ESC- and CM-treated patients. Consequently, the effectiveness of the ESC strategy in controlling pelvic sepsis in the short-term is presumably the basis of the improved pouch function in the long-term. Following these study results, it remains unknown which factor resulted in the preservation of pouch function (e.g., Endo-sponge (Braun Medical) or early surgical closure). However the whole strategy, in which Endo-sponge (Braun Medical) therapy facilitates early surgical closure, seems promising as it reduces time of pelvic sepsis. Therefore, this strategy should become standard care for the treatment of anastomotic leakage.

To increase the results of ESC in daily clinical practice, early diagnosis of the anastomotic leakage is essential. Late initiation (> 3–6 weeks) of ESC is less successful, because the chronic sepsis may have already affected the pouch compliance, causing retraction of anastomotic edges precluding surgical closure. As such, a strict postoperative algorithm to monitor the integrity of the anastomosis has been designed using the negative predictive value of CRP (see flowchart, Figure 8.1a and b).[21] Although literature is conflicting,[22] most studies point towards the direction that it safe to omit pouch diversion (modified two-stage).[23–26] The 14% leak rate in this study represents the total leak rate and not the generally used 30 days and in-hospital leak rates in diverted pouches. These rates should not be compared with each other, since a considerable percentage of leaks are diagnosed late and are not included in the reported leak rate. According to literature looking at leaks rates at 1 year after IPAA surgery, the number is between 15% and 20%.[3,4,27] Therefore, leak rates depend on the time frame chosen to report outcomes, explaining the discrepancy between studies. These study results, following the early diagnosis of the leaks using CRP, CT scanning, and pouchoscopy (Figure 8.1b of the manuscript) in combination with the 'back-up plan' ESC, support the policy to primarily refrain from diverting ileostomies, as the pelvic sepsis can be controlled in a timely manner.

The limitations of this study include the small number of patients with anastomotic leakage. Nevertheless, the differences in pouch function and failure between ESC and CM cannot be ignored. Furthermore, the intuitive logic of improved long-term results based on improved leakage control may also be a prominent factor advocating for ESC. The inevitable difference in time period between ESC and CM limits the study, as with time the approach concerning diversion of the IPAA, preoperative medication, and laparoscopy changed. Additionally, likely unknown or unmeasured confounders changed over time. It would be inappropriate to build a multivariable model because of the small leakage numbers. Therefore, it was decided to not directly compare ESC with CM. Instead, we analysed the results of both strategies in comparison with the control patients of the same study period. Between both strategies and their controls, none of these baseline differences occurred any more. However, since the ESC and the corresponding controls had a shorter follow-up time compared with CM and the corresponding control group, the pouch failure rates in these groups might be underestimated. Yet, it is questionable if a longer follow-up would also lead to a significant increase of pouch failures, as a persistent leak seems prevented with ESC. Furthermore, the analyses seems justified, as the pouch failure rates of both control groups were comparable. Moreover, the significant association of CM with pouch failure also remained after the Kaplan-Meier analyses for 7 years (i.e., the maximum follow-up of the ESC and corresponding control group). As treatment allocation for pouch leakage (ESC or CM) was only dependent on time (standard treatment before or after 2010), it is unlikely that selection bias has occurred. The generalisability of the results is limited, as it is a single-centre study. Inversely, as ESC was only performed in an expert centre, the influence of a learning curve on the results is restricted.

The response rate to the questionnaire was greater than 80% to the validated questionnaire, without baseline differences between non-responders and responders, ensuring a high external validity. Furthermore, the reliability of the novel pouch dysfunction questionnaire has been endorsed.[13] Pouch dysfunction is a key patient-reported outcome. Following the supplementary analyses, the pouch dysfunction score is highly associated with the patient-reported dysfunction on QoL (i.e., a higher pouch dysfunction score represents an increased patient-reported impact on QoL, Supplementary Table S8.2). However, 'some' negative impact on QoL could not be distinguished from 'major' negative impact on QoL. This was also seen in the validation study. Likely, this group was underpowered, since only 21 (8%) patients reported a major negative impact on QoL due to pouch dysfunction symptoms. It is postulated that the majority of patients with such severe dysfunction actually already had pouch failure.

In conclusion, in contrast to CM, the ESC approach is associated with the preservation of pouch function and preclusion of pouch failure. This observation is likely related to the quick resolution of anastomotic leakage, precluding chronic pelvic sepsis.

Funding
This work was supported by the company B. Braun Medical B.V. grant number 22225, without having any influence on the trial design, data collection and analysis, interpretation of results, or manuscript development.

Acknowledgment
T. Mackay, MD, for English editing.

References

1. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol 2012;107:1228–35.
2. Sahami S, Konté K, Buskens CJ, et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. United European Gastroenterol J 2017;5:554–62.
3. Sossenheimer PH, Glick LR, Dachman A, et al. Abnormal pouchogram predicts pouch failure even in asymptomatic patients. Dis Colon Rectum 2018;62:463–9.
4. Santorelli C, Hollingshead J, Clark SK. Clinical value of pouchogram prior to ileostomy closure after ileal pouch anal anastomosis. Tech Coloproctol 2018;22:541–4.
5. Sahami S, Bartels SAL, D'Hoore A, et al. A multicentre evaluation of risk factors for anastomotic leakage after restorative proctocolectomy with ileal pouch-anal anastomosis for inflammatory bowel disease. J Crohns Colitis 2016;10:773–8.
6. de Buck van Overstraeten A, Mark-Christensen A, Wasmann KA, et al. Transanal versus transabdominal minimally invasive (completion) proctectomy with ileal pouch-anal anastomosis in ulcerative colitis: a comparative study. Ann Surg 2017;266:878–83.
7. Bartels SA, Gardenbroek TJ, Aarts M, et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. Br J Surg 2015;102:281–7.
8. Weidenhagen R, Gruetzner KU, Wiecken T, Spelsberg F, Jauch KW. Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method. Surg Endosc 2008;22:1818–25.
9. Verlaan T, Bartels SA, van Berge Henegouwen MI, Tanis PJ, Fockens P, Bemelman WA. Early, minimally invasive closure of anastomotic leaks: a new concept. Colorectal Dis 2011;13(Suppl 7):18–22.
10. Gardenbroek TJ, Musters GD, Buskens CJ, et al. Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem. Colorectal Dis 2015;17:426–32.
11. Caulfield H, Hyman NH. Anastomotic leak after low anterior resection: a spectrum of clinical entities. JAMA Surg 2013;148:177–82.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
13. Brandsborg S, Nicholls RJ, Mortensen LS, Laurberg S. Restorative proctocolectomy for ulcerative colitis: development and validation of a new scoring system for pouch dysfunction and quality of life. Colorectal Dis 2013;15:e719–25.
14. Ternant D, Aubourg A, Magdelaine-Beuzelin C, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. Ther Drug Monit 2008;30:523–9.
15. Forbes SS, O'Connor BI, Victor JC, Cohen Z, McLeod RS. Sepsis is a major predictor of failure after ileal pouch-anal anastomosis. Dis Colon Rectum 2009;52:1975–81.
16. Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. Ann Surg 2003;238:605–14; discussion 614–7.
17. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. Ann Surg 2003;238:229–34.
18. Sagap I, Remzi FH, Hammel JP, Fazio VW. Factors associated with failure in managing pelvic sepsis after ileal pouch-anal anastomosis (IPAA) – a multivariate analysis. Surgery 2006;140:691–703; discussion 703–4.
19. Lightner AL, Dattani S, Dozois EJ, Moncrief SB, Pemberton JH, Mathis KL. Pouch excision: indications and outcomes. Colorectal Dis 2017;19:912–6.
20. van der Ploeg VA, Maeda Y, Faiz OD, Hart AL, Clark SK. The prevalence of chronic peri-pouch sepsis in patients treated for antibiotic-dependent or refractory primary idiopathic pouchitis. Colorectal Dis 2017;19:827–31.
21. Warschkow R, Beutner U, Steffen T, et al. Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. Ann Surg 2012;256:245–50.
22. Mark-Christensen A, Erichsen R, Brandsborg S, et al. Pouch failures following ileal pouch-anal anastomosis for ulcerative colitis. Colorectal Dis 2018;20:44–52.
23. Weston-Petrides GK, Lovegrove RE, Tilney HS, et al. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. Arch Surg 2008;143:406–12.

24. Mennigen R, Senninger N, Bruewer M, Rijcken E. Pouch function and quality of life after successful management of pouch-related septic complications in patients with ulcerative colitis. Langenbecks Arch Surg 2012;397:37–44.
25. Sahami S, Buskens CJ, Fadok TY, et al. Defunctioning ileostomy is not associated with reduced leakage in proctocolectomy and ileal pouch anastomosis surgeries for IBD. J Crohns Colitis 2016;10:779–85.
26. Mark-Christensen A, Erichsen R, Brandsborg S, et al. Pouch failures following ileal pouch-anal anastomosis for ulcerative colitis. Colorectal Dis 2018;20:44–52.
27. Widmar M, Munger JA, Mui A, et al. Diverted versus undiverted restorative proctocolectomy for chronic ulcerative colitis: an analysis of long-term outcomes after pouch leak short title: outcomes after pouch leak. Int J Colorectal Dis 2019;34:691–7.

Supplementary Table S8.1. Baseline patient and treatment characteristics questionnaire responders and non-responders

Total n = 334		Responders n = 280	84%	Non-responders n = 54	16%	*P* value
Gender (M)		148	52.9%	31	57.4%	0.737
Age at IPAA surgery	Mean (SD)	38	(13)	31	(11)	0.193
Diagnose	UC	255	91.1%	47	87.0%	0.580
	IBDU	25	8.9%	7	13.0%	
ASA score	1	67	24.0%	16	29.6%	0.655
	2	201	72.0%	36	66.7%	
	3	11	4.0%	2	3.7%	
BMI	Mean (SD)	24	(4)	24	(5)	0.672
Smoking	Yes	32	11.4%	6	11.1%	0.785
	No	217	77.5%	42	77.8%	
	Previously	27	9.6%	4	7.4%	
	Unknown	4	1.4%	2	3.7%	
Preoperative medication	None	170	65.0%	27	50.0%	0.380
	Steroid	34	13.0%	9	16.6%	
	Azathioprine	49	18.8%	15	27.8%	
	Biologicals	11	4.2%	3	5.6%	
Time functioning IPAA, years	Mean (SD)	8	(4)	9	(4)	0.677
IPAA stages	1-stage	63	22.5%	9	16.7%	0.419
	2-stage	39	13.9%	11	20.4%	
	Modified 2-stage	148	52.9%	27	50.0%	
	3-stage	30	10.7%	7	12.9%	
J-pouch design		270	96.4%	54	100.0%	0.693
Primary diversion		70	25.0%	19	35.2%	0.222
Postoperative complications (CD ≤ 3)*	None	152	55.0%	30	53.6%	0.460
	CD 1-2	52	18.6%	14	25.9%	
	CD 3-4	74	26.4%	10	15.5%	
Type	Conventional	22	7.9%	2	3.7%	0.081
	ESC	18	6.4%	0	0%	
	Control	240	85.7%	52	96.3%	

* All complications within 30 days of surgery or during first admission were reported by means of the Clavien-Dindo classification, a complication ≥ 3 was considered a severe complication (re-intervention, Intensive Care management, or causing death).[1] All anastomotic leaks, intra-abdominal abscesses and deep wound infections were reported as surgical site infections.[2]

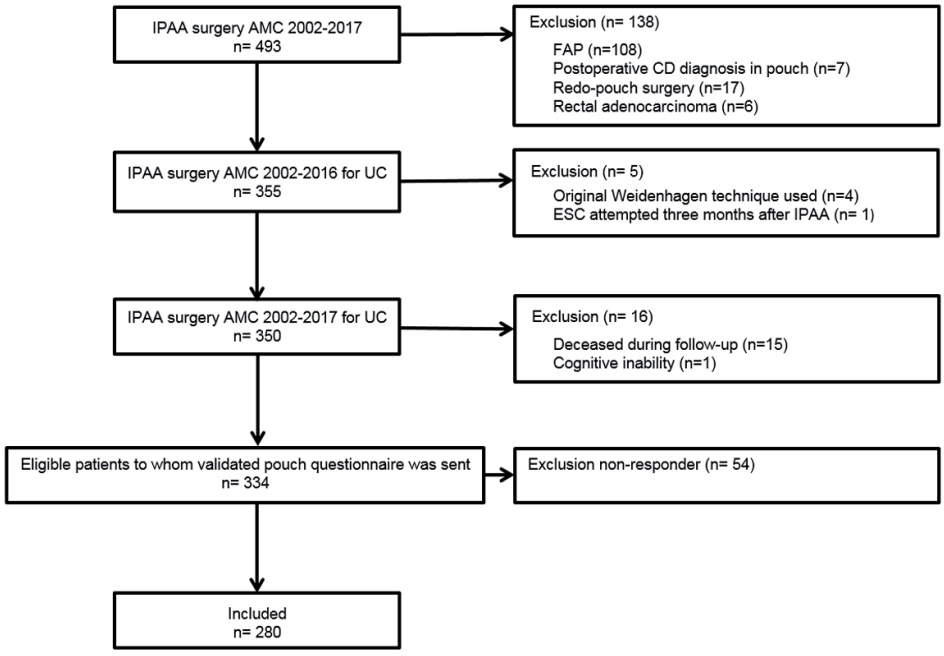
References

1. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg [Internet]. 2009 Aug [cited 2017 Jun 19];250(2):187–96. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-200908000-00002
2. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. J Am Coll Surg [Internet]. 2016 Jan 1 [cited 2018 Feb 23];224(1):59–74. Available from: http://dx.doi.org/10.1016/j.jamcollsurg.2016.10.029

Supplementary Table S8.2. Reliability of pouch dysfunction questionnaire: Differences between the reported impact of pouch dysfunction on QoL and PDS. Additional to the questionnaire, patients were also asked how the pouch function impacted their QoL. Fifty-five patients reported no -, 96 mild -, 77 some - and 21 major negative affect on QoL.

Impact of pouch dysfunction on QoL	n	Pouch dysfunction score (0–7.5) Mean (SD)	*P* value
No negative affect on QoL	55	0.75 (0.96)	< 0.001*
Mild negative affect on QoL^	96	1.44 (1.28)	
Some negative affect on QoL#	77	2.40 (1.65)	
Major negative affect on QoL‡	21	3.81 (1.82)	

* One-way anova, overall difference $P < 0.001$
^ T-test, no vs. mild, $P = 0.042$
# T-test, mild vs. some, $P = 0.007$
‡ T-test, some vs. major, $P = 0.571$



Supplementary Figure S8.1. In- and exclusion flowchart.
IPAA, ileal pouch-anal anastomosis; FAP, familial adenomatous polyposis; CD, Crohn's disease; UC, ulcerative colitis; ESC, Endo-Sponge® assisted early surgical closure; CM, conventional management.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Chapter 9

The impact of rectal stump inflammation after subtotal colectomy on pouch outcomes in ulcerative colitis patients

Karin A Wasmann, Eline M van der Does de Willebois, Lianne Koens, Marjolijn Duijvestein, Willem A Bemelman, Christianne J Buskens

JCC. 2020; Online ahead of print.

Abstract

Background and aims: Proctitis after subtotal colectomy with ileostomy for ulcerative colitis (UC) is common, but its impact on short- and long-term outcome after pouch surgery is unknown. The aim of this study was to determine the incidence of proctitis after subtotal colectomy and its impact on postoperative morbidity and pouchitis.

Methods: The distal margin of the rectal stump of all consecutive patients undergoing completion proctectomy and pouch procedure for UC, between 1999 and 2017, was revised and scored for active inflammation according to the validated Geboes score, and for diversion proctitis. Pathological findings were correlated to complications after pouch surgery and pouchitis (including therapy-refractory) using multivariate analyses.

Results: Out of 204 included patients, 167 (82%) had active inflammation in the rectal stump and diversion colitis was found in 170 specimens (83%). Overall postoperative complications and anastomotic leakage rates were not significantly different between patients with and without active inflammation in the rectal stump (34.7% vs. 32.4%, $P = 0.79$, and 10.2% vs. 5.4%, $P = 0.54$, respectively). Active inflammation of the rectal stump was significantly associated with the development of pouchitis (54.3% vs. 25.5%, *plog* = 0.02), as well as with therapy refractory pouchitis (14% vs. 0%, *plog* = 0.05). Following multivariate analysis, active inflammation was an independent predictor for the development of pouchitis. Diversion proctitis showed no association with these outcome parameters.

Conclusions: Active inflammation in the rectal stump after subtotal colectomy occurs in 80% of UC patients and is a predictor for the development of pouchitis and therapy-refractory pouchitis.

Introduction

Despite improvements in medical treatment strategies, a colectomy is still required in up to 20% of ulcerative colitis (UC) patients.[1,2] For these patients, subtotal colectomy with ileostomy, followed by completion proctectomy and reconstruction with ileal pouch-anal anastomosis (IPAA), is the treatment of choice.[3] In the era of extensive treatment with biologics, it is preferred to perform the IPAA some months after the subtotal colectomy (modified two- and three-stage IPAA) to enable patients to recover and wean off drugs.[4,5] Proctitis in the rectal stump after subtotal colectomy is common. It is unclear how often proctitis occurs, what the origin of the proctitis is, and what the consequences are for early- and long-term results after pouch surgery. It is suggested that patients with active inflammation in the rectal stump are at increased risk for anastomotic leakage during IPAA surgery.[6] In addition, it has been speculated that patients with persistent active inflammation in the rectal stump, despite subtotal colectomy, have a different prognostic phenotype of UC and are at higher risk of pouchitis when compared with patients with no (diversion) proctitis[7,8]—specially since pouchitis is hardly ever seen in patients undergoing pouch procedure for familial adenomatous polyposis coli (FAP).[9]

The aim of this study was to determine the incidence of active inflammation and diversion proctitis in the rectal stump after a subtotal colectomy in UC patients, and to correlate these pathological findings to short- and long-term outcomes.

Materials and methods

Patients

All consecutive UC patients who underwent a subtotal colectomy with end ileostomy, followed by a completion proctectomy with pouch procedure with or without a defunctioning ileostomy (modified stage two- or three-stage procedure), between January 1999 and October 2017 at the Amsterdam UMC, Amsterdam, the Netherlands, were included from a prospectively maintained database. Patients: with Crohn's disease, colorectal dysplasia, or carcinoma requiring total mesenteric excision; younger than 18 years; or who underwent a proctocolectomy and pouch procedure in one stage, and of whom the pathological resection specimen was not available or of too low quality to reassess microscopic examination; were excluded.[10] This study was granted a waiver from the medical ethics committee. Reporting of the data adheres to the STROBE Statement.[11]

Histological features

The primary endpoint was the number of patients with active inflammation in the rectal stump according to the validated Geboes grading system. For clinical relevance the distal margin of the rectal stump was scored, as UC generally starts distally with more pronounced inflammation.[12] After pouch surgery, the specimen was handled by the pathologist according to standard operating procedures, which included collection of the distal resection margin of the rectal stump in paraffin blocks. All haematoxylin and eosin (H&E)-stained slides of the distal margin were revised by a dedicated pathologist and two researchers blinded to clinical outcome. In case of inter-observer variation, consensus was established by re-evaluation of the slides using a multiheaded microscope.

The Geboes score (GS) consists of grades 0 to 5: 0] structural (architectural changes); 1] chronic inflammatory infiltrate; 2A] eosinophils in lamina propria; 2B] neutrophils in lamina propria; 3] neutrophils in epithelium (cryptitis); 4] crypt destruction; and 5] erosions or ulcerations. A higher score indicates more severe histological inflammation (see Supplementary Table 1, available as Supplementary data at ECCO-JCC online).[13] Recently, a GS cut-off of > 3, compared with the original cut-off of > 2, is suggested to be more clinically relevant in distinguishing between UC patients in histological remission or activity (also in the context of the Robarts Histopathology and Nancy Indexes).[14,15] Hence, active inflammation in the resection margin was defined as a GS of > 3. Within the GS 5.1–5.4 score, GS 5.1 and 5.2 were considered not applicable, as elements of active inflammation could not be reliably scored in an obliterated lumen.[16]

Diversion proctitis can also present as mucosal inflammation, but with different histopathological features allowing for discrimination of this entity from active inflammatory bowel disease. Diversion is defined as the occurrence of lymphoid follicular hyperplasia in the lamina propria.[17–20] Diversion proctitis is also scored in the distal margin. Consequently, patients could have pathological characteristics of both active and diversion proctitis in the same slide, which could result in overlapping groups.

Variables and outcomes

Patient and disease characteristics were collected from a prospectively maintained pouch database. Active inflammation in the rectal stump was correlated to postoperative complications and pouchitis.

Postoperative complications were defined as any deviation from the normal postoperative course within 90 days after IPAA creation. Complications were graded according to the Clavien-Dindo Classification, and included for analysis if the score was 2 or higher.[21] If a patient had more than one complication, only the most severe complication was graded. Anastomotic leakages were classified according to the required management as: Grade A, conservatively treated leakage (antibiotics); Grade

B, leakage requiring active therapeutic intervention (e.g., percutaneous drainage), but manageable without re-laparotomy/re-laparoscopy; and Grade C, leakage requiring surgical intervention.[22]

Patients were classified as having pouchitis if they were given medical therapy in the presence of clinical findings and/or endoscopic findings compatible with the diagnosis of pouchitis. Patients were categorised into three groups: one episode of pouchitis; multiple episodes; or therapy-refractory pouchitis. Therapy-refractory pouchitis was scored when patients required maintenance therapy or immunosuppressive therapy. Patients who were discharged from the Amsterdam UMC, and had their follow-up at the gastroenterology department of the referring hospital, were contacted by post, mail, or phone to assess frequency, dates, and treatment of pouchitis. If necessary the treating physician was contacted. Inflammation restricted to the remaining cuff, based on endoscopy, was defined as cuffitis.

Statistical analyses

Differences in baseline characteristics and postoperative outcomes, between patients with and without active inflammation in the distal margin of the rectal stump, were assessed using a chi square test for categorical variables, or in case of low counts (< 5), a Fisher's exact test; for numerical variables, the unpaired *t*-test was used. For normally distributed variables, mean and standard deviation (SD) were reported; for non-normally distributed variables, median and interquartile range (IQR) were reported. A kappa test was used to assess the overlap between pathological features. Kaplan-Meier analysis was used to compare the 10-year pouchitis-free survival with log rank testing. Confounders for the development of pouchitis were based on risk factors described in previous literature.[23] Using Cox regression, independent factors associated with pouchitis were identified. Variables with a *P* value of $P \leq 0.1$ in the univariable analyses were included in the multivariable model, after assessing multicollinearity; *P* values and confidence intervals (CI) were calculated at a 95% confidence level. For statistical analyses, SPSS Statistics, version 24 (SPSS, Chicago, IL) was used.

Results

Patients and histopathological findings

Out of 398 UC patients who had previouslyundergone subtotal colectomy (STC) followed by completion proctectomy with pouch surgery between January 1999 and October 2017 at the Amsterdam UMC, 204 patients could be included. The main exclusion criterion was one- or two-stage procedures (n = 109), and 21 patients had missing or low-quality histological distal margin rectal stump sections (Figure 9.1). There were 112 men (55%) and the median age was 38 years. A total of 34 patients

(17%) had been using suppositories or enemas (mainly steroids) to treat the rectal stump after subtotal colectomy within the 12 weeks preceding pouch surgery. In 37 patients (18%), no microscopic active inflammation was found in the rectal stump, all graded as GS 2. Of the 167 patients (82%) with a microscopically inflamed distal margin, most patients had a GS of 5.3 or 5.4 (n = 101). Diversion proctitis was demonstrated in 170 resection specimens (83%), and 142 patients (70%) had both active and diversion proctitis. Nine patients (4.4%) had no active inflammation and no diversion proctitis in the rectal stump (Table 9.1). Looking at baseline characteristics, the percentage of patients using anti-inflammatory medication to treat the rectal stump (suppositories

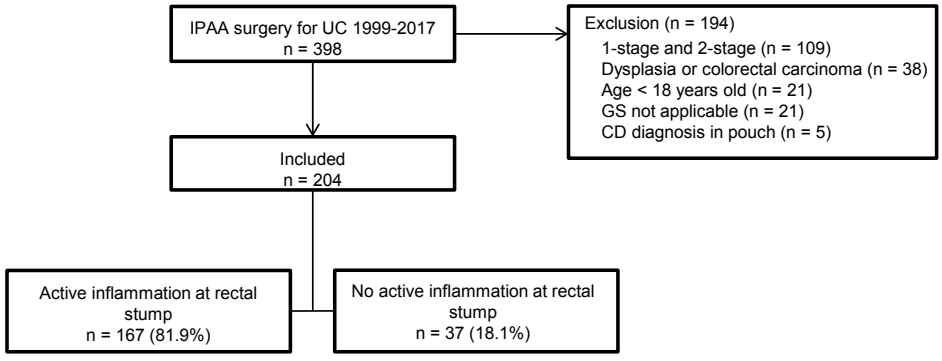


Figure 9.1. Study flowchart. IPAA, ileal pouch anal anastomosis.
GS, Geboes score; CD, Crohn's disease.

Table 9.1. Histological features in the distal margin of the rectal stump

Inflammation									
No active inflammation				**Active inflammation**					
GS 0	**GS 1**	**GS 2**		**GS 3**		**GS 4**		**GS 5**	
n = 0	**n = 0**	**n = 37**		**n = 14**		**n = 52**		**n = 101**	
		2.0	1 (0.5%)	3.0	0 (0.0%)	4.0	0 (0.0%)	5.0	0 (0.0%)
		2.1	3 (1.5%)	3.1	9 (4.4%)	4.1	5 (2.5%)	5.1	n.a.
		2.2	0 (0.0%)	3.2	5 (2.5%)	4.2	32 (15.7%)	5.2	n.a.
		2.3	33 (16.1%)	3.3	0 (0.0%)	4.3	15 (7.4%)	5.3	27 (13.2%)
Diversion proctitis n = 170 (83.3%)									
No active inflammation				**Active inflammation**					
		GS 2 and DP		GS 3 and DP		GS 4 and DP		GS 5 and DP	
		n = 28/37 (75.7%)		n = 10/14 (71.4%)		n = 47/52 (90.4%)		n = 85/101 (84.2%)	

DP occurred in 76% and 85% of patients with non-actively and actively inflamed rectal stumps, respectively, kappa 0.10.
GS, Geboes score; DP, Diversion proctitis.

or enemas) after STC and before pouch surgery was 18% and 11% in the group with and without an microscopically inflamed rectal stump in the resection specimen after pouch surgery, respectively, $P = 0.459$ (Table 9.2).

Table 9.2. Baseline characteristics

	Non-inflamed rectal stump n = 37 (18.1%)		Inflamed rectal stump n = 167 (81.9%)		*P* value
Sex (M)	20	54.1	92	55.1	0.909
Age at IPAA surgery (years), mean SD	35.6	11.9	38.0	11.9	0.782
Time of IPAA surgery					0.461
1999–2010	12	32.4	65	38.9	
2010–2017	25	67.6	102	61.1	
Time between STC and IPAA (months), mean SD	23.9	35.7	19.8	26.3	0.100
BMI (kg/m^2), mean SD	26.3	5.4	23.7	3.9	0.136
Diagnosis					0.498
UC	33	89.2	155	92.8	
IBDU	4	10.8	12	7.2	
PSC	2	5.4	3	1.8	0.224
ASA					> 0.99
I-II	35	97.2	161	96.4	
III-IV-V	1	2.8	6	3.6	
Smoking					0.490
No	26	78.8	106	66.3	
Previously	3	9.1	41	25.6	
Yes	4	12.1	13	8.1	
Complications after STC	6	16.2	36	21.5	0.578
Unknown (STC other center without clear rapport)	9	24.3	31	18.6	
UC left-sided	9	24.3	49	29.3	0.428
UC right-sided	3	8.1	5	3.0	
Pancolitis	11	29.7	57	34.1	
Toxic megacolon	7	18.9	25	15.0	
Unknown (preoperative scopy at other center not received)	7	18.9	31	18.6	
Rectal stump therapy before IPAA (< 12 weeks)	4	11.4	30	18.1	0.459
Steroid supp/enema usage	2	5.7	18	10.8	
Mesalazine supp/enema usage	2	5.7	12	7.2	
Systemic steroid usage before IPAA (< 12 weeks, > 20 mg/day)	0	0.0	12	7.2	0.132
Other systemic medication before IPAA < 12 weeks)[a]					0.547
None	35	97.2	146	87.4	
Mesalazine	1	2.8	10	6.0	
Thioprine	0	0.0	4	2.4	
Anti-TNF	0	0.0	7	4.2	

Table 9.2 continues on next page

Table 9.2. *Continued*

	Non-inflamed rectal stump n = 37 (18.1%)		Inflamed rectal stump n = 167 (81.9%)		*P* value
Pouch procedure					0.467
Open	16	43.2	79	47.6	
Hand-assisted laparoscopic	10	27.0	53	31.9	
Total laparoscopic	11	29.7	34	20.5	
Stage of pouch procedure					0.716
Modified two stage	31	83.8	133	79.6	
Three stage	6	16.2	34	20.4	

ASA, American Society of Anesthesiologists; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; STC, subtotal colectomy; M, male; IPAA, ileal ouch-anal anastomosis; SD, standard deviation; BMI, body mass index; PSC, primary sclerosing cholangitis; TNF, tumour necrosis factor.
[a] Immunosuppressive drug useage was defined as such when patients used steroids, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6MP], and methotrexate [MTX]), or anti-tumour necrosis factor-alpha [anti-TNF] within 12 weeks preceding IPAA, considering the anti-TNF half-life.[24] In case of steroids, patients had to use more than 20 mg/day.[25]

Postoperative complications

Overall complications after pouch surgery did not differ between the two groups (Table 9.3, $P = 0.790$). Seventeen patients (10%) with an actively inflamed rectum developed anastomotic leakage, which was not statistically significantly different from the two patients (5%) without rectal stump inflammation (Table 9.3, $P = 0.536$).

Table 9.3. Short- and long-term outcomes of patient with and without inflamed rectal stump

	No inflamed rectal stump n = 37 (18.1%)		Inflamed rectal stump n = 167 (81.9%)		*P* value
Overall complications	12	(32.4%)	58	(34.7%)	0.790
CD II	5	(13.5%)	25	(21.0%)	
CD III-IV	7	(18.9%)	33	(19.8%)	
Mortality	0	(0.0%)	0	(0.0%)	
Anastomotic leakage	2	(5.4%)	17	(10.2%)	0.536
Grade A	0	(0.0%)	0	(0.0%)	
Grade B	1	(2.7%)	1	(0.6%)	
Grade C	1	(2.7%)	16	(9.6%)	
10-year pouchitis	6	(25.5)*	68	(54.3%)*	0.024**
1 episode	0		22		
Multiple episode	6		46		
Therapy refractory	0		17		

* Cumulative percentages; ** *Plog* rank.

Pouchitis

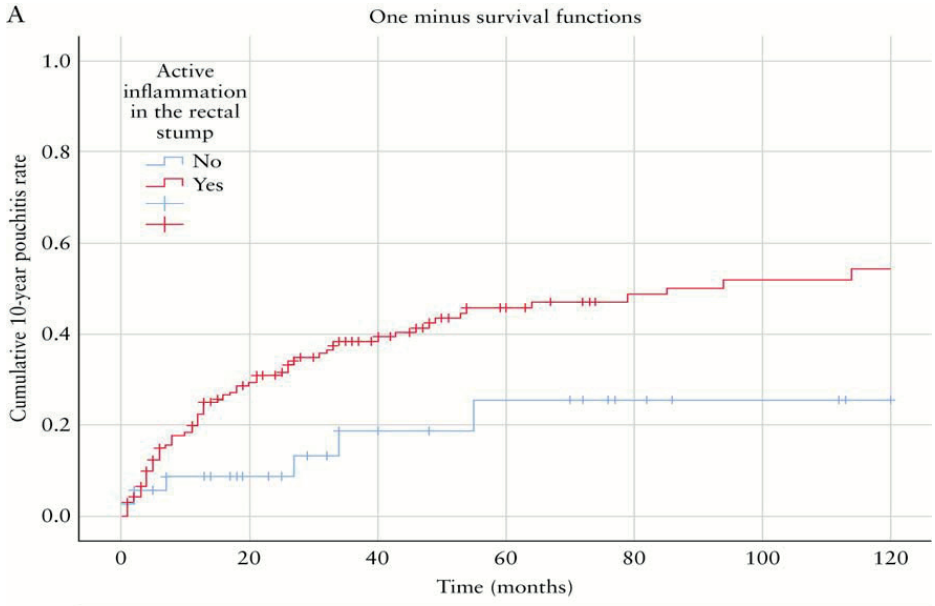
The median follow-up period was 5 years (IQR 2–9). The pouchitis follow-up was up to date for n = 175 (86%) of the patients. The 10-year pouchitis rate was 50%, and was significantly higher in the patient group with an inflamed rectal stump when compared with patients with a non-inflamed rectal stump (54% vs. 26%, *plog* = 0.024, respectively; Table 9.3 and Figure 9. 2a). Therapy-refractory pouchitis did not occur in patients without active inflammation in the rectal stump, and was significantly more frequently seen in patients with active inflammation (14% vs. 0%, *plog* = 0.054, Figure 9.2b). For patients with or without diversion proctitis the 10-year pouchitis rates were comparable (53% vs. 40%, *P* = 0.811). Cuffitis was observed in 17 patients. All these patients had an actively inflamed rectal stump. The 10-year cuffitis rate was not significantly different between patients with and without an inflamed rectal stump (17% vs. 0%, *P* = 0.074). In patients with inflammatory bowel disease unclassified (IBDU) the pouchitis rate was 80.5%.

In univariate analyses, active inflammation in the rectal stump, IBDU diagnosis, and receiving systemic steroid within 3 months before pouch surgery, were associated with the development of pouchitis. As all 12 patients who used systemic steroids within 3 months before pouch surgery had an inflamed rectal stump, steroid useage was excluded from the multivariate model due to multicollinearity. In multivariate analysis, inflammation in the rectal stump (hazard ratio [HR] 2.6, 95% CI: 1.1–6.0, *P* = 0.025) and

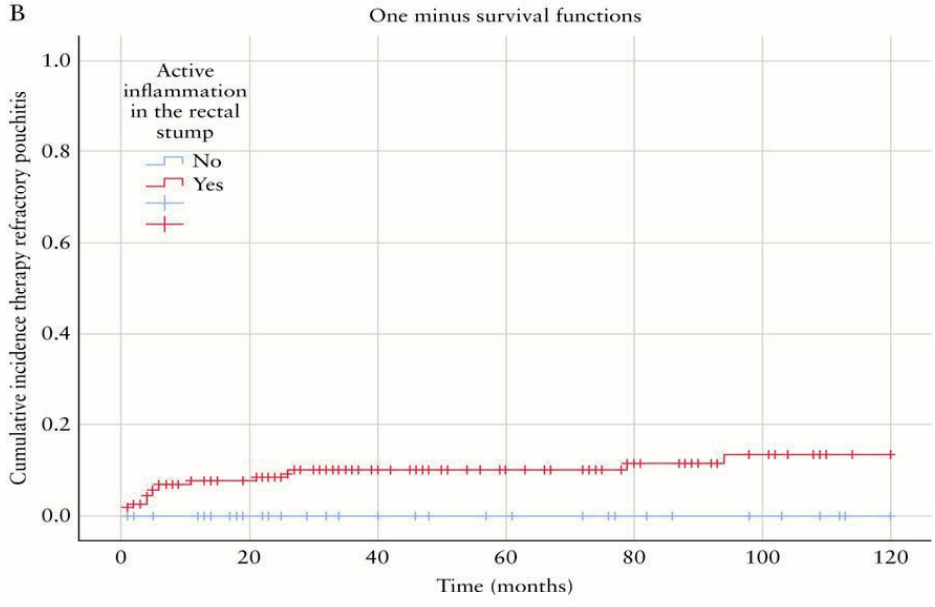
Table 9.4. Multivariate analyses

Risk factors for 10-year pouchitis	Univariate (HR and CI)	*P* value	Multivariate (HR and CI)	*P* value
Clinical factors				
Female	0.914 (0.579–1.445)	0.701		
Diagnosis IBDU (ref: UC)	2.455 (1.258–4.788)	0.008	2.544 (1.304–4.963)	0.006
PSC	1.417 (0.445–4.512)	0.556		
Smoking (ref: no)		0.554		
Previously	1.322 (0.794–2.202			
Yes	1.178 (0.513–2.615)			
Complications after STC	0.980 (0.563–1.706)	0.944		
UC location (ref: right-sided)		0.958		
Left-sided	0.833 (0.288–2.413)			
Pancolitis	0.757 (0.262–2.189)			
Toxic megacolon	0.833 (0.268–2.585)			
Rectal stump therapy before IPAA	0.203 (0.660–2.191)	0.547		
Systemic steroid usage before IPAA	2.725 (1.352–5.492)	0.005	-	
Preoperative medication any	1.001 (0.982–1.021)	0.891		
Anastomotic leakage	0.982 (0.450–2.141)	0.963		
Actively inflamed distal rectal stump	2.523 (1.094–5.815)	0.030	2.592 (1.124–5.978)	0.025
Diversion proctitis distal rectal stump	1.078 (0.581–2.002)	0.812		

UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; STC, subtotal colectomy; IPAA, ileal pouch-anal anastomosis; PSC, primary sclerosing cholangitis; HR, hazard ratio; CI, confidence interval.



No. at risk	T = 0y	T = 5y	T = 10y
No	37	12	2
Yes	167	45	19



No. at risk	T = 0y	T = 5y	T = 10y
No	37	16	3
Yes	167	82	34

Figure 9.2. [a] Kaplan-Meier curve 10-year pouchitis rate in patients with inflamed and non-inflamed rectal stump. [b] Kaplan-Meier curve 10-year therapy refractory pouchitis rate in patients with inflamed and non-inflamed rectal stump.

IBDU diagnosis (HR 2.5, 95% CI: 1.3–5.0, $P = 0.006$) remained significantly associated with the development of overall pouchitis (Table 9.4). Thirteen patients needed permanent defunctioning, of whom nine had pouchitis; all nine also had rectal stump inflammation. However, the incidence of therapy-refractory pouchitis and cuffitis was too low to perform multivariate analysis.

Discussion

This is the first study that systematically assessed inflammation in the rectal stump by a validated pathological scoring system, and correlated results to short- and long-term morbidity after pouch surgery. The study showed that the majority of patients (82%) had an actively inflamed rectal stump after subtotal colectomy, which was significantly associated with the development of pouchitis and therapy-refractory pouchitis. Active inflammation in the rectal stump was not significantly associated with overall postoperative complications or anastomotic leakage.

Previous studies suggested that it is difficult to differentiate between active inflammation and diversion colitis, as diversion colitis mimics or superimposes IBD changes.[26,27] Although discrimination might indeed be difficult endoscopically, microscopically the two pathological entities seem to present at different layers of the bowel wall. In this study, the entities were distinguished in the same H&E section. The occurrence of diversion proctitis (83%) is in accordance with previous series.[28] In contrast to active inflammation, diversion proctitis was not associated with any postoperative complication (including pouchitis). Notably, this difference was not caused by a big variation in occurrence rates between diversion proctitis and active inflammation, since these rates were comparable. In accordance with these findings, no other studies have described an association between diversion proctitis and pouchitis, although it occurs very often after deviation for any kind of indication (e.g., perforated diverticulitis, idiopathic obstipation, and incontinence). Additionally, FAP patients are not known to develop pouchitis, although diversion proctitis occurs frequently in these patients. Large series have demonstrated that primary sclerosing cholangitis (PSC) is a risk factor for pouchitis.[29] In this study, the numbers of patients with PSC (n = 5) seemed too small to show a significant association between PSC and pouchitis.

In this study, the total number of patients with anastomotic leakage was too small to demonstrate significant differences. Therefore despite not being significantly associated, an incidence twice as high in patients with active inflammation, compared with patients without active inflammation in the rectal stump, can still be a clinical relevant difference. It may become apparent in future studies. In univariate analyses, anastomotic leakage seemed not a predictor for pouchitis. However, insufficiently treated chronic anastomotic leakage can imitate pouchitis-like symptoms.[30]

These results of this study strengthen the hypothesis that patients with an actively inflamed rectal stump have a different prognostic phenotype of UC, with a higher risk for pouchitis—specially as an inflamed rectal stump was significantly associated with therapy-refractory pouchitis. In these patients with therapy-refractory pouchitis, a different Crohn's like phenotype was considered, as their disease course was inexplicably severe. However, Crohn's disease could not be pathologically confirmed in these patients. Moreover, patients with postoperative pathologically confirmed Crohn's disease were excluded in this study. This pleads for the theory that different phenotypes can have different risk profiles. Furthermore, all 12 seriously ill patients, requiring systemic steroid useage within 3 months before IPAA surgery, had an inflamed rectal stump. Systemic steroid useage was significantly associated with pouchitis in univariate analyses, but was excluded for multivariate analyses because of this multicollinearity. It suggests that patients requiring systemic steroid have a more aggressive disease type. Furthermore, although not significantly different, a trend between proctitis and cuffitis was observed. It can be speculated that location of inflammation plays a role.

Therefore, it can be advised to prophylactically treat patients with a microscopically inflamed rectal stump, as these patients seem to have a higher risk profile. To facilitate this, pathological evaluation of the rectal stump should be implemented in daily clinical practice.

Ileorectal anastomosis (IRA) can be an alternative to IPAA in highly selected patients with a relatively spared rectum, good rectal compliance, and normal sphincter tone. Potential advantages of IRA are lower morbidity and preserved female fecundity. It could be considered to counsel patients without rectal stump inflammation for ileorectal anastomosis instead of an IPAA, following careful discussion with the patient regarding the increased risk of rectal cancer formation.[31] Last, patients with an inflamed rectal stump can be better informed and should be aware of their increased risk for pouchitis.

Limitations of this study are that pouchitis data were collected retrospectively and that no validated pouchitis score was used. This study emphasises the importance of pathological identification of active inflammation. Although pouchitis cannot be prevented, identifying high-risk patients is important for patient counselling. The follow-up of these patients may be intensified. However, since 80% of patients after an STC seemed to have active inflammation in the rectal stump, a first step for future studies could be to find a more specific marker for therapy-refractory pouchitis—specially as therapy-refractory pouchitis is an important reason for pouch failure.[32] Finally, for clinics performing ileorectal anastomosis, it could be hypothesised that the 20% of patients without active inflammation (regardless of diversion proctitis status) are the eligible patients for this procedure instead of an IPAA.

In conclusion, an actively inflamed rectal stump after STC is a risk factor for pouchitis. Identification of different prognostic UC phenotypes could improve patient counselling for IPAA surgery and pouchitis treatment.

References

1. Targownik LE., Singh H., Nugent Z., Bernstein CN. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. Am J Gastroenterol 2012;107(8):1228–35. Doi: 10.1038/ajg.2012.127.
2. Sahami S., Konté K., Buskens CJ., Tanis PJ., Löwenberg M., Ponsioen CJ., et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. United Eur Gastroenterol J 2017;5(4):554–62. Doi: 10.1177/2050640616679552.
3. Øresland T., Bemelman W., Sampietro G., Spinelli A., Windsor A., Tiret E., et al. European evidence based consensus on surgery for ulcerative colitis. J Crohn's Colitis 2014;52(7):198–204. Doi: 10.1016/j.crohns.2014.08.012.
4. Sahami S., Bartels SAL., D'Hoore A., Fadok TY., Tanis PJ., Lindeboom R., et al. A Multicentre Evaluation of Risk Factors for Anastomotic Leakage After Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease. J Crohns Colitis 2016;10(7):773–8. Doi: 10.1093/ecco-jcc/jjv170.
5. Zittan E., Wong-Chong N., Ma GW., McLeod RS., Silverberg MS., Cohen Z. Modified Two-stage Ileal Pouch-Anal Anastomosis Results in Lower Rate of Anastomotic Leak Compared with Traditional Two-stage Surgery for Ulcerative Colitis. J Crohns Colitis 2016;10(7):766–72. Doi: 10.1093/ecco-jcc/jjw069.
6. Gawad N., El Demellawy D., Wayne C., Bass J., Nasr A. Histologic inflammatory activity of the rectal margin as a predictor of postoperative complication in ileoanal anastomosis (J-pouch) procedure in children with refractory ulcerative colitis. J Pediatr Surg 2016;51(5):783–5. Doi: 10.1016/j.jpedsurg.2016.02.022.
7. Zezos P., Saibil F. Inflammatory pouch disease: The spectrum of pouchitis. World J Gastroenterol 2015;21(29):8739. Doi: 10.3748/wjg.v21.i29.8739.
8. Hashavia E., Dotan I., Rabau M., Klausner JM., Halpern Z., Tulchinsky H. Risk factors for chronic pouchitis after ileal pouch-anal anastomosis: a prospective cohort study. Color Dis 2012;14(11):1365–71. Doi: 10.1111/j.1463-1318.2012.02993.x.
9. Quinn KP., Lightner AL., Pendegraft RS., Enders FT., Boardman LA., Raffals LE. Pouchitis Is a Common Complication in Patients With Familial Adenomatous Polyposis Following Ileal Pouch–Anal Anastomosis. Clin Gastroenterol Hepatol 2016;14(9):1296–301. Doi: 10.1016/j.cgh.2016.04.010.
10. Bartels SAL., Gardenbroek TJ., Aarts M., Ponsioen CY., Tanis PJ., Buskens CJ., et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. Br J Surg 2015;102(3):281–7. Doi: 10.1002/bjs.9701.
11. von Elm E., Altman DG., Egger M., Pocock SJ., Gøtzsche PC., Vandenbroucke JP., et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7. Doi: 10.1016/S0140-6736(07)61602-X.
12. Ordás I., Eckmann L., Talamini M., Baumgart DC., Sandborn WJ. Ulcerative colitis. Lancet (London, England) 2012;380(9853):1606–19. Doi: 10.1016/S0140-6736(12)60150-0.
13. Geboes K., Riddell R., Ost A., Jensfelt B., Persson T., Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47(3):404–9.
14. Magro F., Lopes J., Borralho P., Lopes S., Coelho R., Cotter J., et al. Comparison of different histological indexes in the assessment of UC activity and their accuracy regarding endoscopic outcomes and faecal calprotectin levels. Gut 2018:gutjnl-2017-315545. Doi: 10.1136/gutjnl-2017-315545.
15. Zenlea T., Yee EU., Rosenberg L., Boyle M., Nanda KS., Wolf JL., et al. Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study. Am J Gastroenterol 2016;111(5):685–90. Doi: 10.1038/ajg.2016.50.
16. Sahami S., Wildenberg ME., Koens L., Doherty G., Martin S., D'Haens GRAM., et al. Appendectomy for Therapy-Refractory Ulcerative Colitis Results in Pathological Improvement of Colonic Inflammation: Short-Term Results of the PASSION Study. J Crohn's Colitis 2019;13(2):165–71. Doi: 10.1093/ecco-jcc/jjy127.
17. Yeong ML., Bethwaite PB., Prasad J., Isbister R WH. Lymphoid follicular hyperplasia?a distinctive feature of diversion colitis. Histopathology 1991;19(1):55–62. Doi: 10.1111/j.1365-2559.1991.tb00894.x.
18. Kleinwort A., Döring P., Hackbarth C., Heidecke C-D., Schulze T. Deviation of the Fecal Stream in Colonic Bowel Segments Results in Increased Numbers of Isolated Lymphoid Follicles in the Submucosal Compartment in a Novel Murine Model of Diversion Colitis. Biomed Res Int 2017;2017:5265969. Doi: 10.1155/2017/5265969.

19. Geraghty JM., Talbot IC. Diversion colitis: histological features in the colon and rectum after defunctioning colostomy. Gut 1991;32(9):1020–3.
20. Roe AM., Warren BF., Brodribb AJ., Brown C. Diversion colitis and involution of the defunctioned anorectum. Gut 1993;34(3):382–5.
21. Clavien PA., Barkun J., de Oliveira ML., Vauthey JN., Dindo D., Schulick RD., et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(2):187–96. Doi: 10.1097/SLA.0b013e3181b13ca2.
22. Rahbari NN., Weitz J., Hohenberger W., Heald RJ., Moran B., Ulrich A., et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: A proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339–51. Doi: 10.1016/j.surg.2009.10.012.
23. Hata K., Ishihara S., Nozawa H., Kawai K., Kiyomatsu T., Tanaka T., et al. Pouchitis after ileal pouch-anal anastomosis in ulcerative colitis: Diagnosis, management, risk factors, and incidence. Dig Endosc 2017;29(1):26–34. Doi: 10.1111/den.12744.
24. Ternant D., Aubourg A., Magdelaine-Beuzelin C., Degenne D., Watier H., Picon L., et al. Infliximab Pharmacokinetics in Inflammatory Bowel Disease Patients. Ther Drug Monit 2008;PAP(4):523–9. Doi: 10.1097/FTD.0b013e318180e300.
25. Sahami S., Bartels SAL., D'Hoore A., Fadok TY., Tanis PJ., Lindeboom R., et al. A Multicentre Evaluation of Risk Factors for Anastomotic Leakage After Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease. J Crohns Colitis 2016;10(7):773–8. Doi: 10.1093/ecco-jcc/jjv170.
26. Geraghty JM., Talbot IC. Diversion colitis: histological features in the colon and rectum after defunctioning colostomy. Gut 1991;32(9):1020–3.
27. Komorowski RA. Histologic spectrum of diversion colitis. Am J Surg Pathol 1990;14(6):548–54.
28. Kabir SI., Kabir SA., Richards R., Ahmed J., MacFie J. Pathophysiology, clinical presentation and management of diversion colitis: a review of current literature. Int J Surg 2014;12(10):1088–92. Doi: 10.1016/j.ijsu.2014.08.350.
29. Rahman M., Desmond P., Mortensen N., Chapman RW. The clinical impact of primary sclerosing cholangitis in patients with an ileal pouch–anal anastomosis for ulcerative colitis. Int J Colorectal Dis 2011;26(5):553–9. Doi: 10.1007/s00384-011-1140-9.
30. van der Ploeg VA., Maeda Y., Faiz OD., Hart AL., Clark SK. The prevalence of chronic peri-pouch sepsis in patients treated for antibiotic-dependent or refractory primary idiopathic pouchitis. Colorectal Dis 2017;19(9):827–31. Doi: 10.1111/codi.13536.
31. Andersson P., Norblad R., Söderholm JD., Myrelid P. Ileorectal anastomosis in comparison with ileal pouch anal anastomosis in reconstructive surgery for ulcerative colitis — a single institution experience. J Crohn's Colitis 2014;8(7):582–9. Doi: 10.1016/j.crohns.2013.11.014.
32. Lightner AL., Dattani S., Dozois EJ., Moncrief SB., Pemberton JH., Mathis KL. Pouch excision: indications and outcomes. Color Dis 2017;19(10):912–6. Doi: 10.1111/codi.13673.


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Summary & discussion

Summary

The research presented in this thesis provides insight in the challenges of improving IBD surgical treatment on a national and international level. As described in **chapter 1**, the multicentre, randomised controlled PISA trial was the first study that directly compared the current standard treatment options for high perianal Crohn's fistulas, which include i) chronic seton drainage, ii) anti-TNF medication and iii) surgical closure combined with anti-TNF. The study was powered to provide superiority of seton treatment compared to the other two groups. However, after inclusion of 44 out of the projected 126 patients, the PISA trial was preliminary terminated due to a higher re-intervention rate in the seton group (10/15, versus 6/15 anti-TNF and 3/14 surgical closure patients, $P = 0.02$). The results imply that chronic seton treatment should no longer be advised as the sole treatment for perianal Crohn's fistulas. Patients who declined randomisation, due to a specific treatment preference, were included in a parallel prospective PISA registry cohort (n = 50). Interestingly, in the PISA prospective registry, inferiority of chronic seton treatment was not observed for any outcome measure.

The discrepancy, between the RCT and registry results, raised questions: which results should be used for clinical practice? Randomization in the PISA study may have had influence on participation and outcomes (e.g., external and internal validity). Following, in **chapter 2**, we aimed to assess the influence of patients' preference in RCTs by analyzing partially randomized patient preference trials (RPPT); a RCT and preference cohort combined. We systematically reviewed all RPPTs published between 2005 and 2018, 44 of 3734 identified articles were included (24,873 patients). The outcomes of the RCT and preference cohort were compared. The results showed that patients preference led to the majority of patients refusing randomisation (randomisation refusal > 50% in 26 trials), hence decreasing external validity of the RCT cohort. The reported primary outcomes – reflecting internal validity – were comparable between both cohorts of the RPPTs, mean difference 0.093 (95% CI: -0.178;0.364, $P = 0.502$). Therefore, RPPTs could increase external validity compared with RCTs, without compromising the internal validity.

In contrast to colorectal cancer surgery, during surgery for CD, only macroscopically affected bowel is resected to prevent short bowel syndrome, as the impact of microscopic inflammation at the resection margins on recurrence rates is unclear. **Chapter 3 and 4** searched for a basis to guide these resection margins. In **chapter 3**, both resection margins of 106 consecutive patients undergoing ileocecal resection for Crohn's disease between 2002–2009 were revised and scored for inflammatory characteristics. The results indicated that only active inflammation at the distal colonic resection margin was an independent significant predictor for disease recurrence (88% vs. 43% vs. 51% respectively for distal, proximal, and no involved margins, $P < 0.01$). Hence, a more extensive resection aiming at a non-inflamed ileal margin will not be

beneficial. Moreover, it revealed new insights, suggesting that active inflammation at the distal colonic resection identifies a high risk patient group with L3 disease (ileocolic phenotype) instead of L1 disease only (limited to the ileum). This patient group may benefit from postoperative medical treatment. In **chapter 4**, the inflammatory status of mesenteric macrophages in the mesorectum and the ileocecal mesentery in Crohn's disease compared with non-Crohn's disease was characterized. Proinflammatory and regulatory cells were mapped after sampling three standardised mesentery locations of 51 CD and 11 control patients (17 proctectomies and 45 ileocecal resections). Immune cells from these tissue specimens were analysed by flow cytometry for expression of CD206 in order to determine the inflammatory status. In the mesorectum, proinflammatory macrophages reside next to the inflamed rectal tissue and display a gradient to a more regulatory phenotype further away from the inflamed rectum. The ileocecal mesentery did not contain high amounts of proinflammatory macrophages adjacent to the inflamed ileal tissue. In contrast, creeping fat contained more regulatory macrophages. Therefore, there is currently no basis to perform an extended mesenteric ileocecal resection in Crohn's disease patients.

While striving to meet the quality standards for oncological care, hospitals prioritize oncological procedures more frequently, resulting in longer waiting times for surgery regarding benign diseases like IBD. **Chapter 5** highlights the potential consequences of a longer interval to surgery for IBD patients compared to colorectal cancer surgery in the Amsterdam UMC, location AMC, between 2013–2015. The mean waiting time was more than 10 weeks for IBD patients, twice as long compared to colorectal cancer patients (5 weeks). While awaiting surgery, 1 out of 8 IBD patients had to undergo surgery in an (semi-)acute setting, 19% had disease complications (e.g., > 5% weight loss, abscess formation) and 44% needed additional health care (e.g., (telephone)outpatient clinic appointment, hospital admission). It highlights that the current waiting time for IBD surgery is not medically justified and creates a burden for health care resources. It is time to also set a maximally acceptable waiting time to surgery for IBD patients.

In **chapter 6 and 7**, we set up an international collaboration to compare the short- and long-term outcomes of the new transanal ileal pouch-anal anastomosis (ta-IPAA) technique with the standard transabdominal minimal invasive approach in UC. Ta-IPAA surgery resulted in lower morbidity rates and comparable long-term functional outcomes.

Chapter 8 focussed on the long-term functional outcomes of the novel endo-sponge® assisted early surgical closure (ESC) approach for IPAA leakage in 280 UC patients. Out of the 40 patients with anastomotic leakage, 18 were treated with ESC (2010–2017) and 22 (2002–2009) with conventional management. ESC resulted in comparable pouch function ($P = 0.647$) and comparable pouch failure rates (0/18 vs. 5/133, $P > 0.99$, resp.) versus control patients without leakage. Conventional management resulted in worse

pouch function ($P = 0.016$) and a higher pouch failure rate (5/22 vs. 5/107, $P = 0.013$, resp.) compared to control patients. Therefore, ESC is associated with preservation of pouch function and might prevent pouch failure.

In the last chapter of this thesis, **chapter 9**, the impact of rectal stump inflammation after subtotal colectomy on both short- and long-term pouch outcomes for 204 UC patients operated between 1999 and 2017 was studied. Rectal stump inflammation (found in 82%) was not associated with an increased risk of anastomotic leakage (10.2% vs. non-inflamed 5.4%, $P = 0.54$). However, it was associated with a higher incidence of pouchitis (54.3% vs. non-inflamed 25.5%, $Plog = 0.02$). It was therefore suggested that patients with rectal stump inflammation have a more aggressive phenotype of UC.

Research questions addressed in this thesis

1. *With respect to re-interventions, is seton treatment superior to anti-TNF treatment and surgical closure combined with anti-TNF for patients with a high perianal Crohn's fistula?*
   Chronic seton treatment was not associated with lower re-intervention rates.

2. *Is a partially randomised patient preference trial a valid alternative to a randomised controlled trial regarding internal and external validity?*
   A partially randomised patient preference trial is a valid alternative with a higher participation rate, thereby increasing external validity, while primary outcomes remain comparable, hence preserving internal validity.

3. *What is the predictive value of microscopic inflammation at ileocecal resections margins for postoperative Crohn's recurrence?*
   Inflammation at the distal colonic ileocecal resection margins is associated with an increased disease recurrence rate. Inflammation at the proximal ileal margin is not associated with an increase in disease recurrence. Therefore, more extended ileocecal resection does not seem to be beneficial.

4. *Is there an anatomical variation in mesenteric macrophage phenotypes that can guide surgical resection margins in Crohn's disease?*
   A gradient of pro-inflammatory macrophages in the mesorectum is associated with inflamed adjacent rectal tissue. Hence, resecting that part of mesorectum seems beneficial. A gradient of pro-inflammatory macrophages in the mesentery of the ileocolonic adjacent to inflamed ileal tissue was not observed. Moreover, the creeping fat contained a gradient of regulatory macrophages. Consequently, resecting the mesentery during ileocecal resection seems not beneficial.

5. *Is a longer waiting time for IBD surgery associated with 'waiting list complications'?*
   A longer waiting time for IBD surgery is associated with an increase of semi-acute

surgery and non-surgical complications such as more than 5% weight loss, fistula or abscess formations requiring radiological intervention, dehydration and additional health care consumption.

6. *Is transanal versus transabdominal minimally invasive pouch surgery in UC beneficial regarding short-term morbidity?*
   Transanal minimally invasive pouch surgery is associated with a reduction in post-operative morbidity.

7. *Does transanal versus transabdominal minimally invasive pouch surgery in UC result in superior long-term pouch function?*
   Long-term functional outcome and quality of life after transanal and transabdominal minimally invasive pouch surgery were comparable.

8. *Does Endo-sponge assisted early surgical closure of pouch leakage improve long-term pouch function?*
   Endo-sponge assisted early surgical closure was associated with preservation of pouch function and might prevent of pouch failure, probably due to early and effective treatment of anastomotic leakage.

9. *What is the impact of rectal stump inflammation on anastomotic pouch leakage and pouchitis?*
   Rectal stump inflammation after subtotal colectomy occurs in 80% of UC patients. It is not significantly associated with an increased anastomotic leakage rate of the pouch, but was an independent predictor for the development of (therapy refractory) pouchitis.

Discussion and future perspectives

Regarding research of IBD treatment strategies, a data gap exists for the comparison of surgical versus medical strategies. The PISA study showed how challenging such a comparison can be, yet also revealed considerable lessons learned. To properly translate clinical situations in a trial, some established assumptions should be scrutinised. First of all, surgery should not be seen only as a last resort but also as an alternative to medical treatment. Besides, trials comparing medical therapies in Crohn's disease should not use surgical recurrence as an endpoint. The PISA registry also revealed that relatively few patients chose surgery as a treatment. It touches upon a more extensive problem that patients may not be well informed about the surgical treatment options. A fundamental factor driving this observation is probably due to the majority of Crohn's fistula patients having a long medical history with a gastroenterologist, who advises the patients. Since, the gastroenterologist is probably less familiar with the surgical treatment options and its respective outcomes, shared decision making is likely to be impaired. A vital starting point would be a shift in patient counselling towards earlier visiting a surgeon, paving the way to talk about alternatives, instead of inevitable last resort surgery. Hopefully combined out-patient clinics regarding gastroenterology and IBD surgery, aiming at solid cooperation, will soon become entrenched in modern healthcare on a global scale.

Perianal Crohn's disease

The optimal treatment for patients with perianal Crohn's fistulas remains unknown. While designing the PISA study, results suggested comparable closure rates between the three treatment options. According to the most recent systematic review, the initial remission of drainage rate after anti-TNF treatment is 44%.[1] Initial closure of fistulas in CD following surgical closure seems higher (65%).[2] A future trial comparing these treatments head-to-head would be of great importance for these patients. Ideally all types of patients with perianal CD fistulas should be represented in large numbers. These recent closure rates also suggest that a substantial number of patients fail their therapy. For these patient, hyperbaric oxygen seems an option.[3] To conduct such studies, consensus on the definition of a closed fistula should be reached. The definition of a fibrotic tract without collections on MRI can be correlated to patient reported outcomes to develop a firm endpoint.

Designing surgical trials

The PISA study results challenge the current dogma of the RCT being the 'gold standard'. However, the assumption that trial participants are passive recipients of interventions is not valid. Patient preferences can influence RCT participation and outcomes. Additionally, an RCT is costly, time consuming and does not correct for learning curves. Modern research should try to adapt in order to find a healthy balance between limiting

bias effects and drawing conclusions applicable for routine practice. Especially now that 'big data' is becoming more established in medical research, more pragmatic designs can be considered such as patient preference designs or a cohort-embedded RCT (also known as TWICS or randomised registry trial).[4,5]

Ileocecal resection

Yet to be researched, but why not start with an ileocecal resection for patient with uncomplicated terminal ileitis, avoiding medical treatment? At a minimum, the short- and long-term results of the LIR!C study induce a shift in the current step-up treatment approach for uncomplicated terminal ileitis; ileocecal resection has shown to be an alternative treatment for anti-TNF instead of a last resort treatment.[6,7] It's likely that more ileocecal resections will be performed. The results of this thesis suggest that microscopically inflamed distal colonic resection margin is associated with a higher disease recurrence rate, as it identifies undiagnosed L3 disease (ileocolonic instead of ileum only Crohn's disease). As the recurrence rate for L3 disease is significantly higher, the colon should be accurately scoped before surgery, in order for patients to be thoroughly counselled. Additionally, pathology reports should specifically address the inflammatory state of the distal resection margin, as patients with an inflamed distal margin should be considered for prophylactic treatment. Furthermore, a microscopically inflamed proximal resection margin and mapping macrophages phenotypes in the ileocecal mesentery did not result into a prognostic value. These findings intuitively support performing stricturoplasties for selected patients, in which the affected bowel is left in situ.[8] However, ongoing research suggests that the mesentery does play a role in driving (recurrences of) CD. The specific role is probably dependent on Crohn's location, phenotype and patient characteristics. Therefore a patient-tailored surgical approach would be desirable. In this regard a fluorescent-guided surgical approach demonstrating the extent of inflammation could be an interesting step forward. Bearing in mind that we stand at the beginning of understanding the IBD anatomy and the related role of the mesentery, we should foster the current cooperation between laboratory researchers and surgeons. Samples of resection specimens being directly analysed in the laboratory is a fertile soil for future research.

Waiting list complications

The observation that patients with IBD have to wait longer for surgery compared to patient with colorectal cancer illustrates that IBD care has taken a back seat. Quality criteria like regular multidisciplinary team meetings, centralisation of care and healthcare regulatory bodies setting the norm for time to treatment in IBD should become equally established as their respective counterparts in oncology.[9] Public awareness must be raised to fuel these developments.

Pouch surgery

Innovation in pouch surgery is rising, as illustrated with the introduction of the ta-IPAA distal resection. To suppress the negative side effect of the learning curve, this thesis emphasises the importance of centralisation. For the treatment of pouch leakage endo-sponge assisted surgical closured is advised. This requires good collaboration between the gastroenterologist and the surgeon advocating for IBD referral centers. Also for pouch surgery fluorescent-guided surgery seems promising to further reduce the anastomotic leak rate. The prognostic value of an inflamed rectal stump on pouch outcomes should be further analysed. The results of the MIRACLE study, aiming to identify the best pouch practices throughout Europe, are eagerly awaited.[10]

In conclusion, surgery could be introduced earlier and more often is the multidisciplinary management of IBD.

References

1. Lee, M. J. et al. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. Clin. Gastroenterol. Hepatol. (2018). doi:10.1016/j.cgh.2018.01.030
2. Stellingwerf, M. E., van Praag, E. M., Bemelman, W. A. & Buskens, C. J. P426 Meta-analysis of endorectal advancement flap vs. ligation of the intersphincteric fistula tract for Crohn's and cryptoglandular high perianal fistulas. J. Crohn's Colitis 12, S320–S320 (2018).
3. Lansdorp, C. A. et al. Hyperbaric oxygen therapy for the treatment of perianal fistulas in Crohn's disease (HOT-TOPIC): study protocol of a prospective interventional cohort study with one-year follow-up. Undersea Hyperb. Med. 46, 45–53
4. K.A. Wasmann, MD1, P.C. Wijsman 2, MD, S. van Dieren3, MD, W.A. Bemelman 1, and C. J. B. Using patient's preference in randomized controlled trials. Abstr. ESCP (2018).
5. Ahmed, H. U. et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat. Rev. Clin. Oncol. 11, 482–491 (2014).
6. Ponsioen, C. Y. et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol. Hepatol. 2, 785–792 (2017).
7. Stevens, T. et al. OP03 Reduced need for surgery and medical therapy after early ileocaecal resection for Crohn's disease: Long-term follow-up of the LIR!C trial. J. Crohn's Colitis 14, S003–S004 (2020).
8. Stebbing, J. F., Jewell, D. P., Kettlewell, M. G. & Mortensen, N. J. Recurrence and reoperation after strictureplasty for obstructive Crohn's disease: long-term results [corrected]. Br. J. Surg. 82, 1471–4 (1995).
9. Luzietti, E. et al. Comparison of guidelines for the management of rectal cancer. BJS Open 2, 433–451 (2018).
10. Bemelman WA on behalf of the surgeons of S-ECCO and ESCP. An international multi-interventional registry study for chornic ileoanal pouch leaks in UC (the Miracle-project).


RETHINKING
DOGMAS
RETHINKING
DOGMAS

Appendices

Nederlandse samenvatting

Dit proefschrift laat zien hoe uitdagend het kan zijn om de chirurgische behandeling van inflammatoire darmziekten (IBD) te verbeteren op nationaal en internationaal niveau.

Zoals beschreven in **hoofdstuk 1** was de PISA-studie is de eerste studie die de huidige drie behandelingen voor perianale Crohnse fistels met elkaar heeft vergeleken. In een multicenter, gerandomiseerde setting werden langdurige seton drainage, anti-TNF medicatie en chirurgisch sluiten van de fistel in combinatie met anti-TNF medicatie met elkaar vergeleken. De hypothese van de studie was dat seton drainage zou lijden tot de minste reïnterventies. Bij de eerste tussenanalyse (na een derde van het beoogde aantal inclusies) bleek echter dat er significant meer reïnterventies voorkwamen in de seton groep (10/15 seton versus 6/15 anti-TNF and 3/14 chirurgisch sluiten, P = 0.02). Omdat op dat moment de hypothese van de studie al kon worden verworpen, werd de studie vroegtijdig gestopt. Het lijkt er dus op dat langdurige seton drainage niet langer moet worden geadviseerd als enige behandeling voor perianale Crohnse fistels. Patiënten die niet gerandomiseerd wilden worden vanwege een behandelingsvoorkeur werden geïncludeerd in het prospectieve PISA registratie cohort (n = 50). Interessant om te zien was dat de slechte resultaten van de langdurige seton drainage niet naar voren kwamen uit de analyses van de registratie studie.

Deze discrepantie tussen de uitkomsten van beide studies roept vragen op. Op welke resultaten moeten we varen voor de dagelijkse praktijk? Mag je überhaupt kiezen voor één studie of moeten alle resultaten meegenomen worden? De baselinekarakteristieken van beide studies waren niet verschillend. Het zou kunnen dat het randomiserende karakter van de PISA-studie invloed heeft gehad op het aantal deelnemende patiënten en op de studie-uitkomsten. Om die eventuele invloed te onderzoeken is gepoogd het effect van patiëntenvoorkeur in gerandomiseerde gecontroleerde studies (RCT) te meten (**hoofdstuk 2**). Dit is gedaan door studies te analyseren waarin patiënten konden worden geïncludeerd op basis van randomisatie, maar ook op basis van hun eigen behandelvoorkeur (partially randomised patient preference trial: RPPT). Alle RPPT's gepubliceerd tussen 2005 en 1018 zijn bekeken, waarna 44 van de 3724 artikelen geïncludeerd konden worden (24.873 patiënten). Vervolgens werd binnen elke studie de RCT met het voorkeurscohort vergeleken. Die analyses lieten zien dat het bieden van een keuze voor een behadeling er in resulteert dat de meeste patiënten randomisatie weigeren (> 50% in 26 studies). Dat heeft negatieve gevolgen voor de externe validiteit van een RCT. Voor alle onderzochte RPPT's gold dat de primaire uitkomsten van de RCT-patiënten niet verschilden van die van de patiënten in het voorkeurscohort (interne validiteit). Concluderend kan het gecombineerde karakter van de RPPT de externe validiteit vergroten zonder afbreuk te doen aan de interne validiteit.

Tijdens darmresecties bij IBD-patiënten wordt alleen het macroscopische aangedane stuk darm gereseceerd. Dit gebeurt op deze manier omdat, in tegenstelling tot darmresecties bij colorectale maligniteiten, de impact van positieve resectiemarges bij IBD onduidelijk is. In **hoofdstuk 3** werden bij 106 patiënten die een iloecoecaalresectie ondergingen vanwege de ziekte van Crohn (CD) beide resectiemarges gereviseerd en gescoord op inflammatiekarakteristieken. De resultaten suggereerden dat alleen inflammatie in de distale resectiemarge van het colon een onafhankelijke voorspeller was voor ziekterecidief (88% en 43% recidiefpercentages bij respectievelijk inflammatie in de resectiemarge distaal, inflammatie in de resectiemarge proximaal, tegenover 51% recidieven wanneer beide marges vrij van inflammatie waren, $P < 0.01$). Het reseceren van een ruimer stuk ileum is in dit kader dus niet zinvol. Daarnaast lieten de resultaten zien dat actieve inflammatie in het distale colon een patiëntengroep identificeert met ileocolische ziekte (Montreal L3) in plaatst van ziekte beperkt tot het terminale ileum (L1). Deze patiëntengroep zou gebaat kunnen zijn bij medicatie postoperatief ter preventie van ziekterecidief. In **hoofdstuk 4** zijn pro-inflammatoire en regulatoire macrofagen op 3 locaties in het mesenterium van 51 Crohn-patiënten en 11 controlepatiënten op een gestandaardiseerde manier in kaart gebracht (17 proctectomiën en 45 ileocoecaalresecties). De macrofagen werden geanalyseerd door middel van flowcytometrie met de expressie van membraam eiwit CD206. Er werd gezien dat naarmate het rectum ernstiger aangedaan was het aangrenzende mesorectum ook relatief meer pro-inflammatoire macrofagen bevatte. In het mesenterium in de ileocoecaalhoek werd dit echter niet geobjectiveerd. Derhalve is er ook op basis van deze resultaten geen bewijs gevonden om een uitgebreidere ileocoecaalresectie ter verrichten.

Om aan de kwaliteitseisen te voldoen van oncologische zorg wordt in ziekenhuizen vaak prioriteit gegeven aan oncologische zorg ten faveure van benigne ziektebeelden zoals IBD. Dit kan resulteren in langere wachttijden voor de laatst genoemde groep. **Hoofstuk 5** belicht de potentiele gevolgen van een langere wachttijd tot IBD chirurgie in het Amsterdam UMC, locatie AMC. De gemiddelde wachttijd bij deze patiënten was meer dan tien weken, twee keer zo lang als bij patiënten met colorectale carcinomen. Gedurende de wachttijd onderging één op de acht IBD-patiënten chirurgie in een semiacute setting, ondervond 19% complicaties ten gevolge van ziekteprogressie (o.a. > 5% gewichtsverlies of abces vorming) en had 44% aanvullende zorg nodig (o.a. poliklinische afspraken en ziekenhuisopnames). Dit alles is reden om ook voor IBD-patiënten een maximale wachttijd in te stellen, zoals nu al het geval is voor de oncologische zorg.

In **hoofdstuk 6 en 7** wordt een internationaal onderzoek beschreven waarin de korte en lange termijnuitkomsten van de nieuwe transanale benadering bij het aanleggen van een ileo-anale pouch worden vergeleken met de klassieke transabdominale benadering. Deze transanale techniek resulteerde in minder morbiditeit en vergelijkbare lange termijnuitkomsten.

In 2010 werd met de intrede van de endo-sponge een nieuwe methode in gebruik genomen ter behandeling van naadlekkages na een ileo-anale pouch. Dit maakte het mogelijk om de naad daarna relatief vroeg chirurgisch te sluiten ("endo-sponge assisted early surgical closure", ESC). In **hoofdstuk 8** lag de focus op de lange termijn-resultaten van deze behandeling bij 280 patiënten met colitis ulcerosa (CU). Van de 40 patiënten met een naadlekkage zijn er 18 behandeld middels ESC (2010–2017) en 22 met conventioneel drainbeleid (2002–2009). ESC resulteerde in een vergelijkbare pouchfunctie en pouchfalen (0/18 vs. 5/133) vergeleken met controlepatiënten uit die tijdsperiode zonder naadlekkage. Conventioneel drainbeleid resulteerde in slechtere pouch functie en meer pouch falen (5/22 vs. 5/107) ten opzichte van controlepatiënten uit dezelfde tijdsperiode.

In het laatste hoofdstuk van dit proefschrift (**hoofdstuk 9**) zijn de gevolgen van inflammatie van de rectumstomp na een subtotale colectomie geanalyseerd. Hiervoor werden 204 CU-patiënten met een pouch geïncludeerd. Rectumstomp-inflammatie kwam voor bij 82% van de patiënten. Inflammatie was niet geassocieerd met een hoger risico op naadlekkage (10.2% vs. niet aangedaan rectum 5.4%, $P = 0.54$). Wel was het geassocieerd met een hogere incidentie van pouchitis (54.3% vs. niet aangedaan rectum 25.5%, *Plog* = 0.02). Hieruit wordt gesuggereerd dat patiënten met inflammatie in de rectumstomp een agressiever UC-fenotype hebben.

Onderzoeksvragen uit dit proefschrift

1. *Leidt setondrainage tot minder reïnterventies in vergelijking met anti-TNF behandeling en chirurgisch sluiten van een fistel onder anti-TNF in patiënten met perianale Crohnse fistels?*
   Chronische setondrainage is niet geassocieerd met minder reïnterventies.

2. *Is een 'partially randomised patient preference trial' een geschikt alternatief voor een RCT met betrekking tot interne en externe validiteit?*
   Een 'partially randomised patient preference trial' is een geschikt alternatief waarbij hogere deelname aantallen worden gehaald zonder dat de studie uitkomsten verschillen. De externe validiteit wordt dus vergroot terwijl de interne validiteit gewaarborgd blijft.

3. *Wat is de voorspellende waarde van inflammatie in de resectiemarges na een ileocoecaalresectie op ziekterecidief van Crohn?*
   Inflammatie in de distale resectiemarge van het colon is geassocieerd met een hogere kans op ziekterecidief. Inflammatie in de proximale resectiemarge van het ileum is niet geassocieerd met een hogere kans op ziekterecidief. Een uitgebreidere ileocoecaalresectie lijkt dus niet zinvol.

4. *Kan de uitgebreidheid van chirurgische resectiemarges bij de ziekte van Crohn aangepast worden op basis van het type macrofagen en hun locatie in het mesenterium?*
   In het mesorectum werd gezien dat naarmate het rectum ernstiger aangedaan was het aangrenzende mesorectum ook relatief meer pro-inflammatoire macrofagen bevatte. Het mede-reserceren van dit deel mesorectum lijkt gunstig. In het mesenterium in de ileocoecaalhoek werd dit principe echter niet geobjectiveerd. Het 'creeping fat' ter plaatste van aangedaan ileum bevatte juist meer regulatoire macrofagen. Het ruimer reserceren van het mesenterium tijdens ileocoecaal resectie lijkt niet zinvol.

5. *Is een langere wachttijd tot chirurgie voor IBD geassocieerd met complicaties tijdens de wachttijd?*
   Het langer op de wachtlijst staan voor het ondergaan van chirurgie voor IBD is geassocieerd met een toename in semi-acute chirurgie en in ziekte-gerelateerde complicaties.

6. *Resulteert transanale versus transabdominale minimaal invasieve pouch-chirurgie bij CU-patiënten in lagere postoperatieve morbiditeit?*
   Transanale minimaal invasieve pouch-chirurgie is geassocieerd met lagere post-operatieve morbiditeit.

7. *Resulteert transanale versus transabdominale minimaal invasieve pouch-chirurgie bij CU in betere pouchfunctie?*
   De lange termijn functionele pouch-uitkomsten en kwaliteit van leven waren gelijk tussen de beiden technieken.

8. *Resulteert endo-sponge geassisteerd vroeg chirurgisch sluiten van pouch naadlekkages bij CU in betere pouchfunctie in vergelijking met de conventionele techniek?*
   Endo-sponge geassisteerd vroeg chirurgisch sluiten was geassocieerd met het behoud van pouchfunctie. Door deze tijdige en effectieve behandeling van naad-lekkages kan mogelijk pouchfalen worden voorkomen.

9. *Wat is het risico van inflammatie in de rectumstomp voor het ontwikkelen van een naadlekkage van de pouch en pouchitis na een subtotale colectomie bij CU?*
   Inflammatie van de rectumstomp na subtotale colectomie kwam in 80% voor. Het was niet geassocieerd met een toename in naadlekkage. Het was wel een onaf-hankelijke voorspeller voor het ontwikkelen van (therapie-refractaire) pouchitis.

List of co-authors

Jojanneke van Amesfoort
Vivian Bastiaenen
Marte Becker
Willem Bemelman
Jarmila van der Bilt
Marja Boermeester
Karlien Bruin
Anthony de Buck van Overstraeten
Christianne Buskens
Michele Carvello
Pramodh Chandrasinghe
Annalisa Lo Conte A
Silvio Danese
Susan van Dieren
Marcel Dijkgraaf
Eline van der Does de Willebois
Onur Dolmaci
Manon Duijvenstein
Caterina Foppa
Krisztina Gecse
Michael Gerhards
Jip Groen
Joline de Groof
Geert D'Haens
Roel Hompes
André D'Hoore
Jeroen Jansen
Lotje Klaver
Lianne Koens
Mark Lowenberg
Anders Mark-Christensen
Jonathan van der Meer
Maurits van Montfoort
Marco Mundt
Iris Nagtegaal
Zarah Perry-Woodford
Cyriel Ponsioen
Apollo Pronk
Kees Punt
Bert van Ramshorst
Maud Reijntjes
Hjalmar van Santvoort
Antonino Spinelli
Merle Stellingwerf
Pieter Tanis
Anders Tottrup
Sebastiaan van Tuyl
Koen Vanbrabant
Marlies Verstegen
Janindra Warusavitarne
Pieta Wijsman
Manon Wildenberg
Hans de Wilt
Albert Wolthuis
David Zimmerman

List of publications

1. Treatment of perianal fistulas in Crohn's disease, seton versus anti-TNF versus surgical closure following anti-TNF (PISA): a randomised controlled trial.
   Wasmann KATGM, de Groof EJ, Stellingwerf ME, D'Haens GR, Ponsioen CY, Gecse KB, Dijkgraaf MGW, Gerhards MF, Jansen JM, Pronk A, van Tuyl SAC, Zimmerman DDE, Bruin KF, Spinelli A, Danese S, van der Bilt JDW, Mundt MW, Bemelman WA, Buskens CJ.
   J Crohns Colitis. 2020; 14(8):1049-1056

2. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses.
   Wasmann KA, Wijsman P, van Dieren S, Bemelman W, Buskens C.
   BMJ Open. 2019; Epub ahead of print.

3. The Predictive Value of Inflammation at Ileocecal Resection Margins for Postoperative Crohn's Recurrence: A Cohort Study.
   Wasmann KATGM, van Amesfoort J, van Montfoort ML, Koens L, Bemelman WA, Buskens CJ.
   Inflamm Bowel Dis. 2019; Epub ahead of print.

4. Anatomical Variation in Mesenteric Macrophage Phenotypes in Crohn's Disease.
   Jonathan HM van der Meer, Karin A Wasmann, Jarmila DW van der Bilt, Marte AJ Becker, Marja A Boermeester, Willem A Bemelman, Manon E Wildenberg, Christianne J Buskens
   Clin Transl Gastroenterol. 2020; Epub ahead of print.

5. Complications While Waiting for IBD Surgery-Short Report.
   Wasmann KA; IBD study group Amsterdam UMC, location AMC .
   J Crohns Colitis. 2020;14(2):277-280.

6. Transanal Versus Transabdominal Minimally Invasive (Completion) Proctectomy With Ileal Pouch-anal Anastomosis in Ulcerative Colitis: A Comparative Study.
   de Buck van Overstraeten A, Mark-Christensen A, Wasmann KA, Bastiaenen VP, Buskens CJ, Wolthuis AM, Vanbrabant K, D'hoore A, Bemelman WA, Tottrup A, Tanis PJ.
   Ann Surg. 2017;266(5):878-883.

7. Transanal ileal pouch-anal anastomosis for ulcerative colitis has comparable long-term functional outcomes to transabdominal approach: a multicentre comparative study.
   Chandrasinghe P, Carvello M, Wasmann K, Foppa C, Tanis P, Perry-Woodford Z, Warusavitarne J, Spinelli A, Bemelman W.
   J Crohns Colitis. 2020; 14(6):726-733

8. Endo-sponge Assisted Early Surgical Closure of Ileal Pouch-anal Anastomotic Leakage Preserves Long-term Function: A Cohort Study.
   Wasmann KA, Reijntjes MA, Stellingwerf ME, Ponsioen CY, Buskens CJ, Hompes R, Tanis PJ, Bemelman WA.
   J Crohns Colitis. 2019;13(12):1537-1545.

9. The impact of rectal stump inflammation after subtotal colectomy on pouch outcomes in ulcerative colitis patients.
   Karin A Wasmann, Eline M van der Does de Willebois, Lianne Koens, Marjolijn Duijvestein, Willem A Bemelman, and Christianne J Buskens
   J Crohns Colitis. 2020; Epub ahead of print.

10. Subclassification of Multivisceral Resections for T4b Colon Cancer with Relevance for Postoperative Complications and Oncological Risks.
    Wasmann KATGM, Klaver CEL, van der Bilt JDW, Nagtegaal ID, Wolthuis AM, van Santvoort HC, Ramshorst B, D'Hoore A, de Wilt JHW, Tanis PJ.
    J Gastrointest Surg. 2019; 24(9):2113-2120

11. Laparoscopic surgery facilitates administration of adjuvant chemotherapy in locally advanced colon cancer: propensity score analyses.
    Wasmann KA, Klaver CE, van der Bilt JD, van Dieren S, Nagtegaal ID, Punt CJ, van Ramshorst B, Wolthuis AM, de Wilt JH, D'Hoore A, van Santvoort HC, Tanis PJ.
    Cancer Manag Res. 2019;11:7141-7157.

12. Postoperative abdominal infections after resection of T4 colon cancer increase the risk of intra-abdominal recurrence.
    Klaver CEL, Wasmann KATGM, Verstegen M, van der Bilt JDW, Nagtegaal ID, van Ramshorst B, Tanis PJ, Wolthuis AM, van Santvoort HC, de Wilt JHW, D'Hoore A.
    Eur J Surg Oncol. 2018;44(12):1880-1888.

13. The "Cone" stoma: stoma creation in the presence of significant bowel dilatation.
    Lo Conte A, Wasmann K, Tanis PJ, Buskens CJ, Hompes R, Bemelman WA.
    Tech Coloproctol. 2019;23(3):283-285.

Book chapters

14. Resectional surgery for intestinal strictures – What is state of the art?
    Karin A.T.G.M. Wasmann, Christianne J. Buskens, Pieter J. Tanis, and Willem A. Bemelman
    Springer Science. 2017

15. The complicated pouch
    Willem A. Bemelman, Karin A. Wasmann, Christianne J. Buskens and Pieter J. Tanis
    Springer Science. 2019

PhD portfolio

Name PhD student: Karin Wasmann
PhD period: 1-2-2017 t/m 1-9-2019
Promotores: prof. dr. W.A. Bemelman & prof. dr. G.R.A.M. D'Haens
Copromotor: dr. C.J. Buskens

	Year	ECTS
General courses		
Practical biostatistics	2017	1.1
Oral presentation in English	2017	0.8
Scientific writing in English for publication	2017	1.5
Basic course in legislation and organization for clinical researchers (BROK)	2017	1.0
Clinical Epidemiology: Randomized Clinical Trials	2017	0.6
Clinical Epidemiology: Observational Epidemiology	2018	0.6
Independent data monitoring committee course, EORTC	2018	0.5
Seminars, workshops and master classes		
Weekly Surgical Department Seminars	2017-2019	3.0
Weekly Inflammatory Bowel Disease Seminars	2017-2019	3.0
Journal club	2017-2019	3.0
Medical Business Masterclass	2017	0.8
Workshop Clinical Writing, BJS, Birmingham	2018	1.0
Oral presentations		
Treatment of perianal Crohn's fistulas (PISA)		
Broad, New York	2018	0.5
European Crohn's and Colitis Organisation, Copenhagen	2019	0.5
European Society of Coloproctology, Vienna	2019	0.5
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2019	0.5
Chirurgendagen, Veldhoven	2019	0.5
Tillots Symposium, Amsterdam	2019	0.5
Endosponge treatment of pouch leakage		
Chirurgendagen, Veldhoven	2018	0.5
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2018	0.5
Bbraun, Barcelona	2018	0.5
Inflammation at Ileocecal resection margins and Crohn's recurrence		
IBD Today and Tomorrow, Amsterdam	2017	0.5
European Society of Coloproctology, Berlin	2017	0.5
Chirurgendagen, Veldhoven	2019	0.5
Postoperative complications and peritoneal metastases for T4 colon cancer		
SIS-E, Hamburg	2017	0.5
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2017	0.5
Multivisceral resection for T4b colon cancer		
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2017	0.5
Laparoscopic surgery in T4 colon cancer		
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2017	0.5

	Year	ECTS
Poster presentations		
Partially randomised patient preference trial		
European Crohn's and Colitis Organisation, Copenhagen	2019	0.5
European Society of Coloproctology, Nice	2018	0.5
Inflammation at Ileocecal resection margins and Crohn's recurrence		
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2017	0.5
European Crohn's and Colitis Organisation, Vienna	2018	0.5
Endosponge treatment of pouch leakage		
Nederlandse Vereniging voor Gastroenterologie, Veldhoven	2018	0.5
Anatomical variation of the mesentery		
European Society of Coloproctology, Vienna	2019	0.5
Attended (Inter)national conferences		
European Society of Coloproctology	2017-2019	3.75
Alpine Colorectal Meeting	2018	1.25
Chirurgendagen	2017-2019	3.75
European Crohn's and Colitis Organisation	2017-2019	3.75
Young-ICC Symposium	2017-2019	3.75
Nederlandse Vereniging voor Gastroenterologie	2017-2019	3.75
Surgical Infection Society Europe	2017	1.25
Peritoneal Surface Oncology Group International	2018	1.25
Teaching		
Supervisor master thesis V.P. Bastiaenen	2017	2.0
Supervisor master thesis M. Reijntjes	2017	2.0
Supervisor master thesis E. van der Does de Willebois	2019	2.0
Supervisor bachelor thesis H. Post	2018	1.0
Supervisor bachelor thesis J. Stael	2018	1.0
Other		
Invited peer-review		
Colorectal Disease	2017-2020	2.0
European Journal Surgical Oncology	2019	0.5
British Medical Journal Open	2020	0.5
Journal Crohn and Colitis	2019-2020	1.0
Grants		
ZonMw, Translational research	2019	

Dankwoord

Zonder de bijdragen van vele anderen was dit proefschrift niet als zodanig tot stand gekomen. Allereest wil ik graag alle patiënten bedanken die deel uit hebben gemaakt van dit proefschrift.

Prof. dr. W.A. Bemelman, beste Willem, je mailde me ooit: "we gaan de wereld veroveren". Het is aan anderen om te beoordelen of dat gelukt is, maar de wereld lag zeker aan mijn voeten. Je overtuigingskracht en gedrevenheid werken aanstekelijk, en ik heb de vruchten kunnen plukken van je nationale en internationale connecties. Maar ik benijd je natuurlijk het meeste vanwege je partytricks. Van de pick-up service per motorboot tot entourage met rookmachine, ik hoop dat de wereld er weer snel van kan meegenieten.

Dr. C.J. Buskens, beste Chris, voor jouw "skattieees!" ben ik toch veel te nuchter? Maar ook jij zei ooit heel nuchter: "Als je de impact van een gemiddeld stuk bekijkt, kan je de wetenschap maar beter als een hobby bedrijven". Wij vonden elkaar met een glas rosé bij jou in de achtertuin. Met die gouden formule lukte het ons om binnen een maand een artikel from scratch te publiceren. Altijd haastend door de gang en altijd het laatste woord, jij bedrijft geen droge wetenschap. Soms leek het meer alsof ik in een activistische beweging terecht was gekomen, wat het zo veel boeiender maakte, waarvoor dank!

Prof. dr. G.R.A.M. D'Haens, beste Geert, als dit proefschrift ergens voor staat is het voor de MDL-chirurgie samenwerking. Dank voor het toevoegen van de nuance.

Prof. dr. P.J. Tanis, beste Pieter, jij een rustige Zeeuw en ik een drukke Brabo, maar een no-nonsense mentaliteit en een stevig arbeidsethos hebben we allebei. Na al het monnikenwerk voor de T4 database kon je niet meer om heen. Gelukkig bood je mij de springplank voor mijn wetenschappelijke carrière, waarvoor dank. En zoals gezegd, 2021 wordt ons jaar!

Veel dank gaat uit naar alle leden van de commissie die hierin zitting hebben genomen, en natuurlijk naar alle medeauteurs voor hun samenwerking en de bijdrage aan dit werk.

Lieve Frans, mijn Wendy, mijn paranimf, meerdere keren acknowledged in dit proefschrift. Had ik maar beter opgelet tijdens Engels, dat had jou veel werk kunnen schelen. Natuurlijk staat familie altijd voor elkaar klaar, maar toch ben ik jou het meeste dank verschuldigd! Met de uitgave van dit proefschrift kan ik je eindelijk weer met rust laten, geniet van je vrije tijd!

Beste onderzoekers, assistenten, chirurgen, PA's en secretaresses van G4, bedankt voor de leuke tijd. Er heerst bij jullie een mooie combinatie van gedrevenheid en humor.

Beste collega's van de maag-darm-leverziekten en het lab. Ik begreep vaak weinig van jullie praatjes over medicatie en biochemie, maar de conclusie was altijd helder: we

zijn er nog niet. We hebben elkaar nodig, dank voor alle uitleg en natuurlijk voor de topsamenwerking!

Lieve Lotje, 13-02-2015, een dagje chillen op Playa Cas Abou, wat later de grondslag van dit proefschrift bleek te zijn. Een ware mentor was je. Alle gesprekken, zo veel adviezen. Dank dat je me de grote en kleine kneepjes van het vak hebt geleerd!

Lieve oom Peter en tante Guusje, inderdaad, als je ze nodig hebt zijn ze er: mijn peetoom en peettante. Dank oom Peter voor je reflectie en je altijd even kritische blik. Natuurlijk gaan we dat varkentje wassen, en goed ook. Tante Guusje, al hadden we tot 04:00 uur 's nachts door geschilderd voor de kaft, het had jou niet gedeerd. Ik denk dat iedereen die dit leest kan beamen dat het resultaat prachtig is.

Gelukkig is er ook een leven buiten dit proefschrift, een leven vol familie en vrienden. Ik wil nooit alleen zijn, maar gelukkig ben ik dat door jullie ook zelden.
Lieve nichtjes en broers in Amsterdam, hopelijk blijven jullie allemaal nog lang in de stad. Er is niets zo gezellig als familie in de buurt. Samen sterk in de makelaardij, de bouw, het recht en in de keuken, we proberen het altijd goed voor elkaar te regelen. De zuid-Italianen kunnen nog een lesje van ons leren.
Lieve keizers, dit is alweer het tweede Kuzco boekje en met prof. Pieta en tante Will zullen er nog minstens 2 volgen. Ik ben echt trots op wat we allemaal presteren!
Lieve chickens, 7 moeders rijker op de Hoeve, in jullie ogen was er heel wat werk aan de winkel. Zo meteen staat ze daar dan, jullie ooit zo bleue foetje. Dank voor de mooie jaren! Alsof ik nog niet genoeg familie heb, kreeg ik er nog een hele familie bij, de Curaçao groep ée ée. Het leukste jaar van mijn leven. Laat Coerin niet meer in de steek, de volgende keer gaan we weer gewoon met zijn allen!

En toen ging ze naar het OLVG en waren daar Han en Char, wat een hilariteit. Al staan al je seinen roodgloeiend, als er even geborreld of geroddeld moet worden, dan moet dat gewoon, dank! Natuurlijk ook dank aan alle andere collega's van het OLVG, niet aangenomen worden heeft maar weinig voordelen, maar jullie steunbetuiging is er zeker een van!

Families Wasmann en Van de Klok met oma aan het hoofd. Zo veel familie brengt ook zo veel diversiteit en gezelligheid met zich mee. Ik geniet van alle gekkigheid tijdens de familieweekenden en skivakanties. Family first!

Pa en ma, promoveren moet dat? Een goede dokter helpt mensen! Ben je nou nog niet klaar? En zo meteen de twee meest trotse mensen in de zaal. Jullie laten ons altijd vrij, zolang we maar eerlijk zijn. Een stabiel team, "één lijn", ik zal het nooit vergeten. De warme sfeer die er thuis heerst, overal eten en drank, ik zie steeds meer dat dat eigenlijk niet vanzelfsprekend is. Dank voor alles. Ooit zullen we jullie terugbetalen met heel veel kleinkinderen, wacht nou maar rustig af.

Lieve Coen, mijn held! Jij de neerlandicus en ik de taalvirtuoos, en zo komen we aan bij de laatste alinea welke niet door jou op spelling is gecontroleerd. Dat ik op 'datenight' toch nog even aan mijn dankwoord mag werken en jij gaat koken, zegt zo veel. Je bent zo relaxed, zelfverzekerd en beheerst de trouwheid die nodig is om ondanks alles Fainoort fan te blijven. Je laat me gewoon mijn ding doen, waarvoor dank! De dolle mina's zouden trots op ons zijn. Wat kijk ik uit naar de volgende feesten die we gaan geven, op naar Le Blanc in de huiskamer! Hou van jou, je grootste fan.

About the author

Karin Wasmann was born in 1992 and raised in the small town of Bladel, The Netherlands. She grew up in an ever busy environment with three brothers, her parents, their lovely dog Whiskey and dozens of cousins, which she happily enjoyed. Her dad, being a tourist fanatic, quickly passed on the traveling fever to his daughter. When she was 17 she made her first trip on her own to volunteer in an orphanage in Mandeville, Jamaica.

After finishing secondary school, she moved to Groningen to start her medical education. She joined the student association Vindicat and worked at café Soestdijk. She took every chance to do parts of her study abroad and worked in clinics in Cape Town and throughout parts of South-America. Her interest in surgery was aroused when she got the opportunity to join the Liverteam of the UMCG, where she assisted during liver transplantations. During her masters she was fortunate to follow her internships for one year at the SEHOS, Willemstad, dushi Korsou (Dutch Antillen). At the island, she was tempted by her current partner Coen, learned Papiamentu, but moreover during these extraordinary days at the SEHOS she committed herself to become a surgeon.

In 2016, she was introduced into medical research during her research internship supervised by prof. Pieter Tanis, investigating surgical treatment of T4 colon cancer. After her graduation in 2017, she started her PhD under the supervision of prof. Willem Bemelman, prof. Geert D'Haens and dr. Christianne Buskens at the AMC. Her thesis focuses on the surgical improvement of inflammatory bowel disease. She was given the opportunity to participate in European collaborations, was involved in developing an alternative trial design and visited many international conferences to present their work. Currently, she enjoys being a clinical doctor at the department of surgery at the OLVG-Oost in Amsterdam under the supervision of dr. Michael Gerhards. She continues her research and is looking forward in making the next step in her surgical career.